Statins and Postoperative Risk of Atrial Fibrillation Following Coronary Artery Bypass Grafting

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Atrial fibrillation (AF) is a common complication after coronary artery bypass grafting. Atrial remodeling has been observed in AF and has been associated with the development of this arrhythmia. Because 3-hydroxy-3-methylglutaryl coenzyme A inhibitors (statins) have been demonstrated to modify remodeling, we hypothesized a protective role of statins against postoperative AF. We also hypothesized that extracellular matrix turnover and brain natriuretic peptide (BNP) might be related to such atrial remodeling. We studied 234 consecutive patients who underwent coronary artery bypass grafting (173 men; 65 ± 9 years of age) in whom the occurrence of postoperative AF was monitored. In a subgroup of 66 patients, we measured plasma levels of matrix metalloproteinase-1 (MMP-1), its inhibitor, tissue inhibitor matrix metalloproteinase-1 (TIMP-1; as indexes of extracellular matrix remodeling), and N-terminus pro-BNP (related to left ventricular function) at baseline and at 24 hours after surgery. Of 234 patients, 66 (28.2%) developed postoperative AF. In multivariate analysis, previous AF was related to an increase in the development of AF (odds ratio 11.92, 95% confidence interval 2.37 to 59.98, p = 0.026), whereas statin use was related to a decrease in arrhythmia (odds ratio 0.52, 95% confidence interval 0.28 to 0.96, p = 0.038). A higher TIMP-1/MMP-1 ratio at 24 hours after surgery was present in those who did not develop postoperative AF (p = 0.043). Statin use was associated with increased TIMP-1 levels and TIMP-1/MMP-1 ratio (p = 0.027 and 0.036, respectively). No significant relations to N-terminus pro-BNP were seen. In conclusion, previous AF and nonuse of statins are significantly associated with AF after coronary artery bypass grafting. Statin use may be protective against AF after coronary artery bypass grafting, possibly due to alterations in the extracellular matrix and remodeling after coronary artery bypass grafting. **(Am J Cardiol 2006;97:55–60)**

Atrial fibrillation (AF) is a common complication after cardiac surgery.[1] We hypothesized that statin use would be associated with a decreased incidence of AF after coronary artery bypass grafting. In addition, we hypothesized that extracellular matrix turnover and brain natriuretic peptide (BNP) might be related to such atrial remodeling, which is related to postoperative development of AF. To test these hypotheses, we studied consecutive patients from 2 Spanish university centers and analyzed the possible independent influence of previous treatment with statins on development of AF. Further, we studied the relation of AF development to plasma levels of matrix metalloproteinase-1 (MMP-1) and its inhibitor, tissue inhibitor matrix metalloproteinase-1 (TIMP-1; as indexes of extracellular matrix remodeling), and levels of N-terminus pro-BNP (NT–pro-BNP) at baseline and at 24 hours after surgery.

Methods

We prospectively studied 234 consecutive patients (173 men; mean age 65 ± 9 years) who underwent coronary artery bypass grafting surgery between February 2002 and January 2003 at 2 university tertiary hospitals. Clinical features were noted, and a detailed transthoracic preoperative echocardiogram was obtained (to assess left atrial diameter, end-diastolic left ventricular diameter, and left ven-

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The study was supported by Grant 2002 from the Fundación Juan Gil Albert, Diputación de Alicante, Alicante, Spain and Grant 2002, the Young Investigator's Award, from Sociedad Valenciana Cardiología, Valencia, Spain.

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0002-9149/06/$ – see front matter
doi:10.1016/j.amjcard.2005.07.124

tricular ejection fraction). Patients who had previous permanent/persistent AF or atrial flutter, paced rhythm, or infective endocarditis and those who underwent emergency surgery, valvular surgery, or Maze's procedure were excluded. We also excluded those patients who had concomitant pathologies (e.g., malignancy or inflammatory disease). Several surgical variables (including on-pump/off-pump coronary artery bypass grafting, pump time, duration of procedure, or number of bypass grafts) were also noted and included in our analyses. Plasma lipid levels (total cholesterol, triglycerides, and high- and low-density lipoprotein cholesterols) were measured on a Hitachi Modular D-P analyzer (Mannheim, Germany) with reagents from Roche Diagnostics GmbH (Mannheim, Germany). The statin pretreatment group included 144 patients (62%) who received 1 statin during a median of 31 days (range 10 to 420). Most received an intermediate statin dose.

