Preoperative statins for the prevention of atrial fibrillation after cardiothoracic surgery

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Objective: Recent studies have suggested that statins reduce atrial fibrillation after cardiothoracic surgery, but the use of proven prophylactic strategies such as beta-blockers and amiodarone in these studies was not provided. Therefore, we sought to determine whether preoperative statin use could reduce the incidence of post-cardiothoracic surgery atrial fibrillation in a population who already had a high background use of beta-blockers and appreciable use of prophylactic amiodarone.

Methods: Patients undergoing cardiothoracic surgery from the randomized, controlled Atrial Fibrillation Suppression Trials I, II, and III were evaluated in this nested cohort evaluation. The patients' demographics, surgical characteristics, medication use, and incidence of post-cardiothoracic surgery atrial fibrillation (atrial fibrillation >5 minutes duration) were uniformly and prospectively collected as part of Atrial Fibrillation Suppression Trials I, II, and III. Multivariate logistic regression was used to calculate adjusted odds ratios with 95% confidence intervals.

Results: Overall, 331 patients (59.6%) received a statin preoperatively and 224 patients (40.4%) did not. The study population had an average age of 67.8 ± 8.6 years, 77.1% were male, 14.6% had valve surgery, 6.1% had a history of atrial fibrillation, 12.6% had a history of heart failure, 84.0% received postoperative beta-blockade, and 44.1% received postoperative prophylactic amiodarone. In total, 174 patients (31.4%) developed post-cardiothoracic surgery atrial fibrillation. Upon multivariate logistic regression, statin use was associated with a reduction in post-cardiothoracic surgery atrial fibrillation (adjusted odds ratio: 0.60; 95% confidence interval 0.37–0.99). Higher intensity statin dosing (equivalent of ≥ 40 mg of atorvastatin) seemed to be associated with the greatest reductions in post-cardiothoracic surgery atrial fibrillation (adjusted odds ratio: 0.45; 95% confidence interval 0.21–0.99).

Conclusions: In a population with appreciable beta-blocker and amiodarone use, adjunctive preoperative statin use was still associated with a 40% reduction in patients' odds of developing post-cardiothoracic surgery atrial fibrillation.

Approximately 666,000 cardiothoracic surgeries (CTS) were performed in the United States in 2003.¹ One of the most common complications after CTS is the development of atrial fibrillation (AF). Although typically self limiting, post-CTS AF can increase a patient's risk for hemodynamic instability and stroke.² Moreover, it prolongs the length of stay and increases total hospital costs.^{2,3} Beta-blockers and amiodarone are thus commonly used to prevent post-CTS AF and have been effective according to a recent meta-analysis.⁴ Even with prophylactic beta-blockade and/or amiodarone, up to 40% of patients still develop post-CTS AF.⁴⁻⁷

Given the antiadrenergic effects of beta-blockers and amiodarone, the risks of hypotension, bradycardia, and heart block are elevated. Additional adjunctive strategies to further impede sympathetic functioning will likely exacerbate these adverse events; therefore, a novel strategy for reducing post-CTS AF is required.

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Abbreviations and Acronyms

AF = atrial fibrillation
 CI = confidence interval
 CTS = cardiothoracic surgery

Inflammation may be a causative factor in the development of postoperative and nonsurgical AF.⁸⁻¹¹ Given the ability of statins to attenuate inflammation,¹²⁻¹⁴ previous studies have assessed the relationship between statin use pre-CTS and the subsequent development of AF after surgery.¹⁵⁻¹⁸ Unfortunately, none of these studies assessed statin efficacy when added to appreciable prophylaxis with beta-blockers and amiodarone. Whether statins would still maintain efficacy when added to a population receiving higher levels of prophylactic beta-blockers and amiodarone is not known.

By combining the patient data from 3 randomized and controlled clinical trials, the Atrial Fibrillation Suppression Trials (AFIST) I, II, and III,^{6,7,19} we had 555 patients who had undergone CTS from whom to conduct a “nested” study. All of the data were prospectively determined during the trials, end point definitions were the same, postoperative beta-blocker administration was high, and use of prophylactic amiodarone was substantial. We therefore examined the impact of preoperative statin use on the incidence of postoperative AF in this nested population.

