

Statins Do Not Reduce Atrial Fibrillation After Cardiac Valvular Surgery: A Single Centre Observational Study

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Published online: 16 December 2010

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Abstract

Introduction Statins may theoretically reduce postoperative atrial fibrillation (AF) in patients after cardiac valvular surgery due to preservation of endothelial function and anti-ischaemic, anti-inflammatory and anti-remodelling effects. **Methods** Two hundred seventy-two patients who underwent cardiac workup and subsequently cardiac valvular surgery without AF and concomitant coronary artery bypass grafting (CABG) at our hospital were selected. Preoperative drug use and postoperative AF were recorded. AF was defined as any episode of AF longer than 10 s. In

addition, results from echocardiography and blood samples were retrieved.

Results Baseline characteristics were as follows: mean age was 65 ± 11 years, 142 (52%) patients were male, 189 (70%) had undergone aortic valve surgery and the mean left ventricular ejection fraction was $57 \pm 12\%$. Statins were used by 79 patients (29%). Statin users, more often, had a prior percutaneous coronary intervention (25% vs 9%, $p < 0.001$) or CABG (24% vs 4%, $p < 0.001$), diabetes mellitus (22% vs 5%, $p < 0.001$) and more often used β -blockers (51% vs 24%, $p < 0.001$). Patients in the non-statin group more often had surgery on more than one valve (10% vs 3%, $p = 0.043$) and had a higher cholesterol level (222 ± 48 vs 190 ± 43 mg/dl, $p < 0.001$). Postoperative AF occurred in 54% (43/79) of the patients with and in 55% (106/193) of the patients without statins ($p = 0.941$). There was also no difference in the timing of onset of AF or duration of hospital stay.

Conclusion In this observational study, statin use was not associated with a reduced incidence of AF in patients after cardiac valvular surgery.

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Keywords Cardiac surgery · Atrial fibrillation · Statin

Introduction

Cardiac valvular surgery has excellent long-term survival results and is the treatment of choice in patients with severe valvular disease [1]; however, postsurgical morbidity remains high. Frequent complications such as atrial fibrillation (AF) may worsen prognosis, prolong hospital stay and increase medical costs. Therefore, it is important to improve strategies to reduce postsurgical morbidity. In this respect, statins are interesting drugs. Statins have shown to reduce morbidity and mortality in a broad range of patients

with cardiovascular diseases [2, 3]. In addition to cholesterol-lowering properties, experimental and clinical data suggest that statins may also exhibit anti-inflammatory, endothelial protective, antioxidative and anti-remodelling effects [4–8]. Indeed, statins may prevent AF after coronary artery bypass grafting (CABG) surgery [9, 10]; however, this does not prove a pleiotropic effect since this may be caused by the vasoprotective effects of statins and reduction of ischaemia, thereby preventing AF. Ischaemia due to coronary artery disease is less likely to play a major role after valvular surgery; however, few data exist on the possible protective effects of statins after cardiac valvular surgery. Therefore, we hypothesise that statins may reduce AF and shorten hospital stay after cardiac valvular surgery.

Methods

Study Population

In retrospect, 272 consecutive patients undergoing cardiac valvular surgery in our department between July 1996 and March 2004 were identified. Patients with AF on the day of surgery or with concomitant CABG were excluded to avoid treatment bias due to symptomatic coronary artery disease. Patients referred from other hospitals were excluded because of incomplete pre- and postoperative data for this observational study. After these exclusions, our study cohort consisted of 272 patients who underwent cardiac valvular surgery without concomitant CABG in our hospital during this period. Patients with prior cardiac surgery, including CABG, were not excluded.

Data Collection

Echocardiographic data were collected from our routine clinical database. In addition, admission levels of haemoglobin and creatinine were retrieved as well as the maximal creatinine phosphokinase in the first 24 h after surgery.

Each medical chart was reviewed for preoperative medication, including statins, β -adrenergic receptor blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and antiarrhythmic drugs. These drugs needed to be prescribed for at least 1 week prior to surgery if a drug was considered to be given.

