

# Effect of Surgery for Atrial Fibrillation Associated With Mitral Valve Disease

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**Background.** The purpose of this study is to evaluate the effect of surgery for atrial fibrillation (AF) associated with mitral valve disease.

**Methods.** From September 1994 to December 2006, 244 patients who underwent mitral valve surgery were enrolled in this study. The maze procedure or pulmonary vein isolation was concomitantly performed in 147 patients, while the remaining 97 patients were not surgically treated for AF. The patients were divided into 3 groups based on their cardiac rhythm at discharge from the hospital: the sinus group (108 patients), the intractable AF group (39 patients), and the untreated AF group (97 patients). The clinical features and late results of patients were compared among these groups.

**Results.** Early mortality rate was 0.7% and no major morbid events had occurred. Follow-up was completed in 95.6% of the patients and the mean follow-up period was

6.03 years. Actuarial survival was not significant between the sinus and AF groups. Actuarial freedom from thromboembolism at 5 and 10 years was 96.5% in the sinus group, 82.4% and 78.1%, respectively, in the intractable AF group, and 93.4% and 89.1%, respectively, in the untreated AF group; statistical significance was observed among the 3 groups ( $p = 0.01$ ). By means of multivariate analysis, intractable AF was found to be the only risk factor for thromboembolism and other complications.

**Conclusions.** Atrial fibrillation associated with mitral valve disease should be treated, because restoration of the sinus rhythm might lead to a lower incidence of thromboembolism and valve-related complications in the later period.

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The maze procedure is a widely accepted surgical intervention method for treating atrial fibrillation (AF). It is also recognized as an effective procedure for treating permanent AF associated with mitral valve disease [1–3].

Atrial fibrillation is one of the major risk factors involved in stroke or peripheral embolism, and eliminating AF may prevent such embolic events. There have been many reports on the efficacy of the maze procedure associated with mitral valve disease [1–3], but the influence of postoperative cardiac rhythm on an embolic event remains unclear. We hereby report our midterm results of AF surgery combined with mitral valve surgery and the influence of cardiac rhythms on postoperative embolic events.

## Patients and Methods

The Ethics Committee of Kurume University School of Medicine approved this study. The Institutional Review Board approved the current study, and individual patient consent was waived because the study was retrospective.

### Patients

From September 1994 to December 2006, 244 patients with mitral valve disease and chronic AF underwent

surgery at the Kurume University Hospital. There were 101 men and 143 women with a mean age of 62.3 years (range, 29 to 80 years). The etiologies of mitral valve disease were mitral valve stenosis in 119 patients, mitral valve regurgitation in 117 patients, and prosthetic valve failure in 8 patients. Of them, 27 (11.1%) patients had a history of stroke. The mean duration of having AF was 6.2 years (range, 3 months to 40 years).

Mitral valve replacement was performed in 169 patients (mechanical prosthesis was used in 155 patients and biologic prosthesis, 14 patients), and mitral valve repair was performed in 75 patients. Concomitant tricuspid annuloplasty was performed in 142 patients. Surgical intervention for AF was carried out concomitantly due to the patients' clinical condition, the surgeon's preference, or due to the following indications: (1) an AF history of less than 20 years; (2) a cardiothoracic ratio of less than 70%; (3) a left atrial dimension of less than 70 mm; and (4) f-wave voltage at the V1 lead of more than 0.1 mV. As a result, AF was surgically treated in 147 patients, and the remaining 97 patients were untreated. Preoperative patient characteristics are listed in Table 1. Informed consent was obtained from all patients for examinations and surgical procedures.

### Surgical Techniques

The Cox maze or the Kosakai maze procedure [4] was the surgical procedure employed for treating AF. Since 1999,

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Table 1. Preoperative Patient Characteristics

Characteristics	All Patients	Sinus Group	Intractable AF Group	Untreated AF	p Value
No. of patients	244	108	39	97	
Male/female	101/143	43/65	17/22	41/56	0.814
Age (years)	62.3 ± 10.1	61.8 ± 10.2	63.7 ± 9.4	61.6 ± 10.7	0.556
NYHA III or IV	70	32	10	28	0.933
LA dimension (mm)	54.9 ± 10.3	53.1 ± 8.8	60.0 ± 12.3	57.1 ± 9.5	0.651
CTR (%)	58.6 ± 6.6	57.5 ± 5.7	61.3 ± 8.1	59.1 ± 8.1	0.389
AF Duration (years)	8.9 ± 6.8	7.7 ± 4.7	10.8 ± 9.4	8.3 ± 6.2	0.568
F-wave in V1 (mV)	0.18 ± 0.07	0.2 ± 0.06	0.13 ± 0.04	0.16 ± 0.08	0.721
History of stroke	27	16	4	7	0.298
Previous cardiac op.	26	7	5	14	0.097
CAD	3	1	1	1	0.710
MVR/MVP	169/75	69/39	28/11	72/25	0.347
Maze/LAP	114/33	82/26	32/7	—	—
TAP	142	53	16	56	0.084

