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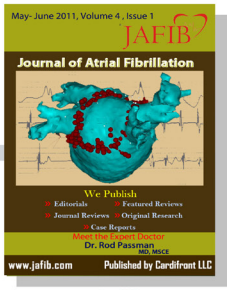

Preoperative Statin use is not Associated with a Reduced Risk of Atrial Fibrillation After Cardiac Surgery

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Abstract

Introduction: Postoperative atrial fibrillation (POAF) is prevalent after cardiac surgery and associated with significant morbidity and costs. Statins are commonly used in this population and may be a preventative strategy for PAOF. We wished to examine the effect of preoperative statin use on the risk of POAF after cardiac surgery.

Methods: A retrospective, observational study was conducted using data from 489 adult patients who underwent cardiac surgery at a single institution. Univariate analyses and unconditional logistic regression were used to determine the impact of preoperative statin use on the probability of developing POAF, while controlling for the baseline risk of POAF and the use of amiodarone prophylaxis (AMP). A baseline risk index was calculated for each patient using a previously validated model. Patients with chronic atrial fibrillation or missing data were excluded.

Results: Mean patient age was 63 (SD=13) years, 73% were male, 68% underwent isolated coronary artery bypass grafting, 16% underwent isolated valve surgery, with 13% underwent combined CABG and valve surgeries, and 3% underwent other forms of cardiac surgery. POAF occurred in 27% of patients receiving statins and 24% of those not receiving statins (p=0.3792). After controlling for baseline risk of POAF and the use of AMP, we found that preoperative statins were not associated with reductions in POAF (OR=1.19, 95%CI=0.782-1.822, p=0.4118).

Conclusions: Multiple factors impact the development of POAF after cardiac surgery including patient demographics, comorbidities, surgical type, and concomitant medications. In this study, after adjustment for these factors the preoperative use of statins did not significantly influence the development of POAF.

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Introduction

Postoperative atrial fibrillation (POAF) is the most common complication following open heart surgery including coronary artery bypass surgery (CABG) and/or valve surgery, and is a significant source of morbidity and mortality.[1-3] Each year in the United States, POAF following open heart surgery occurs in approximately 26% of patients with an estimated range of 17-35% and in some reports as high as 50%.[1,2] The high incidence of POAF has an impact on the health care system in many ways including patient morbidity, health care costs, and length of hospital stay. [3]

Beta blockers and amiodarone have been shown to decrease the incidence of POAF and have been used as prophylaxis based on their ability to suppress arrhythmias. In recent years, several investigators have suggested that statins may be a possible therapeutic alternative to lower the incidence of POAF based on their potential pleiotropic properties .[4-17] Statins have been shown to have anti-inflammatory properties and have demonstrated reductions in chemokines and chemokine receptor expression in endothelial cells and macrophages.[12,14] While the etiology of POAF is likely multifactorial, inflammation has been proposed as a possible contributing factor .[14]

The findings from prior studies examining the use of statins after cardiac surgery for the prevention of POAF are inconsistent.[5-11]The objective of this study was to evaluate the impact of preoperative statin therapy on the risk of developing POAF following cardiac surgery, while controlling for contemporary prophylactic strategies and subjects' baseline risk for developing POAF.

Methods

After approval from our institutional review board, a retrospective, observational, cohort study was conducted using data from 489 adult patients who underwent cardiac surgery in 2003. During this time period, our research group had previously collected extensive medication administration and heart rhythm data and also calculated a baseline risk index for postoperative atrial fibrillation (described below) on this cohort.[18]For this investigation we supplemented this existing dataset with additional information regarding preoperative statin use.

Data sources included institution-specific data from the Society of Thoracic Surgeons national database plus medical and medication administration records. All adult patients (≥18 years old) who underwent cardiac surgery in 2003 were eligible for the study. Patients with a preoperative diagnosis of chronic atrial fibrillation or those with incomplete medical records were excluded. Patients were considered to have received statin therapy preoperatively if a statin was listed on their home medication list at hospital admission. All patients were placed on continuous telemetry throughout their hospital stay. POAF was defined as the persistence of atrial fibrillation for > 4 hours following cardiac surgery as documented in the patient's medical record flow sheet. We elected to use this more ridged criteria for POAF as prolonged POAF is likely to impact outcomes more significantly than paroxysmal atrial fibrillation.