In the postoperative period, cardiac rhythm was continuously monitored for the first 36 to 48 hours. Subsequently, a daily 12-lead electrocardiogram or in case of any symptom was performed until patients were discharged. All patients were followed for 1 month after cardiac surgery, and all events, mainly the presence of AF (as confirmed by electrocardiogram), were recorded.

In a subgroup of 66 patients from Hospital Virgen de la Arrixaca (Murcia, Spain), blood samples were obtained at baseline and 24 hours after cardiac surgery to test our second hypothesis in relation to MMP/TIMP and BNP. All recruited subjects gave their written informed consent to enter the study, which was approved by the local research committee and was performed in accordance with the Declaration of Helsinki.

Blood samples and laboratory assays: Venipuncture was performed on the morning of surgery and 24 hours afterward on patients who had been fasting for >12 hours. Blood samples were drawn atraumatically. Platelet-poor plasma and serum fractions were obtained by centrifugation at 2,200*g* for 20 minutes. Aliquots were stored at −80°C for batch analysis.

MMP-1 and TIMP-1 plasma levels were assayed by enzyme-linked immunosorbent assay (Biotrack, Amersham Pharmacia Biotech, Uppsala, Sweden). Inter- and intra-assay variations for determining MMP-1 and TIMP-1 were <13% and <9%, respectively, with lower detection limits of 1.7 and 1.25 ng/ml, respectively. The ratio of TIMP-1 to MMP-1 was also calculated. Serum samples were used for measurement of NT–pro-BNP using a pro-BNP assay on an Elecsys 2010 analyzer (Roche Diagnostics GmbH). Total assay precision ranged from 1.8% at 800 pmol/L to 2.7% at 20.7 pmol/L, and the detection limits were 0.6 and 4,130 pmol/L, respectively. Picomoles per liter were converted to picomoles per milliliter by multiplying values by 8.457.

Statistical analysis: Continuous variables were tested for normal distribution by Kolmogorov-Smirnov test. Data that were not normally distributed are presented as median (interquartile range). Results are expressed as percentages for categorical variables. Comparisons between groups were performed by unpaired *t* test or by the Mann-Whitney U test. Paired comparisons were performed by Wilcoxon's test. Categorical data were compared with the chi-square test, and Fisher's exact test was performed, if relevant. Survival analysis was conducted using Cox proportional hazards models. Univariate analysis was used to examine different variables and development of AF after surgery. Multivariate analysis (logistic regression) was then undertaken with the development of AF or the use of statins as dependent variables; we included as independent variables in the model those that showed a p value <0.150 in univariate analysis. The strength of the association of variables with the development of AF was estimated by calculating the odds ratio and 95% confidence intervals. Multivariate Cox's regression was also performed with forward stepwise selection. All variables that were associated with the end point in univariate analysis and had a p value ≤0.150 were included. A 2-sided p value <0.05 was considered statistically significant. Statistical analyses were carried out with SPSS version 11.0 (SPSS Inc., Chicago, Illinois).

Table 1
Clinical characteristics of the entire group and the substudy group

	Entire Group (n = 234)	Substudy Group (n = 66)
Men	173 (74%)	45 (68%)
Age (yrs)	65 ± 9	65 ± 9
Medical history		
Hypertension	146 (62%)	45 (68%)
Diabetes	96 (41%)	31 (47%)
Dyslipidemia	136 (58%)	39 (59%)
Smoking	61 (26%)	10 (29%)
ACS <30 days	141 (60%)	49 (74%)
Previous paroxysmal AF	10 (4%)	0 (0%)
Current treatment		
β-Blocker	177 (76%)	51 (77%)
ACEI	81 (35%)	26 (39%)
Statins	144 (62%)	39 (59%)
Euroscore	3 (0–5)	5 (4–8)
Ejection fraction <40%	32 (18%)	12 (18%)
Total cholesterol (mg/dL)	178 (147–207)	171 (141–197)
LDL cholesterol (mg/dL)	108 (82–137)	102 (76–126)
Coronary stenosis		
Left main coronary artery	91 (39%)	34 (52%)
Right coronary artery	167 (71%)	44 (67%)
Cardiopulmonary bypass	143 (61%)	31 (47%)

Values are numbers of patients (percentages), means ± SD, or medians (interquartile ranges).