Materials and Methods**Design and Population**

Our study prospectively evaluated a nested cohort of 555 patients who underwent coronary artery bypass grafting and/or valvular surgery as part of the AFIST I, II, and III. This study was approved by the Hartford Hospital Institutional Review Committee after expedited review.

AFIST I⁶ was a randomized, double-blind, placebo-controlled trial that assessed the effect of oral amiodarone or placebo on the incidence of AF after cardiac surgery ($n = 217$). Patients enrolled less than 5 days before surgery received 6 g of amiodarone or placebo during 6 days beginning on preoperative day 1. Patients enrolled at least 5 days before surgery received 7 g during 10 days beginning on preoperative day 5. AFIST II⁷ was a 2×2 factorial study that assessed the effect of 2 active treatments (amiodarone and atrial septal pacing) on the incidence of AF after cardiac surgery ($n = 160$). Patients were initially randomized to either amiodarone or placebo and then randomized further to either atrial septal pacing or no pacing. AFIST III¹⁹ was a randomized controlled trial that assessed the effect of aortic fat pad maintenance on the incidence of postoperative AF in patients ($n = 178$) undergoing coronary artery bypass graft surgery for the first time.

Data with respect to patient demographics, surgical characteristics, medication use, and postoperative AF were prospectively and uniformly collected as part of AFIST I, II, and III. In AFIST I, II, and III, the primary end point was the development of post-CTS

AF within 30 days of cardiac surgery. AF was defined as episodes lasting more than 5 minutes as documented by continuous telemetry. Statin use and dose were recorded. The statins were converted to atorvastatin equivalents using the following conversions: atorvastatin 10 mg = simvastatin 5–20 mg, lovastatin 10–40 mg, pravastatin 10–40 mg, fluvastatin 20–80 mg, or cerivastatin 0.1–0.4 mg; atorvastatin 20 mg = simvastatin 40 mg, pravastatin 80 mg; rosuvastatin 5 mg, or cerivastatin 0.8 mg; atorvastatin 40 mg = simvastatin 80 mg or rosuvastatin 10 mg; atorvastatin 80 mg = rosuvastatin 20 mg.²⁰⁻²²

Statistical Analysis

Continuous variables are presented as means with standard deviations and were compared between groups using a Student *t* test or Mann–Whitney test when appropriate. Dichotomous variables are presented as percentages and were compared between groups using a chi-square or Fisher exact test when appropriate.

Because this was an observational study, the investigators had no control over which patients received statins. As a result, significant differences in observed demographic, surgical, and medication use characteristics were expected. To control for these potential confounders and to avoid a biased estimate of treatment effect, we conducted a multivariate logistic regression. Univariate analysis was first performed to examine the relationship between different variables (demographic, surgical, and medication use characteristics) and the development of postoperative AF (dependent variable). All variables that showed a univariate association ($P \leq .20$) with AF occurrence or that were previously demonstrated to be strong independent predictors of AF^{3,6,7,19,23,24} were then entered into a backward, stepwise multivariate regression model. Adjusted odds ratios and 95% confidence intervals (CIs) were calculated for all independent predictors. Statistical analysis was performed with the Statistical Package for the Social Sciences version 15.0 (SPSS Inc, Chicago, Ill).

Results

A total of 555 patients were evaluated, of whom 331 (59.6%) received a statin preoperatively and 224 (40.4%) did not. Overall, the study population had an average age of 67.8 ± 8.6 years, 77.1% were male, 14.6% had valve surgery, 6.1% had a history of AF, 12.6% had a history of heart failure, 84.0% received postoperative beta-blockade, and 44.1% received prophylactic amiodarone. Table 1 depicts the results of univariate comparisons of demographic and perioperative characteristics between patients receiving and not receiving a statin. Similarly, comparisons of demographics and perioperative characteristics between patients developing and not developing post-CTS AF are provided in Table 2.

