De novo atrial fibrillation after mitral valve surgery

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ABSTRACT

Objectives: We sought to determine the incidence and risk factors for de novo atrial fibrillation (>90 days after surgery) in patients without preoperative atrial fibrillation.

Methods: From 2004 to 2014, 2261 patients underwent mitral valve surgery; 1288 patients (57%) did not have a history of atrial fibrillation, and 930 patients had rhythm information more than 90 days after surgery. De novo atrial fibrillation and death probabilities were estimated using a semi-competing risks, multi-state model. Univariable and multivariable risk factors for developing atrial fibrillation were identified using the Fine–Gray model.

Results: The 5- and 10-year incidences of de novo atrial fibrillation were 14% and 23%, respectively. Univariable risk factors were older age, more complex operations, more tricuspid regurgitation, and congestive heart failure (all $P < .05$). Patients with degenerative mitral regurgitation were less likely to develop atrial fibrillation (hazard ratio [HR], 0.4; 95% confidence interval [CI], 0.24–0.65; $P < .001$). Multivariable risk factors for de novo atrial fibrillation were tricuspid valve surgery (HR, 1.80; 95% CI, 1.22, 2.65; $P = .003$), aortic valve surgery (HR, 1.49; 95% CI, 1.03–2.17; $P = .035$), and older age (HR, 1.03; 95% CI, 1.02–1.05; $P < .001$). De novo atrial fibrillation did not affect overall survival ($P = .41$). Among patients who developed de novo atrial fibrillation, we observed increased use of warfarin ($P < .001$) and a strong trend toward an increased risk of stroke ($P = .055$).

Conclusions: De novo atrial fibrillation develops progressively after mitral surgery and is associated with a strong trend toward stroke. Patients at high risk could be studied in a trial to reduce atrial fibrillation. (J Thorac Cardiovasc Surg 2018;156:1515–25)

Freedom from stroke by AF status in follow-up.

Central Message

A steady rate of de novo AF (>90 days postsurgery) develops after MV surgery in patients without a preoperative history of AF and was associated with a trend ($P = .055$) toward increased stroke.

Perspective

Development of de novo AF after MV surgery may affect the risk of stroke and development of functional TR. Identifying patients at risk of developing AF and treating them with prophylactic ablation may reduce the risk of AF, lower stroke risk, and limit late functional TR.

See Editorial Commentary page 1526.

See Editorial page 1514.

Preoperative atrial fibrillation (AF) in patients undergoing surgery for mitral valve (MV) disease is associated with late adverse events and reduced survival.^{1,2} When

AF is identified preoperatively, surgical ablation is recommended to attempt sinus rhythm restoration.^{3,4} Multiple prospective randomized studies have demonstrated that the addition of surgical ablation to MV surgery for patients with preoperative AF significantly increases freedom from AF.^{3,5} The addition of a surgical ablation procedure does not increase morbidity or mortality and has even been associated with better perioperative outcomes.⁶

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Scanning this QR code will take you to the supplemental figures, tables, appendices, and video for this article.

Abbreviations and Acronyms

AF	= atrial fibrillation
AV	= aortic valve
CARD	= Cardiovascular Research Database
CI	= confidence interval
DMR	= degenerative mitral regurgitation
HR	= hazard ratio
MV	= mitral valve
PS	= propensity score
TR	= tricuspid regurgitation
TV	= tricuspid valve

De novo AF, defined in this study as new AF 90 days or more after MV surgery (to exclude patients with only early postoperative AF), has been infrequently studied, and there are little data on incidence and risk factors for this.⁷ We therefore sought to (1) characterize the incidence over time of de novo AF in patients who underwent MV surgery with or without additional cardiac surgical procedures; (2) identify potentially modifiable preoperative or perioperative risk factors for de novo AF, such that a prophylactic AF ablation procedure might be considered; and (3) evaluate the sample size of a potential study designed to reduce the incidence of de novo AF (Video 1).

MATERIALS AND METHODS

Patients

From April 2004 to December 2014, 2261 patients had mitral $\pm$ other cardiac procedures, and of these, 1370 had no AF history and therefore no surgical AF ablation. A preoperative Holter monitor was routinely obtained in any patient with symptoms suggestive of arrhythmias to confirm absence of AF. After excluding patients who refused to participate in the Bluhm Cardiovascular Institute's Clinical Trials Unit Cardiovascular Research Database (CARD) at Northwestern University (IRB#STU00012288), 1288 patients (94%) were included. Of those, 930 (72%) had follow-up heart rhythm information at 90 days or more after surgery and comprise the study cohort. Preoperative, intraoperative, and postoperative data were obtained from CARD, and the Society of Thoracic Surgery database definitions were used for complications. Reported stroke includes transient ischemic attack and cerebrovascular accident (hemorrhagic or ischemic). Postoperative AF includes patients with new AF or atrial flutter persisting longer than 1 hour or requiring treatment before discharge per Society of Thoracic Surgeons definitions.

Atrial Fibrillation Monitoring and Clinical Follow-up Protocols

Unlike Northwestern patients treated with AF ablation who undergo a regimen of postoperative AF monitoring,⁸ these patients were not routinely monitored. Test results and office visits were prospectively collected by patient surveys at 6 and 12 months postdischarge and annually thereafter. Records pertaining to reported office visits, echocardiography and rhythm information, operations, cardioversions, catheter ablation, or hospitalizations were obtained and analyzed. Mortality data were

aggregated continuously consulting sources that included (1) CARD registry; (2) reviews of medical records and correspondence with the treating physician; (3) online death indexes, including the Social Security Death Index and genealogy resources (ancestry.com); and (4) newspaper death notices. With the use of these sources, mortality follow-up information was available on 100% of the cohort.