ACEI = angiotension-converting enzyme inhibitor; ACS = acute coronary syndrome; LDL = low-density lipoprotein.

Results

Clinical characteristics are listed in Table 1. Of 234 patients, 66 (28.2%) developed postoperative AF. In univariate anal-

Table 2
Univariate analysis exploring the association between different variables and the development of postoperative atrial fibrillation

	p Value	OR (IQR)
Men	0.367	1.44 (0.73–2.85)
Age		
Q1–Q2	0.725	0.87 (0.39–1.92)
Q1–Q3	0.279	1.53 (0.71–3.30)
Q1–Q4	0.021	3.13 (1.30–7.56)
Medical history		
Hypertension	0.585	1.18 (0.65–2.14)
Diabetes	0.785	1.08 (0.61–1.93)
Dyslipemia	0.689	0.89 (0.50–1.58)
Smoking habit	0.290	0.69 (0.35–1.37)
Functional class (NYHA)	0.296	1.29 (0.80–2.07)
Previous AF	0.003	11.44 (2.36–55.47)
Current treatment		
β-Blocker	0.552	0.81 (0.41–1.60)
ACEI	0.530	0.82 (0.45–1.52)
Statins	0.024	0.51 (0.29–0.92)
Recent acute coronary syndrome (<30 ds)	0.529	0.83 (0.46–1.48)
Ejection fraction <40%	0.206	0.55 (0.21–1.40)
Total cholesterol	0.836	1.00 (0.99–1.01)
LDL cholesterol	0.701	1.00 (0.99–1.01)
Coronary stenosis		
Left main coronary artery	0.180	0.66 (0.36–1.20)
Right coronary artery	0.219	0.68 (0.36–1.26)
Cardiopulmonary bypass	0.317	0.75 (0.42–1.33)
Euroscore	0.505	1.03 (0.94–1.33)

IQR = interquartile range; OR = odds ratio; NYHA = New York Heart Association; Q1 = ≤60 years; Q2 = 60 to 65 years; Q3 = 66 to 71 years; Q4 = >72 years. Other abbreviations as in Table 1.

Table 3
Multivariate analysis (regression analysis, enter method) exploring the association between different variables and development of postoperative atrial fibrillation

	p Value	OR (IQR)
Previous AF	0.003	11.92 (2.37–59.98)
Age		
Q1–Q2	0.845	0.92 (0.40–2.11)
Q1–Q3	0.294	1.54 (0.69–3.44)
Q1–Q4	0.063	2.23 (0.96–5.18)
Statins	0.038	0.52 (0.28–0.96)

Abbreviations as in Tables 1 and 2.

ysis, only previous AF (p = 0.003) and the oldest quartile (p = 0.021) were associated with postoperative AF (Table 2). The use of statins was also associated with less AF (p = 0.024). There were no statistical differences between development of AF and type of statin used (p = 0.527). In multivariate analysis, previous AF (p = 0.026) and statin use (p = 0.038) were associated with the development of AF (Table 3). Within the entire cohort, 144 patients (61.5%) were treated with statins at the time of coronary artery bypass grafting. In multivariate analysis, statin use was associated with dyslipidemia (odds ratio 7.4, 95% confidence interval 3.92 to 13.99, p <0.001), systolic dysfunction (odds ratio 3.45, 95% confidence interval 1.19 to 9.98,