Baseline risk for POAF was calculated for each patient using a validated model consisting of 11 variables.[15] This index stratifies patients into 3 risk groups: low, moderate, and high risk. Model variables that increased the risk of having POAF develop included: advancing age, a history of atrial fibrillation or chronic obstructive pulmonary disease, patients undergoing heart valve surgery, or patients whose beta-blockers or angiotensin converting enzyme inhibitors are withdrawn after surgery. Variables that decrease the risk of having POAF develop include the use of postoperative beta-blocker alone, both preoperative and postoperative beta-blockade or angiotensin converting enzyme inhibition, postoperative nonsteroidal anti-inflammatory drugs, or postoperative potassium supplementation. In this risk index, each of these variables possesses their own contribution weights. When the weights are totaled, patients are classified as low-risk (< 14 points), moderate-risk (14 to 31 points), or high-risk (> 31 points). We combined patients in the moderate-risk and high-risk groups into a single elevated-risk group. The final risk index (as a continuous variable) was included in the multivariate logistic regression model to control for baseline risk of POAF. Medication exposure was collected from medication administration records. Medication administration to the

patient was verified by reviewing Pyxis MedStation 2000 dispensing records. Amiodarone prophylaxis was defined as documented administration of greater than or equal to 1 day of either intravenous or oral amiodarone, or a combination of both routes, between postoperative days 0 to 4, prior to the onset of any POAF. Timing of amiodarone administration was compared with the onset of POAF to verify patients had received amiodarone as prophylactic therapy. To be counted in the risk index calculation, medications (i.e. beta blockers, ACE inhibitors, NSAIDs, potassium) were required to administered for greater than or equal to 1 day of between postoperative days 0 to 4, prior to the onset of any POAF.

Using SAS (version 9.1.4) and an a priori alpha level of 0.05 to indicate statistical significance, univariate analysis (t-tests, Wilcoxon rank sum, and chi square tests) and unconditional, logistic regression, utilizing stepwise selection (model entry and retention were set at 0.15 and 0.05, respectively) were used to determine the impact of preoperative statin use on the probability of developing POAF, while controlling for the baseline risk of POAF and the use of amiodarone prophylaxis (AMP). Successful model convergence was noted during the stepwise selection procedure. Interactions between model variables were assessed by incorporating the product of the various explanatory factors and assessing their impact on the model. Statistically significant variable interactions did not exist. Goodness of fit for the model was assessed by evaluating the Hosmer and Lemeshow test which indicated the predicted responses generated by our model were not statistically different from that which we observed. Model overfitting was checked by determining if each explanatory variable included in the model had at least 10 positive outcomes. Odds ratios and their corresponding 95% confidence intervals were calculated for the explanatory variables by exponentiation of the values of the regression coefficients (see TABLE 2).

Results

A total of 489 patients were included in the analyses. Baseline demographics are listed in [TABLE 1]. The mean patient age was 63 (SD=13) years, 73% were male, 68% (n=334) underwent isolated coronary artery bypass grafting, 16% (n=79) underwent isolated valve surgery, with 13% (n=61) underwent combined CABG and valve surgeries, and 3% underwent other cardiac surgical repair of aortic aneurysms (n=7), atrial septal defects (n=5), and patent foramen ovale (n=4). Beyond inclusion of valve surgery in the risk index, the other surgical procedures did not signifincantly influence the probability of developing POAF when included in the model, and thus did not remain in the final model. Subjects receiving preoperative statins were more likely to be older and have a history of hypertension, prior MI and prior CABG. Patients in the statin group were also more likely to be undergoing CABG rather than valve surgery during the index admission and more likely to be prescribed preoperative and postoperative beta blockers. Left ventricular ejection fraction was not different between the statin and nonstatin groups (46%+/-14% among statin users, and 47%+/- 14% among non statin users, p=0.5984). Based on the calculated risk index, 51% of patients were consid-

Table 2 Logistic regression analysis of the influence of the POAF risk index and the use of amiodarone prophylaxis and statins on the occurrence of postoperative atrial fibrillation (N=489)