In total, 174 patients (31.4%) developed AF after cardiac surgery (36.6% vs 27.8% in the non-statin and statin groups, respectively; crude odds ratio: 0.68; 95% CI: 0.46–0.96). Of the 174 patients, only 1 developed AF after discharge but within 30 days. On multivariate analysis (Table 3), the preoperative use of statins was associated with a statistically significant reduction in AF (adjusted odds ratio: 0.60; 95% CI: 0.37–0.99). Benefit was also seen with nonsteroidal,

TABLE 1. Patient demographics, surgical characteristics, and medication use by statin use

	No statin (n = 224)	Statin (n = 331)	
Variable	n (%)	n (%)	P value
Preoperative characteristics			
Age, y (mean ± SD)	69.4 ± 8.7	66.7 ± 8.4	<.001
Male gender	172 (76.8)	256 (77.3)	.88
Participant in AFIST I	118 (52.8)	99 (29.9)	<.001
Participant in AFIST II	59 (26.3)	101 (30.5)	.29
Participant in AFIST III	47 (21.0)	131 (39.6)	<.001
History of diabetes mellitus	64 (28.6)	120 (36.3)	.06
History of hypertension	156 (69.6)	253 (76.4)	.08
History of smoking	132 (58.9)	194 (58.6)	.94
History of myocardial infarction	69 (30.8)	136 (41.1)	.01
Family history of CAD	84 (37.5)	133 (40.2)	.53
History of angina	158 (70.5)	250 (75.5)	.19
History of heart failure	34 (15.2)	36 (10.9)	.13
EF, % (mean ± SD)	49.2 ± 13.1	50.2 ± 12.1	.46
>45	137 (61.6)	204 (61.6)	.40
25-45	77 (34.4)	119 (36.0)	
<25	10 (4.5)	8 (2.4)	
Prior AF	13 (5.8)	21 (6.3)	.79
History of cerebrovascular disease	11 (4.9)	16 (4.8)	.97
History of COPD	33 (14.7)	43 (13.0)	.56
History of mitral regurgitation	58 (25.9)	54 (16.3)	.01
Vessels >50% occluded	2.6 ± 1.1	2.9 ± 0.8	.003
Preoperative medical therapy			
Beta-blocker	145 (64.7)	264 (79.8)	<.001
CCB	48 (21.4)	49 (14.8)	.04
Digoxin	12 (5.4)	16 (4.8)	.78
ACEI or ARB	96 (42.9)	168 (50.8)	.08
Surgical characteristics			
Valve surgery	51 (22.8)	30 (9.1)	<.001
On-pump surgery	166 (74.1)	207 (62.5)	.004
Duration of surgery, min, (mean ± SD)	289.4 ± 87.0	290.8 ± 104.5	.87
No. of grafts, n, (mean ± SD)	3.5 ± 1.8	3.9 ± 1.4	.005
No. of arterial Grafts, n, (mean ± SD)	1.4 ± 1.2	1.8 ± 1.2	<.001
No. of venous grafts, n, (mean ± SD)	2.2 ± 1.5	2.2 ± 1.3	.81
Postoperative medication use			
Amiodarone	101 (45.1)	144 (43.5)	.71
Beta-blocker	180 (80.4)	286 (86.4)	.06
CCB	17 (7.6)	37 (11.2)	.16
Digoxin	73 (32.6)	74 (22.4)	.007
Corticosteroids	77 (34.4)	71 (21.5)	.001
NSAIDs	54 (24.1)	73 (22.1)	.57
ACEI/ARB	86 (38.4)	132 (39.9)	.73
Beta-blocker withdrawal	18 (8.0)	32 (9.7)	.51
ACEI/ARB withdrawal	35 (15.6)	68 (20.5)	.14

SD, Standard deviation; AFIST, Atrial Fibrillation Suppression Trial; CAD, coronary artery disease; EF, ejection fraction; COPD, chronic obstructive pulmonary disease; CCB, calcium channel blocker; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; NSAID, nonsteroidal anti-inflammatory drug.

preoperative beta-blocker, and prophylactic amiodarone administration ($P \leq .04$ for all). Age, number of arterial grafts, beta-blocker withdrawal (patient treated with preoperative beta-blocker but not receiving postoperative beta-blocker before onset of AF), and histories of AF, diabetes mellitus,

and mitral valve regurgitation were positive risk factors for developing AF after surgery ($P \leq .04$ for all).