AF = atrial fibrillation; CAD = coronary artery disease; CTR = cardiothoracic ratio; LA = left atrium; LAP = left atrial procedure; MVP = mitral valvuloplasty; MVR = mitral valve replacement; NYHA = New York Heart Association; TAP = tricuspid annuloplasty.

pulmonary vein isolation or left atrial reduction has been used as a simplified left atrial procedure for patients without severe tricuspid regurgitation [5]. Tricuspid regurgitation was considered as an important factor while deciding upon the surgical procedure; this is because it has been reported that patients with tricuspid regurgitation who require tricuspid annuloplasty have a higher recurrence rate of AF after left atrial isolation [6].

The surgical technique for AF was as follows. In all patients, standard cardiopulmonary bypass with bicaval cannulation was used. Incision and cryoablation lines were created as Kosakai's modification [4]. Briefly, a temporary transection of the superior vena cava was performed for good exposure of the left atrium. Cryoablation was used to avoid cutting the sinus node artery, which may result in sick sinus syndrome. The excess left atrial tissue was trimmed to approximately 4 cm. All of the right atrial appendage and a part of the left atrial appendage were preserved.

In candidates for the left atrial procedure, all 4 pulmonary veins were isolated as a box formation by using a cut and saw technique. In patients with a left atrial dimension of more than 55 mm, the left atrial appendage was closed from the left atrial side or resected along with the surrounding left atrial tissue [5]. No additional cutting or cryoablation was performed in these patients.

#### Evaluations and Follow-Up

Preoperative and perioperative data were collected from medical records, and follow-up data were obtained from our outpatient clinic records or by correspondence with referring physicians. The condition of the patients, cardiac rhythm depicted on an electrocardiogram, and medications at follow-up were analyzed. The endpoint for analysis was either the patient's death or completion of the study (June 30, 2007).

All patients were administered warfarin for 3 months after surgery. The target range of the prothrombin time international normalized ratio (PT-INR) was 1.8 to 2.5.

Warfarin administration was continued if the patient's cardiac rhythm exhibited AF at 3 months after surgery or the patient had a mechanical valve implant. Definitions of cardiac or noncardiac death were in accordance with the guidelines of the Society of Thoracic Surgeons and the American Association for Thoracic Surgery [7].

In order to analyze the influence of cardiac rhythm and the effects of AF surgery, the patients were divided into 3 groups based on their cardiac rhythm at discharge: (1) Sinus group: patients who had their sinus rhythm restored after AF surgery; (2) intractable AF group: patients who continued to exhibit AF despite AF surgery; (3) untreated AF group: patients who were not surgically treated for AF.

#### Statistical Methods

Continuous variables were expressed as mean ± standard deviation. The characteristics of the 3 groups were compared by using  $\chi^2$  analysis for nominal variables and a nonparametric analysis of variance test for continuous or ordinal variables. Survivals and freedom from late complications were estimated using the Kaplan-Meier method. Survival curves were compared using a log-rank test. The risk factors for late death, embolic events, and cardiac complications were analyzed by using both univariate and multivariate analysis with the Cox proportional hazards model.

#### Results

##### Operative Results

Of the 244 patients, 5 (2.0%) died during hospitalization. The cause of death was low output syndrome with multiple organ failure in 4 patients and sepsis caused by pneumonia in 1 patient. Major perioperative complications were observed in 26 patients (10.7%). Resternotomy for bleeding was performed in 11 patients (8 patients with AF surgery and 3 without AF surgery). Postoperative low