Statistical Analyses

Data summaries included the mean and standard deviation or median and interquartile range for continuously distributed variables, such as age and left ventricular ejection fraction. For discrete or categorical variables, such as gender or postsurgical complications, we have reported counts and percentages. Comparisons between patients who developed de novo AF during follow-up and those who did not were based on the 2-sample *t* test with unequal variances and Satterthwaite's approximation or the Wilcoxon rank-sum test for continuous variables. Comparisons involving discrete or categorical variables were based on the chi-square or Fisher exact test (when cell counts were <5).

To estimate the probabilities of de novo AF, death, or AF-free survival, we used a 3-state Markov model that relies on the Aalen-Johansen estimator, as implemented in the R package *etm*.⁹ Comparisons between patients with and without de novo AF were made at 1, 2, 3, 5, and 10 years after the index surgical procedure, both in the entire cohort and separately for those with degenerative mitral regurgitation (DMR), rheumatic, and ischemic MV cause, as well as the group with mixed causes or otherwise hard to classify that were grouped together as "other." Overall survival was estimated using the Kaplan-Meier estimator.

To identify univariable or multivariable risk factors for de novo AF during follow-up, the subdistribution functions were modeled using the Fine-Gray model implemented in the R package *survival*.¹⁰ We report (sub) hazard ratios and corresponding 95% confidence intervals (Table E1). To assess whether postoperative AF was associated with a higher risk of de novo AF during follow-up or with overall survival, we have used 1-to-1 propensity score (PS) matching. A total of 32 variables (included in the online Appendix, Table E2, and Figure E1), including demographics (age, body mass index), medical history, preoperative medications, and concomitant procedures (aortic valve [AV], TV surgery) were used to create the PS model of which the outcome was postoperative AF. A caliper of size 0.1 logit-PS standard deviation units was used. Association between TV surgery and risk of de novo AF was assessed using a 2-to-1 PS-matched analysis with a size 0.2 logit-PS standard deviation units caliper (Table E3 and Figure E2). Additional information is provided in the Appendix (Tables E4 and E5, Figures E3 and E4).

VIDEO 1. Dr Patrick M. McCarthy and Dr James L. Cox discuss aspects of the article. Video available at: [https://www.jtcvs.org/article/S0022-5223\(18\)31035-3/fulltext](https://www.jtcvs.org/article/S0022-5223(18)31035-3/fulltext).

TABLE 1. Baseline characteristics of patients by de novo atrial fibrillation status in follow-up

Variable	Entire cohort (N = 930)	No AF in follow-up (N = 773)	AF in follow-up (N = 157)	P value
Age	59.9 ± 13.9	58.7 ± 13.8	65.4 ± 13.0	<.001
CHA ₂ DS ₂ -VASc	2.3 ± 1.8	2.2 ± 1.8	2.9 ± 1.7	<.001
Ejection fraction	60.0 (53.0, 65.0)	60.0 (55.0, 65.0)	60.0 (45.0, 63.0)	.004
Left atrial size (cm) (N = 866)	4.3 (3.8, 4.7)	4.3 (3.8, 4.7)	4.3 (3.8, 4.9)	.28
Female	392 (42)	324 (42)	68 (43)	.75
Diabetes	126 (14)	97 (13)	29 (18)	.048
Hypertension	518 (56)	421 (54)	97 (62)	.09
Prior coronary artery bypass	50 (5)	36 (5)	14 (9)	.031
Prior pacemaker	27 (3)	17 (2)	10 (6)	.005
Congestive heart failure	312 (34)	247 (32)	65 (41)	.022
Coronary artery disease	302 (34)	233 (31)	69 (45)	.001
Repeat sternotomy	105 (11)	79 (10)	26 (17)	.022
Aortic stenosis	103 (14)	75 (12)	28 (20)	.023
Mitral stenosis	92 (11)	68 (10)	24 (17)	.008
New York Heart Association class				.033
Class I	278 (30)	244 (32)	34 (22)	
Class II	345 (38)	280 (37)	65 (42)	
Class III	234 (25)	185 (24)	49 (31)	
Class IV	63 (7)	55 (7)	8 (5)	
TR >2+	165 (18)	128 (17)	37 (25)	.024
MV cause				<.001
Degenerative	479 (52%)	424 (55%)	55 (35%)	
Ischemic	90 (10%)	64 (8%)	26 (17%)	
Rheumatic	51 (5%)	43 (6%)	8 (5%)	
Other	310 (33%)	242 (31%)	68 (43%)	

Values are mean ± standard deviation; n (%); or median (first quartile, third quartile). AF, Atrial fibrillation; CHA₂DS₂-VASc, congestive heart failure, hypertension, age, diabetes, stroke, vascular disease; TR, tricuspid regurgitation; MV, mitral valve.

By using methods for binomial proportions, we have estimated the required sample size for 2-arm randomized study designed to detect a 5-year 40% reduction of AF (from 13.6% to 8.2%) with 80% power at 2-sided 5% α -level. Because 406 of 930 participants (43.7%) were at risk at 5 years, we have applied an inflation factor of 930/406 = 2.02 to compensate for the loss to follow-up.

Statistical significance was declared as the 2-sided 5% alpha level, and there were no adjustments for multiplicity. As such, on average, 1 in 20 associations identified might be spurious. All analyses were performed in R v. 3.1.1 (<http://cran.r-project.org>) and SAS v. 9.3 (SAS Institute, Inc, Cary, NC).