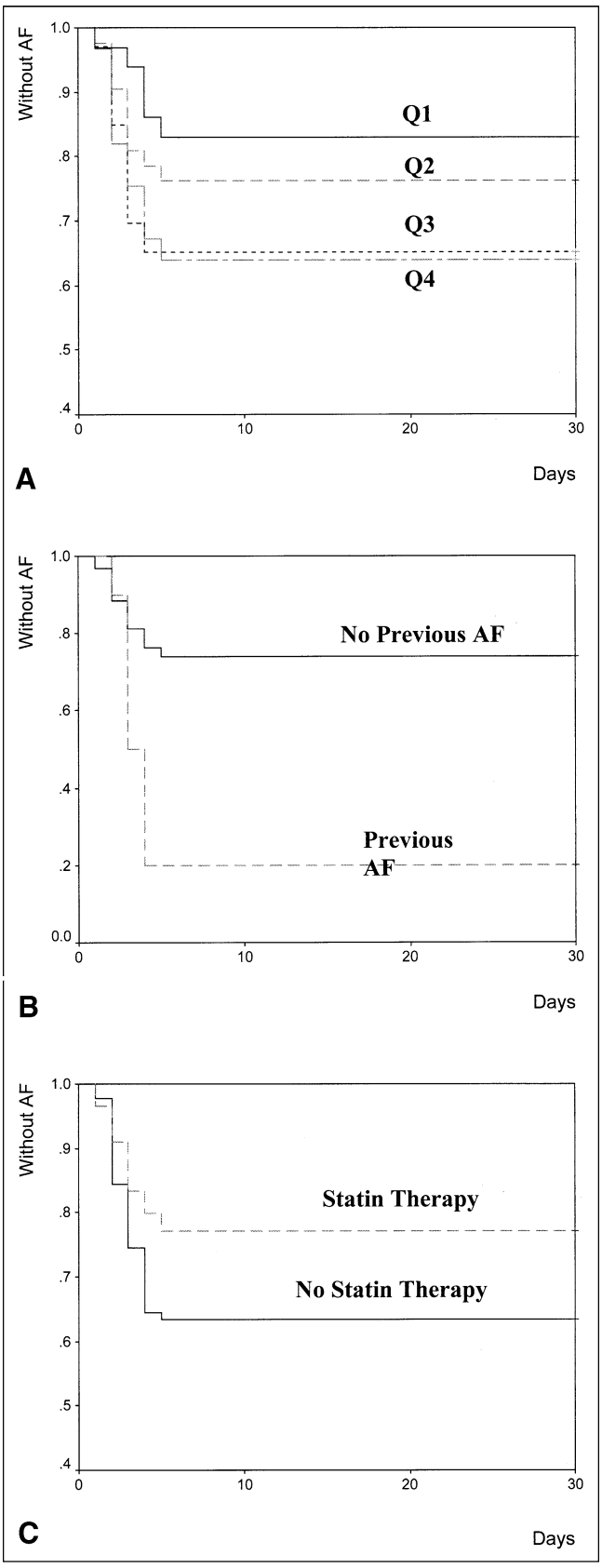

Figure 1. Kaplan-Meier survival curves represent postoperative development of AF by *(A)* age quartiles (Q1 ≤60 years; Q2 60 to 65 years; Q3 66 to 71 years; Q4 >72 years), *(B)* previous AF, and *(C)* statin therapy.

Table 4
Research indexes and postoperative development of atrial fibrillation

Research Markers	AF	No AF	p Value
Baseline MMP-1 (ng/ml)	3.26 (2.60/4.00)	3.45 (2.95/4.11)	0.589
Baseline TIMP-1 (ng/ml)	789 (685/1,089)	755 (617/1,161)	0.646
Baseline TIMP-1/MMP-1 ratio	207.9 (199.0/346.4)	232.3 (154.7/318.4)	0.444
Baseline NT–pro-BNP	310 (144/610)	461 (192/1,141)	0.267
24-h MMP-1 (ng/ml)	2.31 (1.70/2.83)	1.97 (1.79/2.23)	0.317
24-h TIMP-1 (ng/ml)	972 (602/1,649)	1297 (896/2,161)	0.186
24-h TIMP-1/MMP-1 ratio	335.8 (229.8/650.3)	587.7 (328.5/1,047.5)	0.043
24-h NT–pro-BNP	1,097 (184/1,894)	1,741 (555/3,352)	0.089
24-h percent MMP-1	75 (53/106)	60 (49/73)	0.211
24-h percent TIMP-1	104 (81/173)	155 (91/260)	0.120
24-h percent TIMP-1/MMP-1 ratio	126 (88/314)	269 (124/494)	0.054
24-h percent NT–pro-BNP	153 (66/1047)	255 (108/555)	0.501

Values are medians (25th to 75th percentiles values). Statistical analysis by Mann-Whitney U test.
Abbreviations as in Table 1.

p = 0.023), and absence of disease in the left main coronary artery (odds ratio 0.49, 95% confidence interval 0.26 to 0.92, p = 0.027).