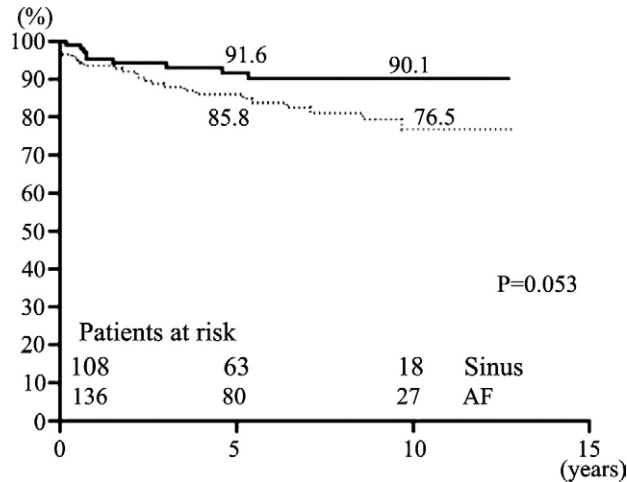


Fig 1. Actuarial survival curves for sinus and AF rhythm. (AF = atrial fibrillation; — = sinus; ··· = AF.)

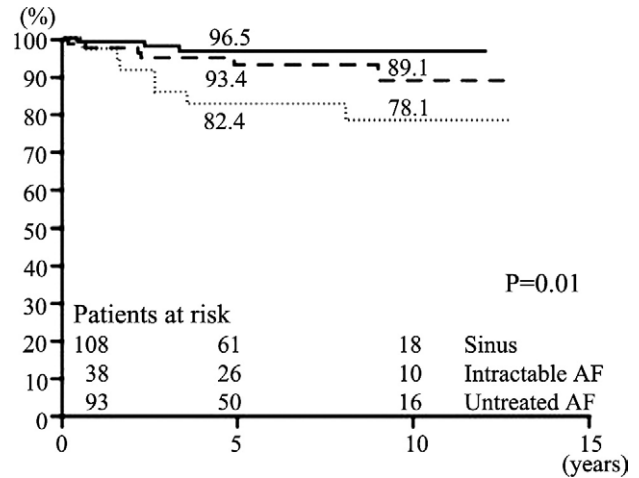


Fig 2. Actuarial freedom from thromboembolism. (AF = atrial fibrillation; — = sinus; ··· = intractable AF; --- = untreated AF.)

cardiac output was observed in 12 patients (8 patients with AF surgery and 4 without AF surgery). In patients who underwent AF surgery, 4 patients had perioperative myocardial infarction, possibly due to cryoablation around the circumflex artery, but a postoperative coronary angiogram revealed no stenosis or occlusion of the coronary arteries. Other complications, including a left ventricular rupture, aortic dissection caused by aortic cannulation, and mediastinitis, were observed in 1 patient each and were successfully treated.

Among the 147 patients who underwent AF surgery, 108 (73.5%) had their sinus rhythm restored until discharge from the hospital. The Cox maze procedure was performed in 10 patients, while the Kosakai maze procedure was performed in 104 patients. A left atrial procedure was performed in 33 patients. Based on the procedures, the sinus rhythm restoration rate was 71.9% (82 of 114 patients) with maze procedure and 78.8% (26 of 33 patients) with the left atrial procedure. None of the patients underwent pacemaker implantation during their hospital stay.

Based on the postoperative cardiac rhythm recorded, the patients were divided into the 3 groups mentioned

above: 108 patients belonged to the sinus group; 39 to the intractable AF group; 97 to the untreated AF group.

Late Outcome

Follow-up was completed in 234 patients (97.9% of operative survivors), with a mean duration of 6.03 years (range, 4 months to 12.8 years). There were 28 (11.5%) late deaths during the follow-up period. Valve-related deaths occurred in 13 patients, including stroke in 4 patients, anticoagulation related cerebral bleeding in 3 patients, prosthetic valve endocarditis in 1 patient, and sudden or unexplained death in 5 patients. Cardiac death as well as valve-related death was observed in 17 patients. An additional 4 patients died of congestive heart failure with well-functional operated valves. At the follow-up, AF rhythm developed in 3 patients (2.9%) of the sinus group, sinus rhythm was restored in 1 patient (2.6%) of the intractable AF group, and AF rhythm developed in 8 patients (8.2%) of the untreated AF group. However, these patients had no complications during follow-up. Among the patients with a sinus rhythm, 4 died due to cardiac-related causes (anticoagulation-related cerebral