RESULTS

The preoperative characteristics of study participants are summarized in Table 1. Concomitant procedures included AV surgery (n = 199; 21%), tricuspid valve (TV) surgery (n = 118; 13%), and coronary artery bypass grafting (n = 248; 27%). MV disease cause distribution was DMR (n = 479; 52%), rheumatic (n = 51; 5%), ischemic (n = 90; 10%), and “other” (n = 310; 33%).

MV disease was treated by repair (n = 728; 78%) or replacement (n = 202; 22%). Rhythm assessment was based on 1 or more sources: electrocardiogram (881; 95%); Holter monitor (176; 19%); implantable pacemaker or loop recorder (130; 14%); outpatient telemetry (97; 10%); cardiac rehabilitation (59; 6%); or other (59; 6%). The mean follow-up time was 4.6 ± 3.0 years (median, 4.4; interquartile range, 1.9-7.0; maximum, 11.1 years).

Of the 930 patients, 157 (17%) developed de novo AF. They were significantly older at the time of index surgery (65 ± 13 years vs 59 ± 14 years, $P < .001$), had more comorbidities, and underwent more complex surgeries (prior coronary artery bypass [9% vs 5%, $P = .031$], prior pacemaker implantation [6% vs 2%, $P = .005$], congestive heart failure [41% vs 32%, $P = .022$], and coronary artery disease [45% vs 31%, $P = .001$]) than patients who were AF-free during follow-up. In addition, patients with de novo AF underwent more concomitant procedures than those without de novo AF, including

TABLE 2. Operative, predischARGE, and postoperative characteristics by de novo atrial fibrillation status in follow-up

Variable	Entire cohort (N = 930)	No AF in follow-up (N = 773)	AF in follow-up (N = 157)	P value
Perfusion time (min)	98.5 (76.0, 135.0)	96.0 (75.0, 134.0)	115.0 (82.0, 152.0)	<.001
Crossclamp time (min)	80.0 (63.0, 110.0)	79.0 (62.0, 108.0)	89.0 (68.0, 121.0)	.008
Coronary artery bypass	248 (27%)	190 (25%)	58 (37%)	.001
AV surgery	199 (21%)	150 (19%)	49 (31%)	.001
TV surgery	118 (13%)	82 (11%)	36 (23%)	<.001
Mitral surgery				.012
Repair	728 (78%)	617 (80%)	111 (71%)	
Replacement	202 (22%)	156 (20%)	46 (29%)	
Total intensive care unit, h	31.0 (24.3, 68.8)	30.5 (24.2, 66.9)	44.3 (26.0, 72.3)	.038
Total length of stay (d)	6.0 (5.0, 9.0)	6.0 (5.0, 9.0)	7.0 (6.0, 11.0)	<.001
PredischARGE pacemaker	43 (5%)	27 (3%)	16 (10%)	<.001
Postoperative AF	291 (31%)	214 (28%)	77 (49%)	<.001
DischARGE on antiarrhythmics	241 (26%)	177 (23%)	64 (41%)	<.001
Readmission within 30 d	97 (10%)	70 (9%)	27 (17%)	.003
Most recent postoperative TR (N = 879)				<.001
None/trivial	383 (44%)	330 (45%)	53 (36%)	
Mild	351 (40%)	301 (41%)	50 (34%)	
Moderate	115 (13%)	83 (11%)	32 (22%)	
Moderate-severe	13 (1%)	9 (1%)	4 (3%)	
Severe	17 (2%)	10 (1%)	7 (5%)	
TR ≥3-4+ anytime in follow-up (N = 879)	48 (5%)	29 (4%)	19 (13%)	<.001

Values are mean ± standard deviation; n (%); or median (first quartile, third quartile). AF, Atrial fibrillation; AV, aortic valve; TV, tricuspid valve; TR, tricuspid regurgitation.

coronary artery bypass (37% vs 25%, $P = .001$), AV surgery (31% vs 19%, $P = .001$), and TV surgery (23% vs 11%, $P < .001$). The de novo AF group had significantly longer median perfusion and crossclamp times (Table 2), and the incidence of predischARGE pacemaker implantation was higher (10% vs 3%, $P < .001$). Total median length of stay was longer (7 vs 6 days, $P < .001$), and the incidences of anticoagulant events (3% vs 0%, $P = .001$), antiarrhythmics on discharge (41% vs 23%, $P < .001$), and 30-day readmissions (17% vs 9%, $P = .003$) were higher in the de novo AF group. Patients who developed in-hospital postoperative AF were more likely to develop late de novo AF (28% vs 49%; $P < .001$) during follow-up.

De Novo Atrial Fibrillation During Follow-up

The incidence of de novo AF 1, 5, and 10 years after index surgery was 5.0%, 13.6%, and 22.7%, respectively (Figure 1, A). A trend toward an increased risk of stroke (Figure 2, A) was observed among patients who developed de novo AF ($P = .055$). The absolute risk of stroke was 5.8% for those who developed AF

during follow-up and 1.7% among those who did not. The use of warfarin at last clinical follow-up was also significantly higher for patients with de novo AF (47.1% vs 14.5%; $P < .001$).

Survival was not different ($P = .41$) among those who developed de novo AF during follow-up (Figure 2, B) and those who did not. Mortality varied depending on the underlying cause of MV disease. In the patients with DMR (Figure 3, A), mortality was 0%, 4.0%, and 7.9% at 1, 5, and 10 years, respectively. Among patients with ischemic mitral regurgitation (Figure 3, B), mortality at 10 years was 27.9%.