When subgroup analysis evaluating the impact of different statin dosing intensities was performed, statin doses equivalent to ≥ 40 mg per day of atorvastatin resulted in

TABLE 2. Patient demographics, surgical characteristics, and medication use by postoperative cardiothoracic surgery atrial fibrillation status

	No post-CTS AF (n = 381)	Post-CTS AF (n = 174)	
Variable	n (%)	n (%)	P value
Preoperative characteristics			
Age, y (mean ± SD)	66.7 ± 8.5	70.2 ± 8.4	<.001
Male gender	301 (79.0)	127 (73.0)	.12
Participant in AFIST I	153 (40.2)	64 (36.8)	.45
Participant in AFIST II	111 (29.1)	49 (28.2)	.81
Participant in AFIST III	117 (30.7)	61 (35.1)	.31
History of diabetes mellitus	118 (31.0)	66 (37.9)	.11
History of hypertension*	280 (73.5)	129 (74.1)	.87
History of smoking*	228 (59.8)	98 (56.3)	.43
History of myocardial infarction*	139 (36.5)	66 (37.9)	.74
Family history of CAD	149 (39.1)	68 (39.1)	>.99
History of angina	288 (75.6)	120 (69.0)	.10
History of heart failure	37 (9.7)	33 (19.0)	.002
EF, % (mean ± SD)*	50.3 ± 12.6	49.1 ± 12.3	.31
>45	238 (62.5)	103 (59.2)	.22
25-45	128 (33.6)	68 (39.1)	
<25	15 (3.9)	3 (1.7)	
Prior AF	15 (3.9)	19 (10.9)	<.001
History of cerebrovascular disease	17 (4.5)	10 (5.7)	.51
History of COPD	45 (11.8)	31 (17.8)	.06
History of mitral regurgitation	64 (16.8)	48 (27.6)	.003
Vessels >50% occluded	2.8 ± 0.9	2.6 ± 1.1	.07
Preoperative medical therapy			
Statin	142 (37.3)	82 (47.1)	.04
Beta-blocker	291 (76.4)	118 (67.8)	.03
CCB	63 (16.5)	34 (19.5)	.39
Digoxin	16 (4.2)	12 (6.9)	.18
ACEI/ARB	182 (47.8)	82 (31.1)	.89
Surgical characteristics			
Valve surgery	42 (11.0)	39 (22.4)	<.001
On-pump surgery*	258 (67.7)	115 (66.1)	.71
Duration of surgery, min, (mean ± SD)	283.9 ± 81.9	304.1 ± 124.8	.02
No. of grafts, n, (mean ± SD)	3.8 ± 1.5	3.7 ± 1.7	.11
No. of arterial grafts, n, (mean ± SD)*	1.6 ± 1.2	1.6 ± 1.2	.82
No. of venous grafts, n, (mean ± SD)	2.2 ± 1.4	2.1 ± 1.4	.28
Postoperative medication use			
Amiodarone	191 (50.1)	54 (31.0)	<.001
Beta-blocker	327 (85.8)	139 (79.9)	.08
CCB	31 (8.1)	23 (13.2)	.06
Digoxin	70 (18.4)	77 (44.3)	<.001
Corticosteroids*	100 (26.2)	48 (27.6)	.74
NSAIDs	101 (26.5)	26 (14.9)	.003
ACEI/ARB	147 (38.6)	71 (40.8)	.62
Beta-blocker withdrawal	28 (7.3)	22 (12.6)	.04
ACEI/ARB withdrawal	70 (18.4)	33 (19.0)	.87
Statin withdrawal	54 (14.2)	20 (11.5)	.39

CTS, Cardiothoracic surgery; AF, atrial fibrillation; SD, standard deviation; AFIST, Atrial Fibrillation Suppression Trial; CAD, coronary artery disease; EF, ejection fraction; COPD, chronic obstructive pulmonary disease; CCB, calcium channel blocker; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; NSAID, nonsteroidal, anti-inflammatory drug. *These independent variables were included in the multivariate analysis in addition to the variables with a $P \leq .20$ because of previous evidence they are strong independent predictors of postoperative AF.