Atrial Fibrillation

AF was defined as any episode of AF longer than 10 s. Rhythm data during admission were attained by retrieving

all electrocardiographic and Holter recordings from the medical chart. Data on previous episodes of AF were attained from the chart and from our clinical ECG database.

Statistical Analysis

All statistics were performed by SPSS version 11.0. Results are presented as the mean value \pm SD for continuous variables and as the percentage of total patients for categorical data. The independent samples *t* test was used for comparison of continuous variables and the χ^2 test for categorical variables. Potential predictors of hospital stay were related to the duration of stay in days using linear regression analysis. For this purpose, the duration was log-normalised since it was skewed.

Cholesterol levels were missing in 41 (15%) patients. Therefore, we first assessed whether the missing status was statistically informative using a dummy variable. Since this was not the case, the missing values were imputed using ‘the mean value of the whole group’ approach. Multivariable logistic regression was performed to test whether statin prescription was associated with postoperative AF occurrence when correcting for potential confounders. Variables entered in the model were age, sex, New York Heart Association class, previous AF, history of percutaneous coronary interventions (PCI), history of CABG, prior valvular surgery, pulmonary hypertension, haemoglobin level, atrial size, the use of β -blockers, antiarrhythmic drugs, aortic valve surgery, combined surgery on more than one valve and the use of statin and the propensity score. The effect of statin prescription on occurrence of postoperative AF might be biased by the absence of randomisation in this observational study, and therefore a propensity score was added to the multivariate logistic regression model in order to correct as well as possible for the propensity of a physician to select patients for prescribing statins. Individual propensity scores were calculated by means of backward deletion logistic regression (see “Methods”). The propensity score was added as a continuous variable to the multivariable logistic regression analysis. The variable for statin prescription and its propensity score were kept at all times in the model regardless of their significance, since this was the main effect we wanted to test.

Results

The mean age of the patients was 65 ± 11 years, the mean left ventricular ejection fraction was $57 \pm 12\%$, 142 patients (52%) were male and 20% had a history of AF (Table 1). Aortic valve replacement was performed in 189 (70%)

Table 1 Baseline characteristics and comparison between statin users and non-statin users

	All N=272	Statin users N=79	Non-statin users N=193	P
Age (years)	65±11	65±11	65±11	0.510
Male (%)	142 (52)	41 (52)	101 (52)	0.948
Previous history, n (%)				
NYHA I	37 (14)	8 (11)	29 (15)	
NYHA II	55 (21)	16 (22)	39 (21)	
NYHA III	146 (56)	41 (56)	105 (56)	
NYHA IV	23 (9)	8 (11)	15 (8)	0.728
AF	54 (20)	17 (22)	37 (19)	0.659
PCI	37 (14)	20 (25)	17 (9)	<0.001
CABG	26 (10)	19 (24)	7 (4)	<0.001
Valve surgery	23 (9)	10 (13)	13 (7)	0.111
Diabetes	27 (10)	17 (22)	10 (5)	<0.001
COPD	31 (12)	8 (11)	23 (12)	0.743
Hypertension	110 (40)	37 (47)	73 (38)	0.169
Pulmonary hypertension	107 (41)	30 (39)	77 (42)	0.641
Laboratory				
Haemoglobin (mmol/l)	8.4±1.0	8.4±1.0	8.4±1.0	0.741
Creatinine (μmol/l)	98 (78–104) ^a	106 (74–107) ^a	94 (79–103) ^a	0.604 ^b
Cholesterol (mg/dl)	212±49	190±43	222±48	<0.001
Echocardiography				
Left atrial size (mm)	48±8	49±7	48±8	0.894
LVEF (%)	57±12	56±11	58±12	0.349
Drugs, n (%)				
ACE-I	127 (47)	41 (52)	86 (45)	0.271
Beta-blocker	87 (32)	40 (51)	47 (24)	<0.001
AAD	44 (16)	12 (15)	32 (17)	0.777
Surgery, n (%)				
Emergency	12 (4)	3 (4)	9 (5)	0.752
Aortic valve	189 (70)	57 (72)	132 (68)	0.541
Mitral valve	78 (29)	19 (24)	59 (31)	0.280
>1 valve	21 (8)	2 (3)	19 (10)	0.043
Mechanical prosthesis	201 (75)	62 (81)	139 (72)	0.166
ECC time (min)	105±42	102±35	106±45	0.430
ACC time (min)	75±29	70±22	77±31	0.075