Among patients with rheumatic MV disease (Figure 1, B), the incidence of de novo AF was 2% during the first year, increased to 15.8% at 5 years, and reached 23% at 10 years. Among patients with DMR (Figure 3, A), the incidence of de novo AF steadily increased (3.4% and 9.1% at 1 and 5 years, respectively) to 22.3% 10 years after index surgery. For patients with ischemic MV disease (Figure 3, B), the incidence of de novo AF was initially higher than the other causes (10.1% at 1 year, 15.1% at 5 years) but was similar by year 10 (22.9%). In unadjusted analyses, the risk of de novo AF was significantly higher

FIGURE 1. Multi-state models summary of probabilities of de novo AF, death, and AF-free survival in (A) the entire cohort (N = 930) and (B) rheumatic MV cause. AF, Atrial fibrillation; MV, mitral valve.

in the ischemic MV disease group compared with the DMR group (hazard ratio, 2.31; 95% confidence interval, 1.45-3.69; $P < .001$) (Table 3). After covariate adjustments, this difference was no longer significant (hazard

ratio, 1.48; 95% confidence interval, 0.90-2.42; $P = .12$) (Table 4).

In PS-matched analyses, there was a trend toward an increased risk of de novo AF for patients who underwent

FIGURE 2. Freedom from stroke by AF status in follow-up (A) and overall survival by AF status in follow-up (B). *MV*, mitral valve; *AF*, Atrial fibrillation.

TV surgery ($P = .068$) (Figure 4, A). After PS matching, patients who developed postoperative AF had a higher risk of de novo AF during follow-up ($P = .015$) (Figure 4, B).

Tricuspid Regurgitation in Late Follow-up

Patients who developed de novo AF had more late significant tricuspid regurgitation (TR) that was severe or greater ($P < .001$) (Table 2).

FIGURE 3. Multi-state models summary of probabilities of de novo AF, death, and AF-free survival in (A) degenerative MV cause and (B) ischemic MV cause. AF, Atrial fibrillation.

Risk Factors for De Novo Atrial Fibrillation During Follow-up

Preoperative and intraoperative univariable risk factors for developing de novo AF are displayed in Table 3. The multivariable model (Table 4) identified age at surgery (1.03 [1.02, 1.05]), TV surgery (1.73 [1.17, 2.56]), and “other” cause MR versus DMR (1.68 [1.11, 2.52]) as independent risk factors for developing de novo AF. Prior pacemaker ($P = .11$)

and repeat sternotomy ($P = .28$) were not significantly associated with an increased de novo AF risk. Left atrial size and low ejection fraction were not found to be significant risk factors for de novo AF (Table E1).

DISCUSSION

Summarization of AF in follow-up continues to remain challenging, despite several useful recent

TABLE 3. Summary of significant univariate risk factors for developing de novo atrial fibrillation

Variable	HR	95% CI	P value
Age, y	1.04	(1.03-1.05)	<.001
Diabetes	1.60	(1.07-2.41)	.021
Hypercholesterolemia	1.43	(1.04-1.96)	.027
Hypertension	1.56	(1.13-2.16)	.007
Prior cerebrovascular accident	1.74	(1.02-2.96)	.043
Prior coronary artery bypass	1.94	(1.12-3.35)	.019
Prior pacemaker	3.10	(1.63-5.90)	<.001
Congestive heart failure	1.44	(1.05-1.99)	.024
Coronary artery disease	1.79	(1.30-2.46)	<.001
Repeat sternotomy	1.84	(1.21-2.81)	.005
Aortic stenosis	1.90	(1.25-2.87)	.002
Mitral stenosis	1.70	(1.10-2.65)	.018
Coronary artery bypass	1.66	(1.20-2.30)	.003
AV surgery	1.89	(1.35-2.65)	<.001
TV surgery	2.34	(1.62-3.40)	<.001
MV replacement (vs repair)	1.74	(1.24-2.46)	.002
TV regurgitation			
None/trivial	REF	REF	REF
Mild	1.33	(0.92-1.94)	.133
Moderate	1.86	(1.15-3.01)	.011
Moderate/severe	1.67	(0.61-4.62)	.319
Severe	3.52	(1.80-6.89)	<.001
TV regurgitation $\geq 2+$	1.87	(1.29-2.72)	.001
CHADS ₂ score			
0	REF	REF	REF
1	1.98	(1.23-3.18)	.005
2	2.78	(1.69-4.57)	<.001
3	2.48	(1.39-4.44)	.002
4	3.80	(1.77-8.15)	<.001
5	4.66	(1.87-11.13)	<.001
MV cause			
Degenerative	REF	REF	REF
Rheumatic	1.44	(0.68-3.02)	.34
Ischemic	2.31	(1.45-3.69)	<.001
Other	2.25	(1.57-3.21)	<.001

HR, Hazard ratio; CI, confidence interval; AV, aortic valve; TV, tricuspid valve; MV, mitral valve; CHADS₂, Congestive heart failure, hypertension, age, diabetes and stroke.

developments.¹¹⁻¹⁴ Patients undergoing mitral surgery typically have atrial myopathy and dilated atria placing them at risk for AF. There are little data regarding how often this occurs in patients without preoperative AF. This study identified several risk factors for de novo AF, AF was not uncommon and increased over time, and there was a strong trend toward an association with late stroke. Although in our analyses, time to de novo AF

TABLE 4. Summary of multivariable risk factors for developing de novo atrial fibrillation in follow-up

Variable	HR	95% CI	P value
Age	1.03	(1.02-1.05)	<.001
Prior pacemaker	1.75	(0.88-3.48)	.11
Repeat sternotomy	1.29	(0.82-2.02)	.28
AV surgery	1.37	(0.93-2.03)	.108
TV surgery	1.73	(1.17-2.56)	.005
MV cause			
Degenerative	REF	REF	REF
Rheumatic	0.98	(0.45-2.16)	.96
Ischemic	1.48	(0.90-2.42)	.12
Other	1.68	(1.11-2.52)	.013

HR, Hazard ratio; CI, confidence interval; AV, aortic valve; TV, tricuspid valve; MV, mitral valve.

development is measured since surgery time, findings remain virtually unchanged if time since hospital discharge is considered instead (Figures E5-E12).