Factor	b parameter	Odds ratios (95% Wald CI)	p
Intercept	-1.6808	n/a	<0.0001
Preoperative statin use	0.0886	1.194 (0.782-1.822)	0.4118
Postoperative amiodarone prophylaxis	-0.2493	0.607 (0.397-0.930)	0.0218
POAF risk index	0.0474	1.049 (1.030-1.067)	<0.0001

Table 1 Demographics of the study population (N=489)

Variables	Total Group, (N = 489)	Statin - (n=263)	Statin + (n=226)	P value, -/+ Statin
Age, mean years, (SD) ‡ £	63 (13)	61 (15)	65 (11)	0.0009 *
<30, n (%)	10 (2)	10 (4)	0 (0)	
30-39, n (%)	21 (4)	16 (6)	5 (2)	
40-49, n (%)	39 (8)	27 (10)	12 (5)	
50-59, n (%)	123 (25)	58 (22)	65 (29)	0.0023
60-69, n (%)	132 (27)	72 (27)	60 (27)	
70-79, n (%)	118 (24)	57 (22)	61 (27)	
80+, n (%)	46 (10)	23 (9)	23 (10)	
Male gender, n (%)	359 (73)	189 (72)	170 (75)	0.4020
Weight (mean kilograms ± SD) ‡	87 ± 20	85 (19)	90 (21)	0.0019
Preoperative history of:				
Atrial fibrillation £, n (%)	40 (8)	25 (10)	15 (7)	0.2485
Lung disease £, n (%)	68 (14)	33 (13)	35 (15)	0.3490
Heart failure, n (%)	75 (15)	47 (18)	28 (12)	0.0935
Hypertension, n (%)	345 (71)	155 (59)	190 (84)	<0.0001
Myocardial infarction, n (%)	173 (35)	76 (29)	97 (43)	0.0012
Renal failure, n (%)	24 (5)	16 (6)	8 (4)	0.1942
Prior coronary artery bypass surgery, n (%)	48 (10)	16 (6)	32 (14)	0.0028
Prior valve surgery, n (%)	18 (4)	13 (5)	5 (2)	0.1099
CABG during admission, n (%)	334 (68)	153 (58)	181 (80)	<0.0001
Valve surgery during admission £, n (%)	79 (16)	65 (25)	14 (6)	<0.0001
Combined CABG and valve surgery, n (%)	61 (13)	34 (13)	27 (12)	0.7430
Other cardiac surgery, n (%)	15 (3)	11 (4)	4 (2)	0.1230
Surgery status:				
Elective, n (%)	275 (57)	149 (57)	126 (56)	
Urgent, n (%)	195 (40)	99 (38)	96 (42)	0.1200
Emergent, n (%)	17 (3)	13 (5)	4 (2)	
Cross clamp time, median min. (range) †	82 (53-270)	83 (0-270)	80 (0-225)	0.2067
Cardiopulmonary bypass time, median min. (range) †	107(75-403)	111 (0-403)	102 (0-279)	0.0815
Postoperative atrial fibrillation (POAF) related variables:				
Patients at elevated POAF risk (from risk index £), n(%)	238 (49)	129 (54)	109 (46)	0.8566
POAF, n (%)	125 (26)	63 (24)	62 (27)	0.3792
POAF recurrence, n (%)	53/125 (42)	26/63 (41)	27/62 (44)	0.7987
Duration of POAF, in # of days, median (range) †	2 (1-36)	2 (1-28)	2 (1-36)	0.8269
Postoperative use of amiodarone prophylaxis, n (%) ¥	294 (60)	155 (59)	139 (62)	0.5630
Post surgical withdraw of beta-blockers, n (%) £	96 (20)	46 (17)	50 (22)	0.1984
Post surgical withdraw of ACE-inhibitors, n (%) £	132 (27)	62 (24)	70 (31)	0.0699
Pre and postoperative use of beta-blockers, n (%) ¥ £	228 (46)	105 (40)	123 (54)	0.0014
Postoperative use of beta-blockers, n (%) ¥ £	327 (67)	165 (63)	162 (72)	0.0362
Pre and postoperative use of ACE inhibitors, n (%) ¥ £	128 (26)	55 (21)	73 (32)	0.0043
Postoperative use of NSAIDs, n (%) ¥ £	153 (31)	86 (33)	67 (30)	0.4678
Postoperative potassium replacement, n (%) ¥ £	489 (100)	263 (100)	226 (100)	1.0000

ered low-risk for POAF and 49% were considered moderate to high risk. The proportion of subjects at elevated-risk for POAF did not differ between those receiving preoperative statins (46%) and those who did not (54%, p=0.8566)