Table 2. Thromboembolism After Atrial Fibrillation Surgery

Patient	AF Surgery	Valve Surgery	Group	Site of Emboli	Note	Duration from Surgery (mo)
47 F	Maze	MVR	Sinus	Cerebral	Preop. Stroke ×2 Inadequate AC	40
51 F	LAP	MVR	Sinus	Prosthetic valve	Discontinuation of warfarin	5
67 M	Maze	MVR	Sinus	Cerebral	Postop. MI(+) LV dysfunction	28
68 F	Maze	MVR	Intractable	Cerebral (death)	Preop. Stroke ×2	42
69 F	Maze	MVR	Intractable	Coronary	Thrombolysis	18
55 F	LAP	MVR	Intractable	Cerebral	TIA	19
69 F	LAP	MVR	Intractable	Cerebral Prosthetic valve	Reoperation	31
71 F	Maze	MVP	Intractable	LA thrombus	Reoperation	6

AF = atrial fibrillation; AC = anticoagulation; LAP = left atrial procedure; MVP = mitral valvuloplasty; MVR = mitral valve replacement; TIA = transient ischemic attack.

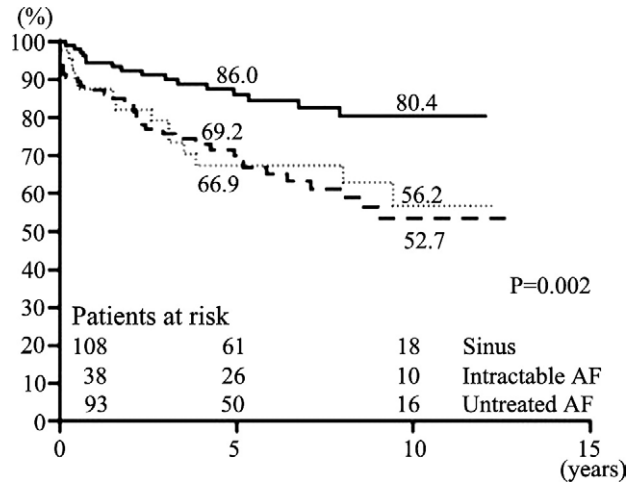


Fig 3. Actuarial freedom from all complications. (AF = atrial fibrillation; — = sinus; ··· = intractable AF; --- = untreated AF.)

bleeding in 2 patients, congestive heart failure in 1 patient, and sudden death in 1 patient), and 6 died due to noncardiac causes. In patients with AF rhythm, 13 died due to cardiac-related causes (stroke in 4 patients, congestive heart failure in 4 patients, anticoagulation-related cerebral bleeding in 1 patient, and sudden-unknown death in 4 patients) and 5 patients died due to noncardiac causes. Actuarial survival in the patients with sinus rhythm at 5 and 10 years was 91.6% and 90.1%, respectively, while that in the AF patients was 85.8% and 76.5%, respectively (Fig 1). There was no statistical significance between the sinus and AF rhythm groups ( $p = 0.053$ ). Actuarial freedom from cardiac death in patients with sinus rhythm at 5 and 10 years was 95.3% and 93.7%, respectively, while that in patients with AF was 88.6% and 81.5%, respectively. There was a statistical significance between the sinus and AF rhythm groups ( $p = 0.033$ ).

Thromboembolism was observed in 14 patients: stroke occurred in 2 patients in the sinus group, 3 patients in the intractable AF group, and 4 patients in the untreated AF group while the remaining 5 patients developed peripheral or valve thrombosis. Among patients who underwent AF surgery, 3 patients in the sinus group were

complicated by stroke or valve thrombosis. Of them, 2 patients were inadequately anticoagulated (PT-INR, 1.58 and 1.15) at the onset, while 1 patient exhibited severe left ventricular dysfunction caused by perioperative myocardial infarction. These may be the possible reasons why even patients with sinus rhythm had thromboembolism. The remaining 5 patients in the intractable AF group were adequately anticoagulated (PT-INR, 2.13 to 2.56). The details of thromboembolism after AF surgery are presented in Table 2. Actuarial freedom from thromboembolism at 5 and 10 years was 96.5% in the sinus group; 82.4% and 78.1%, respectively, in the intractable AF group; and 93.4% and 89.1%, respectively, in the untreated AF group (Fig 2); statistical significance was observed among the 3 groups ( $p = 0.01$ ).

Actuarial freedom from complications such as death, valve deterioration, valve thrombosis, thromboembolism including stroke, anticoagulation-related bleeding, pacemaker implantation, congestive heart failure, and reoperation at 5 and 10 years was 86.0% and 80.4%, respectively, in the sinus group; 66.9% and 56.2%, respectively, in the intractable AF group; and 69.2% and 52.7%, respectively, in the left AF group (Fig 3); statistical significance was observed among the 3 groups ( $p = 0.002$ ).