A study from The Mayo Clinic investigated 573 patients with degenerative MR over 10 years and had similar findings to ours, with 11% and 23% de novo AF at 5 and 10 years compared with our finding of 9.1% and 22.3%, respectively.⁷ Risk factors for AF in that study were advanced age, diabetes, left atrial size greater than 50 mm, and more than mild TR, and as in our study, TV surgery did not increase the risk of late AF (although in our study there was a trend in the unadjusted analysis; $P = .068$) (Figure 4, A). However, Stulak and colleagues⁷ did find that AF reduced late survival ($P = .001$), which we did not. They did not report on late stroke rate.

Unlike in the Mayo study, our cohort included patients with degenerative, rheumatic, ischemic, and other mixed-cause MV disease. The incidence of de novo AF remained similar among these 3 main groups at 10 years (degenerative 22.3%, rheumatic 23%, and ischemic 22.9%) despite mortality differences. Degenerative MV disease was associated with a steady rate of de novo AF and had the lowest mortality rate among the 3 groups at 10 years (7.1%). Patients with ischemic MV disease had a higher mortality at 10 years (27.9%) compared with the other groups, a reflection of the poor outcome associated with this disease. The group with other causes had a higher risk for de novo AF by multivariable analysis (Table 4).

Among patients in whom de novo AF developed during follow-up, there was a trend toward an increased risk of stroke ($P = .055$). This risk potentially could be reduced with closure of the left atrial appendage at the time of surgery; however, this is not routinely performed in the absence of a surgical ablation procedure. If one is willing

FIGURE 4. Estimated probabilities of developing *de novo* AF by (A) TV surgery status and (B) postoperative AF status in PS-matched groups. AF, Atrial fibrillation; TV, tricuspid valve.

to assume a causal relationship between AF and late stroke, then prophylactic treatment of AF may reduce that risk. In our cohort, overall average follow-up was in fact

significantly longer among patients who developed *de novo* AF in follow-up than for those who did not, making selection bias unlikely: 4.96 ± 2.90 years (no *de novo*

AF) versus 5.98 ± 2.76 years (de novo AF) ($P < .001$). Alternative analytic approaches when selection bias is a potential concern include pattern mixture models for informative dropout.¹⁵

Our data show a univariate association between preoperative moderate or greater TR and the risk of de novo AF (25% if de novo AF, 17% if no de novo AF, $P = .024$). In addition, more patients with de novo AF had TR postoperatively. The question of whether TR leads to de novo AF or if de novo AF leads to worsening TR is an important distinction. In one study, right atrial dilation as a result of right heart volume overload in the setting of TR was shown to promote AF.¹⁶ Stulak and colleagues¹⁷ demonstrated that AF after MV surgery increases the risk of progression to TR and that a successful Maze procedure at the time of surgery is associated with a decrease in risk. Some patients may benefit from prophylactic AF ablation to not only limit the development of de novo AF and stroke risk but also limit late TR.

A Potential Trial of Prophylactic Atrial Fibrillation Ablation

An adequately controlled randomized trial to detect a 5-year 40% reduction of AF with 80% power at a 2-sided 5% α -level would require 2392 patients. A targeted trial of prophylactic ablation AF for high-risk patients, however, such as those aged 65 years or more with multiple valve surgery, may be more feasible.

Study Limitations

We acknowledge several limitations of our retrospective study. First, our cohort is heterogeneous because it includes patients who underwent MV surgery for a spectrum of MV diseases, with concomitant cardiac procedures, such as coronary artery bypass grafting and other valvular operations. Second, patients in our cohort had no documented evidence of preoperative AF; however, it is possible that patients had undetected past episodes of AF. Third, we identified heart rhythm information mostly via electrocardiogram. We may have underreported de novo AF because patients were not followed per protocol, such as patients treated with AF ablation. We likely reported more on patients who developed symptomatic AF and sought treatment including rhythm assessment. Patients with de novo AF had a higher rate of pacemaker implant pre-discharge that allowed a more thorough rhythm assessment. Finally, we did not have the clinical information to determine whether AF was paroxysmal, persistent, or long-standing persistent.

CONCLUSIONS

A steady rate of de novo AF (>90 days postsurgery) develops after MV surgery in patients without a known preoperative history of AF. The development of de novo

AF was associated with a trend toward increased stroke risk, but not an overall survival difference. A trial of prophylactic AF ablation, especially in high-risk patients, to limit the development of late AF, stroke, and late TR may be warranted.

Conflict of Interest Statement

A.-C.A.: Atricure consultant. J.L.C.: Atricure consultant, Chairman, Scientific Advisory Board, stockholder. All other authors have nothing to disclose with regard to commercial support.

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Key Words: mitral valve surgery, postoperative atrial fibrillation

APPENDIX

1. Evaluation of Potential Risk Factors for Developing De Novo AF in Follow-up

In addition to the variable presented in the article's main body, we have explored several other potential risk factors for developing de novo AF. Results are shown in the following table.

2. Additional Details Regarding the Propensity Score-Matched Analyses

Postoperative atrial fibrillation versus no postoperative atrial fibrillation comparison. The PS model has modeled the probability of developing postoperative AF based on a logistic regression model with the following covariates: age at the time of surgery, gender, body mass index, creatinine level, left ventricular ejection fraction, diabetes, hypercholesterolemia, hypertension, chronic obstructive pulmonary disease, prior myocardial infarction, history of congestive heart failure, prior coronary artery bypass, prior heart valve procedure, repeat sternotomy, prior cardiovascular intervention, cerebrovascular disease, peripheral vascular disease, prior stroke, prior pacemaker, elective surgery, AV surgery, MV repair or replacement, coronary artery bypass grafting, New York Heart Association Functional Class III or IV, and preoperative medication (beta-blockers, anticoagulants, aspirin, statins, and diuretics).