TABLE 3. Results of multivariate logistic regression*

Variable	Total no. of events/total	AOR (95% CI)	P value
Preoperative statin use	82/224 (36.6)	0.60 (0.37–0.99)	.048
Prophylactic amiodarone use	54/245 (21.1)	0.36 (0.23–0.55)	<.001
Age (per 10 y)	NA	1.60 (1.33–1.87)	<.001
History of AF	19/34 (55.9)	3.57 (1.60–7.80)	.01
History of diabetes mellitus	66/184 (35.9)	1.70 (1.12–2.60)	.01
History of mitral valve regurgitation	48/112 (39.3)	1.71 (1.04–2.83)	.04
Preoperative beta-blocker use	139/409 (34.0)	0.61 (0.38–0.98)	.04
No. of arterial grafts (per graft)	NA	1.22 (1.02–1.47)	.03
Postoperative nonsteroidal use	26/127 (20.5)	0.59 (0.35–0.99)	.04
Beta-blocker withdrawal	22/50 (44.0)	2.17 (1.11–4.25)	.02

AOR, Adjusted odds ratio; CI, confidence interval; AF, atrial fibrillation; NA, not available. *The Hosmer–Lemeshow goodness-of-fit test (χ^2 test statistic = 6.4; degrees of freedom = 8; $P = .58$); area under the receiver operator curve = 0.7.

the greatest reductions in post-CTS AF (55% reduction) compared with those receiving ≥ 20 mg but less than 40 mg (43% reduction) or less than 20 mg (25% reduction) (Figure 1). In addition, patients receiving the equivalent of at least 20 mg of atorvastatin ($n = 144$) had a 40% reduction in the odds of developing post-CTS AF (adjusted odds ratio: 0.60; 95% CI: 0.23–0.99) versus patients receiving lower equivalent doses of statin or no statin therapy ($n = 411$). When patients receiving the equivalent of at least 20 mg of atorvastatin ($n = 144$) were compared with those receiving only low-intensity statin therapy ($n = 187$), there was a nonsignificant 29% reduction in post-CTS AF (adjusted odds ratio: 0.71; 95% CI: 0.41–1.25).

Discussion

To date, meta-analyses have demonstrated the efficacy of only a few prophylactic strategies to reduce post-CTS AF: beta-blockers, amiodarone, sotalol, magnesium, and biatrial pacing.^{4,23} Although beta-blockers, amiodarone, and sotalol

are included in the most recent American College of Cardiology/American Heart Association/European Society of Cardiology practice guidelines for the management of post-CTS AF, only amiodarone and beta-blockers have been shown to be effective and safe when combined.²⁴ However, the use of these therapies can increase the risk of hypotension, bradycardia, and heart block, making it unlikely that additional antiadrenergic drugs can be added to this combination regimen.

Inflammation may be a causative factor in the development of post-CTS AF. Bruins and colleagues⁹ documented the presence of an inflammatory process by measuring levels of interleukin-6 and C-reactive protein early in the postoperative period. Their group demonstrated that these inflammatory markers significantly increased after cardiac surgery, with levels of C-reactive protein peaking around postoperative day 2 and coinciding with the peak incidence of atrial arrhythmias.⁹ The study was rather small, but these findings were complemented by other reports that substantiated the

Figure 1. Effect of statin dosing intensity on the development of postoperative AF. AF, Atrial fibrillation.

role of inflammation in the development of both postoperative and nonsurgical AF.^{8,10,11,18} Statins were subsequently found to attenuate this inflammation. Kumagai and colleagues¹³ showed that atorvastatin was able to decrease C-reactive protein levels while diminishing the AF burden in a canine model of sterile pericarditis. Brull and colleagues²⁵ noted decreased interleukin-6 levels in patients who received statins before cardiac surgery.