POAF occurred in 27% of patients who received preoperative statins compared to 24% of those not receiving statins (p=0.3792). After controlling for the baseline risk of POAF and the use of AMP, we found that statins continued to not be associated with reductions in POAF (See TABLE 2, OR=1.19, 95%CL=0.782-1.822, p=0.4118). The frequency of use for specific statins is described in [TABLE 3]. The most commonly prescribed statins were atorvastatin and simvastatin (37.6% and 49.6%, respectively). Statin dosing was variable, consistent with the typical low and high dose ranges used in clinical practice. There was no significant difference in the use of preoperative statins in the patients who developed atrial fibrillation (50%, 62/125) vs. those who did not develop atrial fibrillation (45%, 164/364), p=0.3792. Likewise there was no significant difference in the use of lipid lowering therapy at hospital discharge in those subjects who did develop atrial fibrillation (66%, 83/125) vs. those who did not (67%, 243/364), p=0.9203. There was no significant difference in the performance of atrial fibrillation preventative surgery at the time of their procedure between those patients who did or did not develop postoperative atrial fibrillation (p=0.1603).

Discussion

Previous observational studies have found that statin therapy prior to and following cardiac surgery reduces the risk of developing POAF. In a nested cohort trial, Lertsburapa et al. evaluated the impact of statins in 555 patients undergoing cardiac surgery. Among the 331 patients who received statins, rates of POAF were reduced by 40% .[5] A study of 362 patients, also found that preoperative statins were associated with a lower risk of POAF (8.2% vs 16.8%, p=0.03) [16] In a well designed, prospective observational study, Mariscalco et al. studied 405 patients undergoing CABG surgery. The effect of statin therapy was evaluated using logistic regression modeling, stratification and propensity scoring. Preoperative statin use was associated with a 42% reduction in POAF (p=0.017). [17] It should be noted that this study included patients with a prior history of AF and those undergoing emergent surgery, thus suggesting a population at higher risk.

In addition to the observational data, one randomized, double-blind, placebo-controlled study has evaluated the impact of preoperative statins on POAF risk. The Atorvastatin for Reduction of Myocardial Dysrhythmia After Cardiac Surgery (ARMYDA-3) compared atorvastatin 40 mg, started seven days prior to surgery, to placebo in 200 patients undergoing elective open heart surgery. [6] This study found that atorvastatin significantly reduced the risk of POAF (OR 0.39, 95%CI 0.18-0.85, p=0.017) and statistically resulted in a shorter length of hospital stay (6.3 vs 6.9 days, p=0.001) While this was the most rigorous study to date, it did not examine the influence of baseline risk for POAF, which is likely an important determinant of the effectiveness of prophylactic regimens.

In contrast to these positive studies, other studies have failed to support the theory that statins reduce the risk of POAF. Virani et al performed a retrospective cohort analysis with a large patient population (n=4044) and found that statin use prior to and following cardiac surgery did not reduce the incidence of POAF.[8] Recently, Miceli et al. reported a significantly higher incidence of POAF in patients undergoing CABG who had taken statins

Table 3 Preoperative Statin Use (n=226)

Statin	# (%) subjects receiving drug	Mean dose (mg) ± SD	Dose range (mg)
atorvastatin	85 (37.6)	22±16	5-80
fluvastatin	3 (1.3)	80±0	80-80
lovastatin	6 (2.7)	22±10	10-40
pravastatin	17 (7.5)	34±24	10-80
rosuvastatin	3 (1.3)	20±17	10-40
simvastatin	112 (49.6)	35±24	5-80

as compared to those patient who had not received statin therapy (n=411, 19.5%, versus 336; 15.8%, p = 0.002). [9]