NYHA New York Heart Association, COPD chronic obstructive pulmonary disease, ACE-I angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, AAD class I or III antiarrhythmic drugs, ECC extracorporeal circulation clamp time, ACC aorta circulation clamp, LVEF left ventricular ejection fraction

^a 25th and 75th percentiles

^b Mann–Whitney *U* results

patients, mitral valve repair or replacement in 78 (29%) patients and 21 (8%) patients had surgery on more than one valve. A total of 201 (75%) patients received a mechanical valve. Table 1 shows the baseline characteristics and a comparison of statin vs non-statin users.

Statin users more often had diabetes mellitus (22% vs 5%, $p<0.001$) and more often used β -blockers (51% vs 24%, $p<0.001$). In addition, these patients more often had a history of PCI (25% vs 9%, $p<0.001$) or CABG (24% vs 4%, $p<0.001$). Patients in the non-statin group more often had surgery on more than one valve (10% vs 3%, $p=0.043$), and a higher cholesterol level (222±48 vs 190±43 mg/dl, $p<0.001$).

Statin Use and Postoperative Atrial Fibrillation

AF occurred after a mean of 4.0±3.7 days in patients without and after 3.7±3.3 days in patients with a statin ($p=0.615$). Table 2 shows the univariate differences in characteristics between patients who had postoperative AF vs the ones without AF. Patients with postoperative AF were older and more often male. In addition, they more often had a history of PCI or pulmonary hypertension, had a lower haemoglobin level, a larger left atrium, more often used an antiarrhythmic drug and were more often operated on more than one valve. AF occurred in 149/272 (55%) of the patients undergoing surgery in sinus rhythm. Forty-

Table 2 Comparison of patients with and without AF

	No AF N=123	AF N=149	<i>P</i>
Age (years)	63±12	67±10	0.002
Male, <i>n</i> (%)	48 (39)	82 (55)	0.009
Previous history, <i>n</i> (%)			
NYHA I	24 (21) ^a	13 (9)	
NYHA II	20 (17)	35 (24)	
NYHA III	64 (55)	82 (57)	
NYHA IV	9 (8)	14 (10)	0.047
AF	12 (10)	42 (28)	<0.001
PCI	19 (15)	12 (8)	0.056
CABG	16 (13)	10 (7)	0.079
Valve surgery	29 (10)	11 (13)	0.198
Diabetes	10 (8)	17 (11)	0.368
COPD	17 (14)	14 (10)	0.219
Hypertension	47 (38)	63 (42)	0.496
Pulmonary hypertension	36 (32)	71 (49)	0.006
Laboratory			
Haemoglobin (mmol/l)	8.6±0.9	8.3±1.1	0.019
Creatinine (μmol/l)	104 (78–106) ^a	92 (78–102) ^a	0.947 ^b
Cholesterol (mg/dl)	211±51	212±47	0.781
Echocardiography			
Left atrial size (mm)	47±8	49±3	0.048
LVEF (%)	57±13	57±11	0.824
Drugs, <i>n</i> (%)			
ACE-I	53 (43)	74 (50)	0.279
Beta-blocker	33 (27)	54 (36)	0.098
Statin	36 (29)	43 (29)	0.941
AAD	13 (11)	31 (21)	0.023
Surgery, <i>n</i> (%)			
Emergency	7 (6)	5 (3)	0.351
Aortic valve	92 (75)	97 (65)	0.084
Mitral valve	32 (26)	46 (31)	0.378
>1 valve	5 (4)	16 (11)	0.037
Mechanical prosthesis	95 (77)	106 (73)	0.384
ECC time (min)	103±43	106±41	0.554
ACC time (min)	74±30	76±28	0.668