Past observational studies have reported an association between preoperative statin use and reduced rates of post-CTS AF.¹⁵⁻¹⁷ ARMYDA-3 was the first clinical trial to evaluate the impact of statin therapy on post-CTS AF.¹⁸ Two hundred patients undergoing elective CTS were randomized to either atorvastatin (40 mg/d, n = 101) or placebo (n = 99) starting 7 days preoperatively. Post-CTS AF occurred in 35% of patients in the atorvastatin arm and in 57% of patients in the placebo arm, representing a 61% reduction ($P = .017$) in AF incidence in those who received statins. Before surgery, beta-blockers were used by 72% and 60% of patients in the atorvastatin and placebo arms, respectively, whereas amiodarone was administered to only 1 patient in each group. Similar to the observational studies, no information was given regarding the rates of postoperative beta-blocker and amiodarone therapy; the 57% incidence of post-CTS AF in the placebo group, however, suggests low use of these treatments.

In our study, patients from AFIST I, II, and III received postoperative beta-blockers and amiodarone approximately 84.0% and 44.1% of the time, respectively. As expected, the withdrawal of a beta-blocker postoperatively significantly increased the incidence of AF, and the use of prophylactic amiodarone significantly reduced the incidence of AF after cardiac surgery. Multivariate analysis, however, also demonstrated that statin use before surgery had a positive and independent effect on AF rates. Specifically, patients taking preoperative statins experienced a 40% reduction in their odds of developing postoperative AF, an effect size comparable to that seen in previous statin studies.^{16,17}

Although our study was observational in nature, a number of characteristics helped limit the effects of confounding and biases on our results. The use of “nested” data from the previously conducted, prospective, randomized, and controlled AFIST I, II, and III likely reduced the impact of selection, misclassification, surveillance, and researcher bias. Our use of multivariate logistic regression to calculate adjusted odds ratios likely minimized much of the confounding during statistical analysis. Data on most of the commonly accepted independent predictors of post-CTS AF identified in the American College of Cardiology/American Heart Association/European Society of Cardiology AF guidelines were available for use in the multivariate adjustment. Yet even with these measures, there is some degree of bias that cannot be extracted during observational trials, representing a limitation. It is also important to note that our multivariable analysis may suffer from a mild degree of over-fitting.

Our study has other limitations that should be noted. First, we converted all statins to an equivalent dose of atorvastatin; although this was necessary to facilitate our high- versus low-intensity comparison, it should be noted that antifibrillatory effects might not be identical across all statins. Although we were able to show that higher intensity statin therapy was a negative independent predictor of post-CTS AF versus the combined group receiving either no therapy or lower intensity therapy, we did not have adequate power to evaluate higher intensity versus lower intensity therapy by itself. However, the adjusted odds of post-CTS AF with higher intensity statin dosing versus the combined “no therapy plus low intensity” group (adjusted odds ratio = 0.60) were similar to the odds for the lower intensity group alone (adjusted odds ratio = 0.71), suggesting that it is a power issue. Although this may be why we showed a 40% reduction in the odds of post-CTS AF compared with the ARMYDA-3 study, which showed a 61% reduction with atorvastatin 40 mg (a high-intensity therapy), we cannot exclude the possibility that our use of beta-blockers and amiodarone attenuated the benefits in our study or that the results were due to chance or population differences. The impact of dosing intensity on results is clearly the most important area for future research because most patients with coronary disease receive statin therapy, but very few receive high-intensity therapy.²⁶ Further research using randomized controlled trials will clearly be needed to answer this.

Conclusions

In patients with appreciable prophylactic use of beta-blockers and amiodarone, preoperative statin administration may still be beneficial in reducing the incidence of AF after CTS.

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