In the univariate Cox analysis, previous AF (p <0.001) and age (p = 0.045) were associated with increased postoperative AF, whereas statin use (p = 0.019) was related to decreased occurrence of AF (Figure 1). In the multivariate Cox proportional hazard model, only previous AF (p <0.002) and statin use (p = 0.015) were associated with development of AF.

MMP-1, TIMP-1, and NT–pro-BNP: Clinical characteristics of the 66 patients included in this substudy are listed in Table 1. Plasma MMP-1 levels were lower (3.28 ng/ml, interquartile range 2.91 to 4.11, vs 2.00 ng/ml, interquartile range 1.78 to 2.32), whereas TIMP-1 levels (767 ng/ml, interquartile range 627 to 1,145, vs 1,277 ng/ml, interquartile range 771 to 2,089), TIMP-1/MMP-1 ratio (230.9, interquartile range 174.9 to 325.9, vs 572.4, interquartile range 309.1 to 958.5), and NT–pro-BNP levels (420 pg/ml, interquartile range 178 to 843, vs 1572 ng/ml, interquartile range 495 to 2,462) were higher at 24 hours after surgery (paired Wilcoxon's text, all p values <0.01).

Of these 66 patients, 13 (19.7%) developed postoperative AF. There were no differences in baseline research indexes between those patients who developed AF and those who did not. A higher TIMP-1/MMP-1 ratio at 24 hours after surgery was present in those who did not develop postoperative AF (p = 0.043). Statin use was associated with increased TIMP-1 levels and TIMP-1/MMP-1 ratio (p = 0.027 and 0.036, respectively). No significant relations to NT–pro-BNP were seen (Table 4).

In this group of 66 patients, statin use remained the only clinical variable that was associated with development of AF (odds ratio 0.21, 95% confidence interval 0.06 to 0.87, p = 0.037). Importantly, when 24-hour TIMP-1/MMP-1 ratios were included in multivariate analysis, statin drugs (p = 0.021) and ratios (p = 0.049) showed a statistical association with development of AF. Statin treatment was associated with great variations in TIMP-1 level and TIMP-1/MMP-1 ratio (p = 0.027 and 0.036, respectively; Figure 2). In multivariate Cox's analysis, only statin use was associated with development of AF (p = 0.040).

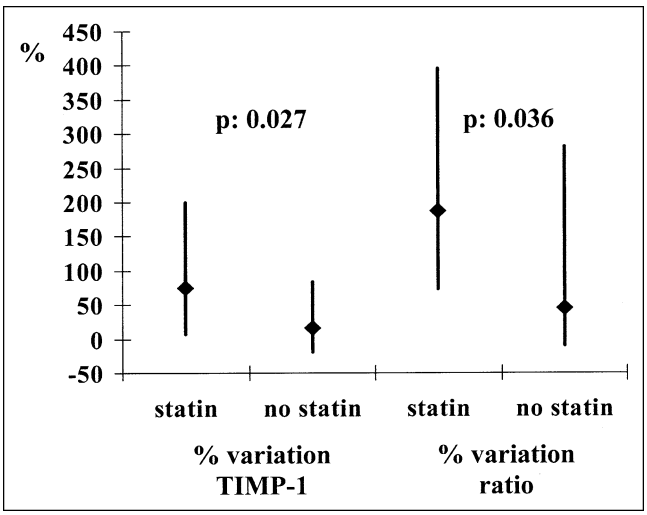

Figure 2. Influence of statin therapy and variation in TIMP-1 levels and TIMP-1/MMP-1 ratio after cardiac surgery.