NYHA New York Heart Association, *COPD* chronic obstructive pulmonary disease, *ACE-I* angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, *AAD* class I or III antiarrhythmic drugs, *ECC* extracorporeal circulation clamp time, *ACC* aorta circulation clamp, *LVEF* left ventricular ejection fraction

^a 25 and 75 percentiles

^b Mann–Whitney *U* results

three out of 79 patients (54%) taking statins developed AF, compared with 106/193 (55%) patients not taking these cholesterol-lowering drugs ($p=0.941$). The incidence of AF in patients without any previous episode of AF was 49% in non-statin users vs 50% in statin users, ($p=0.864$).

In the multivariate analysis, statin use was not associated with AF occurrence ($p=0.345$). Significant predictors of postoperative AF were age, a previous episode of AF, a history of CABG and pulmonary hypertension (Table 3). The mean propensity score for statin use was 0.27 (25th and 75th percentiles, 0.05 and 0.42, respectively).

Table 3 Multivariate analysis with propensity scores for statin

	<i>P</i> value	OR (95% CI)
Age	0.002	1.05 (1.017–1.074)
Previous AF	0.001	4.55 (1.905–10.856)
Previous CABG	0.029	0.24 (0.067–0.867)
Pulmonary hypertension	0.022	1.98 (1.102–3.557)
Statin	0.345	1.49 (0.651–3.403)

Interactions were observed between statin and haemoglobin levels ($p=0.024$); however, statin therapy was still not predictive of postoperative AF in patients with a mean haemoglobin of ≤ 8.41 mmol/l ($p=0.914$) vs those with levels >8.41 mmol/l ($p=0.552$). Other interactions were noted between age and sex ($p=0.013$) and between history of AF and surgery on more than one valve ($p=0.012$).

Statin Use and Length of Hospital Stay and Mortality

The mean length of hospital stay was 13.9 days (25th and 75th percentiles, 7 and 18 days, respectively). The use of statins was not associated with shorter hospitalisation, 4% decrease in hospital stay duration, 95% CI $-18\pm 12\%$ ($p=0.602$). In-hospital mortality was 4% in both statin and non-statin users ($p=0.971$).

Subgroup Analysis

The most powerful predictor of postoperative AF is a history of AF. One may argue that if statins were not able to prevent AF prior to surgery, they may also not prevent AF after surgery. Therefore, another subanalysis was performed in patients without a history of AF. By excluding these, 218 (80%) patients remained in the model, of which 62 (28%) used a statin and 107 (49%) developed AF. Multivariate predictors of postsurgical AF were age ($p=0.015$) and haemoglobin levels prior to surgery ($p=0.035$). Still, the use of a statin was not associated with AF ($p=0.392$).

Another subanalysis was performed in patients without previous PCI or CABG, leaving a total of 226 (83%) patients. In this subgroup, 52 (23%) used a statin and 124 patients (55%) developed AF. When excluding patients with prior CABG, none of the patients undergoing prior valve surgery remained. Except for this, the same variables as in the main model were entered in the multivariate analysis, as all had univariate p values <0.10 . Multivariate predictors of postsurgical AF were age ($p=0.005$) and prior AF ($p=0.001$). The use of statin was not associated with AF ($p=0.782$). In this model, pulmonary hypertension did not reach significance ($p=0.074$).

Discussion

This study shows that treatment with statins is not associated with a reduction of AF in patients undergoing valvular surgery. In line with these observations, statins were not associated with a shorter hospital stay.