#### Risk Factors of Late Morbidity

By means of univariate analysis, we determined that gender (female) and intractable AF were the risk factors of thromboembolism, while age, gender (female), and intractable AF were the risk factors for all other complications. By means of multivariate analysis, we determined that intractable AF with a hazard ratio of 2.60 and 1.68 was the only risk factor for both thromboembolism and all other complications (Table 3).

#### Comment

Various studies [8-11] have reported the effectiveness of AF surgery in terms of restoration to the sinus rhythm, modification of the procedure, and development of an ablation device for creating block lines. However, the main purpose of AF surgery is to eliminate symptomatic tachycardia, hemodynamic impairment caused by the

Table 3. Factors for Late Complication

Variable	Univariate	Multivariate		
	<i>p</i> Value	<i>p</i> Value	Hazard Ratio	95% CI
Factors for thromboembolism				
Female	0.028	0.103	1.57	0.92-2.95
Intractable AF	0.010	0.021	2.62	1.29-5.23
Factors for all complications				
Age	0.049	0.079	1.03	1.00-1.08
Female	0.036	0.118	1.22	0.95-1.59
Intractable AF	0.001	0.018	1.68	1.03-2.63

AF = atrial fibrillation; CI = confidence interval.

loss of atrial contraction, and thromboembolism. The former 2 symptoms are directly related to cardiac rhythm and can be easily investigated, but evaluating the occurrence of thromboembolism requires a long follow-up period. In order to evaluate the effects of AF surgery, it is important to clarify the late outcomes of AF surgery.

It has been reported that maintaining sinus rhythm by AF surgery had a superior effect, even combined with mitral valve surgery [1, 3, 12, 13]. Despite the longer durations for cross-clamp and cardiopulmonary bypass, it has been reported that the mortality and morbidity early after surgery do not differ significantly whether the maze procedure was carried out concomitantly with mitral valve surgery or not [1, 2, 12]. In this study, the mortality of AF surgery combined with mitral valve surgery was 0.7%, and no major morbid events occurred early after surgery. Itoh and colleagues [12] reported that early mortality after the maze procedure combined with mitral valve surgery was 2.1% with a low morbidity in 521 patients. From these results, it was considered that AF surgery could be carried out safely even in combination with mitral valve surgery. It has also been reported that after the maze procedure, the late survival rate was significantly better in patients with sinus rhythm than in those with AF rhythm. In this study, there was no significant difference in the late survival rate between patients with sinus rhythm and those with AF rhythm; however, there was a strong trend toward better survival in patients with sinus rhythm, reaching a *p* value of 0.053. In addition, the main causes of late death in patients with the sinus group were noncardiac reasons in contrast with the AF rhythm group.

Atrial fibrillation itself is a strong factor that causes thromboembolism. Furthermore, in age-matched patients, it caused a fivefold increase in the risk of thromboembolism [14]. Therefore, it has been suggested that treating AF may prevent such complications. The Cox maze procedure is ideal for treating AF. Ad and Cox [15] have reported that maze procedures significantly reduce the incidence of late stroke. In addition, it has also been reported that the maze procedure combined with mitral valve surgery also reduces the incidence of stroke [1, 12, 16]. Despite anticoagulation therapy, thromboembolism occurs at a rate of 2% to 3% per year after mitral valve replacement. In order to solve this problem, Bando and colleagues [13] have reported combined therapy of the maze procedure and mitral valve replacement and they found that restoration of the sinus rhythm significantly reduces the incidence of stroke; this led them to conclude that persistent AF is the most significant risk factor involved in early and late stroke after mitral valve replacement.

The present results reveal that freedom from thromboembolism is significantly higher in patients with sinus rhythm than in those with AF rhythm. Furthermore, patients in the intractable AF group were found to exhibit a higher incidence of thromboembolism even after AF surgery. This result cannot be definitively reasoned, but the difference between the intractable AF group and the untreated AF group may arise due to the incision lines in the atrium. The maze procedure requires multiple inci-

sion lines, which is disadvantageous for atrial contraction. Feinberg and colleagues [17] have reported that the percent atrial filling fraction of the left atrium after the maze procedure was smaller in operated patients than in normal controls. Their results suggest that although the maze procedure restores atrial contraction, normal values are not achieved due to multiple incision lines. On the other hand, AF patients do not exhibit effective atrial contraction and AF itself is one of the biggest risk factors for thromboembolism. Furthermore, intractable AF patients may exhibit decreased atrial mobility because of the multiple incision lines, sutures, subsequent scarring, and a tethering of the posterior wall of the left atrium by the suture line. This may explain why the intractable AF group displayed a higher incidence of thromboembolism in this study.