Similarly, our retrospective observational analysis concluded that preoperative statin use did not significantly reduce the incidence of POAF following cardiac surgery. One limitation of the retrospective study design was the inability to control for statin dosing. Previously, it has been found that higher statin doses may produce more significant reductions in POAF .[5]Likewise, Kourliouros et al provided support for a dose-dependant reduction in POAF with simvastatin and atorvastatin, concluding that low dose statin therapy is not effective for preventing POAF.[10] The majority of our patient population received low to moderate statin doses (TABLE 3). Further, the potency of the various statins used is highly variable. Because inflammation may contribute to a higher incidence of POAF and the anti-inflammatory benefit of statins is likely achieved at higher doses, this may explain the lack of benefit seen in this study cohort. Additionally, we were unable to control for LDL levels or other inflammatory markers to determine whether patients in our study were achieving optimal cardioprotective or anti-inflammatory benefit of statins. For example, it has been shown that lower CRP levels following the administration of statins are associated with improved event free survival following an acute coronary syndrome [12] Future studies could include a more specific analysis of the dose-dependent effects of statins on inflammation and the subsequent influence on POAF.

Baseline risk is a major determinant of the risk for POAF. In particular, it has been shown that valve surgery significantly increases the risk. In a study by Creswell et al., the incidence of atrial arrhythmias was higher in patients undergoing mitral valve replacement and aortic valve replacement versus CABG alone (42.4% versus 48.8% versus 31.9%) .[13] Our patient population included a significant number of patients undergoing valve surgery or combined valve and CABG surgery (TABLE 1). The higher incidence of POAF when valve surgery occurs could explain why our analysis did not support statin use as prophylaxis for POAF. Virani et al found similar results with no reduction in POAF with statin therapy for a study population that included a higher proportion of patients undergoing valve surgery.[8]Our study has several additional limitations. Ourstudy indicated that patients with more co morbidities and thus at increased likelihood to develop POAF, were more likely to be on a statin prior to surgery. However, the calculated risk index for baseline risk for POAF was not different between the groups and was controlled for in the regression model. With the retrospective design of our study, it is difficult to control for events that may or may not have occurred in the perioperative and postoperative time period. Examples include administration or discontinuation of medications that may provide cardio protection or influence the development of POAF, such as steroids and aspirin which were not assessed in this study. We did however verify the administration and timing of drugs used specifically to prevent POAF. The high use of amiodarone and beta blockers may have clouded the results as these agents may reduce POAF, however as they are frequently used in clinical practice, it would not be practical to perform a study in the present era which excluded their prescription.

As previously discussed, we were unable to control for the statin used, dose of statin or duration of therapy. In addition post operative statin use was not available for the analysis. However, our hypothesis was that preoperative statin use would have a greater impact on the occurrence of POAF than would postoperative use where initiation and cellular influence may be delayed and variable. A future carefully controlled double blind prospective study may reduce the impact of these recognized as well as other unrecognized confounding factors.

It is of interest that certain randomized studies [6,7] have suggested a benefit of statins for POAF while some observational studies [8,9] present have not. This suggests the possibility that over-selection in the randomized trials may have reduced the applicability to general clinical practice, or that the inclusion of unrecognized confounders in the observational studies may have reduced the potential benefit of statin therapy. It is also possible that varying criteria for the diagnosis of POAF has led to some of the differences in prior study outcomes. For example the ARMYDA-3 study which demonstrated benefit with statins used a very sensitive definition of POAF (duration of > 5 minutes) as compared to our more stringent definition of duration > 4 hours. Our study is unique in that we included all patients undergoing cardiac surgery and did not limit our research to a homogenous population. Additionally, unlike previous studies we controlled for the use of prophylactic strategies such as amiodarone and beta blockers. It is possible that the use of such agents render the impact of statins on POAF imperceptible unless studied in a very large sample.

Conclusions

In conclusion, this retrospective study did not demonstrate an association between preoperative statin use and the risk of POAF following cardiac surgery. Taken as a whole, the body of evidence examining the relationship between statin use and POAF remains inconclusive and therefore cannot be used to justify the use of statins as a primary prophylactic strategy. However, due to the routine use of statins in the cardiac surgery population for other indications, additional research appears warranted. Future studies focusing more specifically on individual statins and the dose and timing of administration relative to the perioperative period may provide more definitive answers. Likewise, additional studies more fully exploring the potential mechanisms through which statins might impact arrhythmia development may help to further clarify this issue.

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