We have modeled the probability of experiencing postoperative AF and carried out 1-to-1 PS matching with a caliper of size 0.1 logit-PS standard deviation units. The area under the receiver's operating characteristics curve was equal to 0.713, and the Hosmer–Lemeshow test was chi-square = 6.67, degrees of freedom = 8, P value = .57. Summaries of baseline and intraoperative characteristics after PS matching by postoperative AF status are shown in [Table E2](#). Corresponding standardized mean differences are depicted in [Figure E1](#). They confirm that adequate covariate balance has been achieved after PS matching.

TV surgery versus no TV surgery comparison. A similar PS-matched analysis was performed using the same variables as predictors. The caliper PS-matching process used a 2-to-1 matching ratio (no TV surgery vs TV surgery) and was based on a Greedy algorithm. A caliper of size 0.1 logit-PS standard deviation units was used. The area under the receiver's operating characteristics curve was equal to 0.753. The Hosmer–Lemeshow test of calibration was chi-square = 6.62, degrees of freedom = 8, P = .58. Summaries of baseline and intraoperative characteristics before and after PS matching by TV surgery status are shown in [Table E3](#). Corresponding standardized mean differences are depicted in [Figure E2](#). They confirm that adequate covariate balance has been achieved after PS matching.

FIGURE E1. Standardized mean differences before and after PS matching by postoperative AF status. *PS*, Propensity score; *CHADS₂*, congestive heart failure, hypertension, age, diabetes, stroke; *CHADS₂VASC*, congestive heart failure, hypertension, age, diabetes, stroke, vascular disease; *MI*, myocardial infarction; *CABG*, coronary artery bypass grafting; *NYHA*, New York Heart Association; *TR*, tricuspid regurgitation; *AV*, aortic valve; *MV*, mitral valve.

FIGURE E2. Standardized mean differences before and after PS matching by TV surgery status. *PS*, Propensity score; *CHADS₂*, congestive heart failure, hypertension, age, diabetes, stroke; *CHADS₂VASC*, congestive heart failure, hypertension, age, diabetes, stroke, vascular disease; *MI*, myocardial infarction; *CABG*, coronary artery bypass grafting; *NYHA*, New York Heart Association; *AV*, aortic valve; *MV*, mitral valve.

FIGURE E3. Histogram of the number of AF assessment (diagnosis) times during the postsurgical follow-up of the entire cohort. AF, Atrial fibrillation.

All Patients

Rheumatic MV Etiology

Degenerative MV Etiology

Ischemic MV Etiology

FIGURE E4. Estimates of the *de novo* AF incidence based on methods for interval-censored data. AF, Atrial fibrillation; MV, mitral valve.

FIGURE E5. Multi-state models summary of probabilities of de novo AF, death, and AF-free survival in the entire cohort. AF, Atrial fibrillation.

FIGURE E6. Multi-state models summary of probabilities of de novo AF, death, and AF-free survival in rheumatic MV cause. AF, Atrial fibrillation.

FIGURE E7. Multi-state models summary of probabilities of de novo AF, death, and AF-free survival in degenerative MV cause. AF, Atrial fibrillation.

FIGURE E8. Multi-state models summary of probabilities of de novo AF, death, and AF-free survival in ischemic MV cause. AF, Atrial fibrillation.

FIGURE E9. Freedom from stroke by AF status in follow-up. AF, Atrial fibrillation.

FIGURE E10. Overall survival by AF status in follow-up. AF, Atrial fibrillation.

FIGURE E11. Estimated probabilities of developing de novo AF by TV surgery status in PS-matched groups. AF, Atrial fibrillation; TV, tricuspid valve.

FIGURE E12. Estimated probabilities of developing de novo AF by postoperative AF status in PS-matched groups. AF, Atrial fibrillation.

TABLE E1. Summary of left atrial diameter, left ventricular ejection fraction, history of congestive heart failure, and mitral valve cause as potential univariate risk factors for developing de novo atrial fibrillation

Variable	HR	95% CI	P value
Left atrial diameter (continuous)	1.16	(0.95-1.43)	.146
Left atrial diameter (categoric)			
<5 cm	REF	REF	REF
5-6 cm	1.44	(0.96-2.17)	.08
≥6 cm	1.30	(0.41-4.10)	.65
Left ventricular ejection fraction (continuous)	1.01	(0.98-1.002)	.095
Left ventricular ejection fraction (categoric)			
>45%	REF	REF	REF
30%-45%	2.11	(1.42-3.13)	<.001
≤30%	1.04	(0.60-1.82)	.88
History of congestive heart failure	1.44	(1.05-1.99)	.024
MV cause			
Degenerative	REF	REF	REF
Rheumatic	1.44	(0.68-3.02)	.34
Ischemic	2.31	(1.45-3.69)	<.001
Other	2.25	(1.57-3.21)	<.001

HR, Hazard ratio; CI, confidence interval; MV, mitral valve.