Discussion

Among our consecutive patients who underwent coronary artery bypass grafting, those who used statins had a lower incidence of postoperative AF. In multivariate analysis, only nonuse of statin therapy and previous AF[2] were statistically associated with development of AF after coronary artery bypass grafting. Of note, our findings are consistent with recent observations.[3] Further, statins are protective against AF in patients who have stable chronic coronary artery disease[4] and may prevent recurrence of AF after successful cardioversion.[5] Statins are also associated with a

lower recurrence of ventricular tachyarrhythmias in patients who have an implantable cardioverter-defibrillator.[6] One retrospective study found a beneficial effect of preoperative statin therapy with a decrease in the incidences of death, unstable angina, and cardiac arrhythmias.[7]

However, the underlying mechanisms for these beneficial effects of statins remain unclear. In an animal model, atorvastatin prevented development of AF by inhibiting inflammation.[8] More recently, antioxidant actions have been hypothesized to prevent electrical remodeling.[9] Although inflammation has been proposed to have a pivotal role in postoperative AF,[10,11] the present study and others[12,13] suggest that other systems are implicated in the pathophysiology of the development of AF.

Atrial remodeling of the extracellular matrix has been associated with the development and maintenance of AF.[14] We previously reported abnormalities in matrix remodeling in patients who had persistent AF, but these were not independently associated with the presence of AF.[15] In the present study, preoperative markers of interstitial remodeling showed no significant relation to postoperative AF. Similarly, other investigators found no baseline laboratory indexes that reliably predicted the development of AF.[10,16] In the present study, changes in the MMP system were associated with development of AF because a more attenuated TIMP-1/MMP-1 ratio at 24 hours after surgery was seen in those patients who developed postoperative AF. Moreover, patients who received preoperative statin therapy had an increased TIMP-1/MMP-1 response that was possibly related to the protective role of this therapy.

The finding that interstitial fibrosis in atrial tissue is related to underlying co-morbidities[15,17] is in keeping with the hypothesis that structural changes in the atria could promote postoperative AF. The extracellular matrix is a dynamic structure, and time-dependent MMP activation is recognized in different pathologies, such as heart failure and acute coronary syndromes.[18,19] A significant increase in TIMP-1 levels and low concentrations of MMP-1 have also been observed in acute situations.[20,21] Further, TIMPs are the most important inhibitors of MMPs, which counterbalance MMP activation pathways.[22] Thus, the increase in TIMP levels that was observed after coronary artery bypass grafting may reflect a physiologic response to surgery stress.[23,24] Importantly, recently reported new actions (such as fibroblast cell proliferation, apoptosis, collagen synthesis, and myofibroblast differentiation) of TIMPs have extended beyond their classic role as MMP inhibitors.[25]

Our study does not confirm previous observations on the value of BNP in the prediction of postoperative AF.[12] Hutfless et al[13] found that preoperative BNP level and postoperative increases were predictors of mortality after surgery, but they did not evaluate AF as a specific end point. Wazni et al[12] identified high preoperative plasma BNP levels as a strong and independent predictor of postoperative AF in patients who underwent cardiac surgery. NT–pro-BNP and BNP have similar clinical applications, although NT–pro-BNP increases more strikingly in response to ventricular stress than does BNP and has a longer half-life.[26] In our study, NT–pro-BNP increased significantly after surgery but failed to prove a predictive value for the development of AF. This finding is consistent with a lack of association between ejection fraction, functional class, or hypertension (variables that are related to NT–pro-BNP) and development of postoperative AF.

Our data support recent observations that statin drugs prevent the development of AF.[3–5] In the present study, this effect was observed after cardiac surgery, perhaps by modulating extracellular remodeling.[27] Accordingly, statins are able to modify extracellular components by regulating the expression of MMPs or their inhibitors.[28,29] The present findings in this study may have important clinical implications because AF is a frequent complication after cardiac surgery that increases in-hospital morbidity and mortality and prolongs hospital stay.

Study limitations: This study is limited by its design; we could explore only associations, and no causality is implied. Only a randomized, controlled trial could permit a conclusion that statins protect against postoperative AF. A selection bias may have been present because there was no homogenous indication for the use of lipid-lowering agents and thus clinical indexes (e.g., dyslipidemia, systolic dysfunction, and absence of disease in the left main coronary artery) were associated with statin use. In addition, within the subgroup of patients who were selected for MMP and NT–pro-BNP analyses, only 13 developed AF, which represents a small sample. Although no intensive monitoring of AF was performed beyond the first postoperative days, $>70\%$ of AF recurrences are asymptomatic,[30] and less intensive monitoring of AF may introduce error. Further, we analyzed plasma samples and not tissue protease activity, so we could not accurately assess local changes in the MMP system in atrial tissue.

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