Statin and Postoperative AF

Risk factors for atherosclerotic disease such as hypertension and age are associated with an increased risk for AF. This suggests an association between AF and atherosclerotic vascular disease [11]. In contrary to most studies, we excluded concomitant CABG surgery to minimise the effect of atherosclerotic vascular disease. Thus far, several studies after thoracic surgery have shown conflicting results. Four observational studies in patients after CABG and non-cardiac thoracic surgery have shown a decreased postoperative AF incidence with the use of a statin [12–15]. In addition, a randomised trial of 200 patients showed that in patients after CABG surgery, AF was reduced by almost 40% with atorvastatin starting 1 week before the operation (35% vs 57%, $p=0.003$) [9]. This is in accordance with the finding that statins may reduce AF in patients with symptomatic coronary artery disease [10]. Such an effect seems plausible since statins can prevent atherosclerosis and its consequences; however, these data are in conflict with a large retrospective cohort analysis in 4,044 patients in which statins were not associated with AF reduction after CABG [16].

In concert with this, we found no relation between statin treatment and postoperative AF in patients after valvular surgery. Discrepancies between studies may relate to the type of patients. It may be assumed that patients with coronary artery disease respond better to statins than patients undergoing valvular surgery. In addition, the severe valvular disease has already led to a substrate for AF, irrespective of the inflammatory effects caused by the operation. This is illustrated by a higher incidence of AF after valvular surgery compared with CABG surgery. In the latter, postoperative AF is more likely to depend on excess triggers caused by the inflammatory response to surgery. Therefore, reduction of inflammation by statins may decrease the incidence of AF in the CABG patients, but not after valvular surgery.

Our patients may differ significantly from previous studies since they had a high postoperative AF rate suggesting significant remodelling and inflammation not suppressible by statins.

Mechanisms by Which Statins May Prevent AF

Theoretically, statins may reduce postoperative AF by several mechanisms. Firstly, statins may exert systemic anti-inflammatory effects by reducing T cell activation, thereby reducing inflammatory cytokine production such as IL-6 and C-reactive protein (CRP) [17, 18]. A high CRP level is a risk factor for cardiovascular events, including the development and maintenance of AF [4, 19–21]. AF incidence peaks 2–3 days after thoracic surgery when

CRP levels are highest. In addition, higher CRP levels are associated with higher AF burden [20]. Further evidence of an inflammatory basis of AF is supported by atrial biopsies, showing that atrial myocarditis is frequent in lone AF [21]. Inflammation may lead to AF by slowing atrial conduction, thereby facilitating re-entry [22, 23].

Other reported beneficial effects of statins to prevent AF are their antioxidant, anti-remodelling properties, modification of neurohormonal activation of the renin–angiotensin and the autonomic nervous system, direct antiarrhythmic effects by cell membrane ion channel stabilisation, direct protection of the ischaemic myocardium or modulation of the extracellular matrix.

Study Limitations

We performed an observational study, so we did not randomise our patients. This is reflected by the differences in baseline characteristics. Although the statin group more often had diabetes mellitus, the non-statin group more often had surgery on more than one valve and a higher cholesterol level; however, by adding propensity scores to the multivariate analysis, we corrected as well as possible for the differences between the statin and non-statin users.

In addition, the sample size may be too small for drawing firm conclusions; however, no small trend in favour of statin use was seen. In the univariate analysis, a statin was used in 29% of patients with and without AF ($p=0.941$ in univariate analysis). Therefore, it is unlikely that sample size precluded significance, although it cannot be excluded.

All patients in the statin group used a statin for at least 1 week. We did not analyse duration, dosing and the different types of statins. Despite these drawbacks, our study does not support the hypothesis that pleiotropic effects of statins may decrease AF in this population.

Conclusion

Statins are not associated with a decreased incidence of AF after cardiac valvular surgery. Our results conflict with most reports in patients with vascular disease in which statins may be beneficial. Further research should focus on the role of statins in subjects who are not vascularly compromised.

Acknowledgment This study was supported by grant 2003B103 of the Netherlands Heart Foundation.

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