TABLE E2. Summary of baseline characteristics in propensity score-matched groups by postoperative atrial fibrillation status

Variable	No postoperative AF (N = 259)	Postoperative AF (N = 259)	P value
Age (y)	64.7 ± 11.9	64.4 ± 11.3	.76
Body mass index (kg/m ²)	27.5 ± 6.0	27.3 ± 5.3	.69
CHADS ₂	1.5 ± 1.2	1.5 ± 1.2	.91
CHADS ₂ VASC	2.6 ± 1.7	2.5 ± 1.7	.55
Creatinine level, median (Q1, Q3)	1.0 (0.8, 1.1)	1.0 (0.9, 1.2)	.35
Ejection fraction, median (Q1, Q3)	60.0 (50.0, 65.0)	60.0 (50.0, 65.0)	.84
Left atrial size, median (Q1, Q3)	4.3 (3.7, 4.7)	4.3 (3.8, 4.8)	.37
Gender (female)	110 (42%)	103 (40%)	.53
Diabetes	40 (15%)	40 (15%)	1.00
Dyslipidemia	140 (54%)	145 (56%)	.66
Hypertension	172 (66%)	166 (64%)	.58
Chronic lung disease	36 (14%)	32 (12%)	.60
Peripheral vascular disease	15 (6%)	12 (5%)	.55
Cerebrovascular disease	21 (8%)	20 (8%)	.87
Prior stroke	14 (5%)	16 (6%)	.71
Previous myocardial infarction	32 (12%)	30 (12%)	.79
Prior CABG	14 (5%)	17 (7%)	.58
Prior pacemaker	5 (2%)	3 (1%)	.48
Congestive heart failure	88 (34%)	91 (35%)	.78
NYHA class III or IV	87 (34%)	90 (35%)	.78
Coronary artery disease	98 (38%)	97 (38%)	.98
Repeat sternotomy	21 (8%)	28 (11%)	.29
Elective surgery	220 (85%)	221 (85%)	.90
AV stenosis	34 (16%)	36 (17%)	.88
MV stenosis	26 (11%)	31 (13%)	.52
Preoperative anticoagulants	18 (7%)	20 (8%)	.74
Tricuspid regurgitation >2+	47 (19%)	60 (24%)	.14
AV insufficiency			.10
0 = None/trivial	141 (65%)	154 (69%)	
1 = Mild	50 (23%)	31 (14%)	
2 = Moderate	15 (7%)	23 (10%)	
3 = Moderate/severe	1 (0%)	3 (1%)	
4 = Severe	10 (5%)	12 (5%)	
MV insufficiency			.62
0 = None/trivial	3 (1%)	7 (3%)	
1 = Mild	18 (7%)	17 (7%)	
2 = Moderate	39 (15%)	46 (18%)	
3 = Moderate/severe	23 (9%)	23 (9%)	
4 = Severe	176 (68%)	164 (64%)	
Coronary artery bypass	85 (33%)	77 (30%)	.45
AV surgery	61 (24%)	63 (24%)	.84
TV surgery	39 (15%)	38 (15%)	.90
MV surgery type			.92
Repair	194 (75%)	195 (75%)	
Replacement	65 (25%)	64 (25%)	

AF, Atrial fibrillation; CHADS₂, congestive heart failure, hypertension, age, diabetes, stroke; CHADS₂VASC, congestive heart failure, hypertension, age, diabetes, stroke, vascular disease; CABG, coronary artery bypass grafting; NYHA, New York Heart Association; AV, aortic valve; MV, mitral valve; TV, tricuspid valve.

TABLE E3. Summary of baseline characteristics in propensity score–matched groups by tricuspid valve surgery status

Variable	No TV surgery (N = 208)	TV surgery (N = 110)	P value
Age	63.2 ± 14.2	63.4 ± 13.7	.90
Body mass index (kg/m ²)	26.4 ± 5.5	26.4 ± 5.8	1.00
CHADS ₂	1.7 ± 1.4	1.7 ± 1.2	.96
CHADS ₂ VASC	3.0 ± 2.0	3.0 ± 1.6	.97
Creatinine level, median (Q1, Q3)	1.0 (0.8, 1.2)	1.0 (0.9, 1.3)	.49
Ejection fraction, median (Q1, Q3)	60.0 (44.5, 65.0)	60.0 (45.0, 65.0)	.45
Left atrial size, median (Q1, Q3)	4.3 (3.8, 4.7)	4.3 (3.8, 4.9)	.28
Gender (female)	112 (54%)	60 (55%)	.91
Diabetes	47 (23%)	24 (22%)	.87
Dyslipidemia	108 (52%)	56 (51%)	.86
Hypertension	115 (55%)	61 (55%)	.98
Chronic lung disease	24 (12%)	11 (10%)	.68
Peripheral vascular disease	13 (6%)	6 (5%)	.78
Cerebrovascular disease	23 (11%)	11 (10%)	.77
Prior stroke	15 (7%)	8 (7%)	.98
Previous myocardial infarction	38 (18%)	17 (15%)	.53
Prior coronary artery bypass graft	23 (11%)	12 (11%)	.97
Prior pacemaker	8 (4%)	7 (6%)	.31
Congestive heart failure	103 (50%)	54 (49%)	.94
NYHA class III or IV	95 (46%)	50 (45%)	.97
Coronary artery disease	89 (45%)	44 (41%)	.54
Repeat sternotomy	41 (20%)	20 (18%)	.74
Elective surgery	166 (80%)	87 (79%)	.88
AV stenosis	24 (13%)	19 (21%)	.12
MV stenosis	32 (16%)	19 (19%)	.55
Preoperative anticoagulants	23 (11%)	14 (13%)	.66
TR >2+	24 (12%)	81 (80%)	<.001
AV insufficiency			.70
0 = None/trivial	120 (66%)	60 (62%)	
1 = Mild	35 (19%)	19 (20%)	
2 = Moderate	15 (8%)	8 (8%)	
3 = Moderate/severe	3 (2%)	1 (1%)	
4 = Severe	9 (5%)	9 (9%)	
MV insufficiency			.92
0 = None/trivial	9 (4%)	4 (4%)	
1 = Mild	16 (8%)	9 (8%)	
2 = Moderate	37 (18%)	17 (15%)	
3 = Moderate/severe	17 (8%)	12 (11%)	
4 = Severe	128 (62%)	68 (62%)	
Coronary artery bypass grafting	71 (34%)	34 (31%)	.56
AV surgery	42 (20%)	24 (22%)	.73
MV surgery type			.74
Repair	140 (67%)	72 (65%)	
Replacement	68 (33%)	38 (35%)	