Recent match-controlled studies have indicated that the maze procedure combined with mitral valve surgery is favorable for reducing the incidence of late stroke after surgery [16]. Our results also suggest that restoration of the sinus rhythm by AF surgery is effective in reducing the incidence of thromboembolism. However, a higher incidence of thromboembolism was observed in the intractable AF group than in the untreated AF group. These results suggest that the indications for AF surgery should be stringent. Recent advances in endocardial and intraoperative mapping systems have allowed the detection of the cause of AF [18], and some patients with AF have been operated by using "map-guided surgery" with satisfactory results [19]. However, the mapping system cannot be easily introduced in every institution; therefore, we employed transesophageal electrocardiography to easily obtain electrical information on the atrium [20]. With this system, it is possible to select the appropriate procedure and thereby increase the rate of restoration to sinus rhythm.

The limitations of this study are as follows. First, this study is not randomized. The AF surgery is performed in our hospital since 1994, but it did not immediately materialize as a routine procedure for all AF patients in the early period. Therefore, there might have been some bias during follow-up between patients who underwent AF surgery and those who did not. Second, various procedures were employed for AF surgery and mitral valve surgery. It is possible that this diversity in procedures may have affected the results, although the main purpose of this study was to investigate the influence of cardiac rhythms on postoperative embolic events. In addition, it is well known that the cardiac rhythm varies over time after surgery. In this study, there were a few patients with altered cardiac rhythms, but they had no complications during follow-up. It was difficult to divide these patients into groups; hence, we conducted this study by analyzing the rhythm at discharge.

In conclusion, AF associated with mitral valve disease should be treated because restoration of the sinus rhythm might lead to a lower incidence of thromboembolism and valve-related complications in the later period.

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## INVITED COMMENTARY

Among patients undergoing mitral valve surgery, atrial fibrillation (AF) commonly occurs in approximately 40% to 60% of them [1]. Generally, the presence of this dysrhythmia is associated with adverse cardiovascular outcomes, such as stroke events. Although the benefit of rhythm control has not been shown to be superior to rate control among those with lone atrial fibrillation [2], the favorable effects of restoration to sinus rhythm among patients undergoing mitral valve surgery has been shown in several surgical trials [3]. In this issue, Fukunaga and colleagues [4] demonstrated a reduction in thromboembolic events, notably stroke, and a trend in improved long-term survival among patients whose rhythm has been successfully converted to sinus rhythm after undergoing mitral valve surgery. In this retrospective analysis, patients received different procedures for rhythm surgery, with the standard Cox maze performed in only 10 patients with the majority (ie, 104 patients) being treated with the Kosakai maze. The left atrial procedure was performed in 33 patients, and this procedure has not been consistently considered as maze surgery. The variety of procedures performed in this study may contribute to the interpretation of the results of this study.

Earlier surgical trials for AF with concomitant mitral valve surgery compared a strategy with the maze and

without the maze procedure (2 groups). Patients who did not undergo the maze procedure were used as the control group and were matched with those who have undergone the maze procedure. Of note, most of these trials conclude concomitant maze surgery resulted in a significant reduction of thromboembolic events, notably stroke, but with similar long-term survival [3]. On the other hand, the authors used another approach in their analysis. Those with untreated AF were considered as the control group, and patients who have received the maze procedure were considered the other group; these patients were divided into two groups of those with sinus rhythm that has been restored (sinus group) and those that remained in AF (intractable AF). This strategy allowed simultaneous comparison of the effect of cardiac rhythm and the effect of AF surgery on the outcomes. Importantly, the sinus rhythm group showed significant improvement in the freedom from thromboembolic and all complications compared with the other two groups (sinus group, 80%; intractable AF, 56%; and control, 53%;  $p = 0.002$ ). In addition, there is a trend toward improvement in long-term survival for the sinus group. This trend strengthens the argument for restoration of sinus rhythm among patients undergoing mitral valve surgery.

Surprisingly, the intractable AF group has more thromboembolic complications than the untreated AF