TV, Tricuspid valve; CHADS₂, congestive heart failure, hypertension, age, diabetes, stroke; CHADS₂VASC, congestive heart failure, hypertension, age, diabetes, stroke, vascular disease; NYHA, New York Heart Association; AV, aortic valve; MV, mitral valve; TR, tricuspid regurgitation.

TABLE E4. Summary of significant univariate risk factors for developing de novo atrial fibrillation

Variable	Models for time since surgery date		Models for time since hospital discharge date	
	HR (95% CI)	P value	HR (95% CI)	P value
Age, y	1.04 (1.03-1.05)	<.001	1.04 (1.03-1.05)	<.001
Diabetes	1.60 (1.07-2.41)	.021	1.61 (1.08-2.41)	.028
Hypercholesterolemia	1.43 (1.04-1.96)	.027	1.43 (1.04-1.96)	.027
Hypertension	1.56 (1.13-2.16)	.007	1.56 (1.13-2.16)	.006
Prior cerebrovascular accident	1.74 (1.02-2.96)	.043	1.74 (1.03-2.98)	.056
Prior coronary artery bypass	1.94 (1.12-3.35)	.019	1.94 (1.12-3.36)	.031
Prior pacemaker	3.10 (1.63-5.90)	<.001	3.10 (1.63-5.91)	.003
Congestive heart failure	1.44 (1.05-1.99)	.024	1.45 (1.05-1.99)	.025
Coronary artery disease	1.79 (1.30-2.46)	<.001	1.79 (1.30-2.46)	<.001
Repeat sternotomy	1.84 (1.21-2.81)	.005	1.85 (1.21-2.82)	.008
Aortic stenosis	1.90 (1.25-2.87)	.002	1.90 (1.26-2.88)	.005
Mitral stenosis	1.70 (1.10-2.65)	.018	1.71 (1.10-2.65)	.025
Coronary artery bypass	1.66 (1.20-2.30)	.003	1.66 (1.20-2.30)	.003
AV surgery	1.89 (1.35-2.65)	<.001	1.89 (1.35-2.66)	<.001
TV surgery	2.34 (1.62-3.40)	<.001	2.35 (1.62-3.41)	<.001
MV replacement (vs repair)	1.74 (1.24-2.46)	.002	1.75 (1.24-2.47)	.002
TV regurgitation				
None/trivial	REF	REF	REF	REF
Mild	1.33 (0.92-1.94)	.133	1.33 (0.91-1.94)	.135
Moderate	1.86 (1.15-3.01)	.011	1.86 (1.15-3.01)	.012
Moderate/severe	1.67 (0.61-4.62)	.319	1.67 (0.61-4.61)	.321
Severe	3.52 (1.80-6.89)	<.001	3.55 (1.82-6.95)	<.001
TV regurgitation $\geq 2+$	1.87 (1.29-2.72)	.001	1.87 (1.29-2.72)	.002
CHADS ₂ score				
0	REF	REF	REF	REF
1	1.98 (1.23-3.18)	.005	1.99 (1.24-3.19)	.004
2	2.78 (1.69-4.57)	<.001	2.78 (1.69-4.57)	<.001
3	2.48 (1.39-4.44)	.002	2.49 (1.40-4.46)	.002
4	3.80 (1.77-8.15)	<.001	3.83 (1.78-8.21)	<.001
5	4.66 (1.87-11.13)	<.001	4.57 (1.87-11.17)	<.001
MV cause				
Degenerative	REF	REF	REF	REF
Rheumatic	1.44 (0.68-3.02)	.34	1.44 (0.68-3.02)	.34
Ischemic	2.31 (1.45-3.69)	<.001	2.32 (1.45-3.69)	<.001
Other	2.25 (1.57-3.21)	<.001	2.26 (1.58-3.23)	<.001

HR, Hazard ratio; CI, confidence interval; AV, aortic valve; TV, tricuspid valve; MV, mitral valve; CHADS₂, congestive heart failure, hypertension, age, diabetes and stroke.

TABLE E5. Summary of multivariable risk factors for developing de novo atrial fibrillation in follow-up

Variable	Models for time since surgery date		Models for time since hospital discharge date	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.03 (1.02-1.05)	<.001	1.03 (1.02-1.05)	<.001
Prior pacemaker	1.75 (0.88-3.48)	.11	1.74 (0.88-3.47)	.11
Repeat sternotomy	1.29 (0.82-2.02)	.28	1.29 (0.82-2.03)	.27
AV surgery	1.37 (0.93-2.03)	.108	1.37 (0.93-2.03)	.109
TV surgery	1.73 (1.17-2.56)	.005	1.74 (1.18-2.57)	.005
MV cause				
Degenerative	REF	REF	REF	REF
Rheumatic	0.98 (0.45-2.16)	.96	0.98 (0.45-2.16)	.97
Ischemic	1.48 (0.90-2.42)	.12	1.48 (0.91-2.43)	.12
Other	1.68 (1.11-2.52)	.013	1.68 (1.12-2.53)	.013

HR, Hazard ratio; CI, confidence interval; AV, aortic valve; TV, tricuspid valve; MV, mitral valve.