2.3 勧告

データ安全性委員会は上記 2.2 の本試験の安全性に関する結果にもとづいて、主任研究者に対し試験の継続、中止、実施計画の変更を勧告する。

## 3. データ安全性委員会の開催

3.1 開催時期

データ安全性委員会は通常年に一回開催し、本試験のモニタリングを実施する。

重篤な有害事象が発生した等の理由から、主任研究者より委員長あてに開催依頼があった場合、または委員長が委員会を開催する必要性があると判断した場合には、委員長は随時委員会を開催することができる。なお、有害事象の程度および内容によっては、委員間での合意によって電話会議または FAX 会議として開催することができる。

3.2 出席者

データ安全性委員会には「1. 組織」に挙げた委員のほか、運営組織から下記のものが出席できる。

坂東 興　　主任研究者
北村 惣一郎　試験運営委員会委員
福井 次矢　　試験運営委員会委員
佐瀬 一洋　　事務局代表
嘉田 晃子　　解析担当者
京都大学 EBM 共同研究センターデータマネージメント担当者
書記 1 名

ただし、委員のみで行う非公開の審議には、委員のほか書記のみが出席する。また、委員以外には投票権はないものとする。

3.3 議事

データ安全性委員会委員長は以下の議事進行を行う。

1) 試験の進捗状況、運営状況、有害事象等に関する報告
2) 委員と運営組織側出席者間での質疑応答

3) 委員のみによる非公開の審議
薬剤群別有害事象集計の報告
試験の継続、中止、実施計画の変更などに関した討論
4) 試験の継続、中止、実施計画の変更に関する勧告の作成
5) 運営組織側出席者へ勧告を伝える

上記 3)においては書記と解析担当者以外の運営組織側出席者、4) においては書記以外の運営組織側出席者は退席する。

委員のみの非公開の審議中に運営組織側出席者による説明が必要となった場合には、委員長は運営組織側出席者に説明を求めることができる。

委員会終了後、事務局は使用した資料を回収し、封印の上保管する。

## 4. 勧告

委員会終了後、委員長は運営組織側出席者に口頭で、試験の継続、中止、実施計画の変更に関する報告を行う。後日、委員長は同じ内容を「JaSWAT-1 データ安全性委員会審議結果報告書」として、主任研究者あてに事務局へ提出する。

試験の中止を勧告する場合は、詳細な勧告理由を文書にし、主任研究者に提出する。主任研究者はこの中止勧告を試験運営委員会で検討する。その際、主任研究者はデータ安全性委員会での検討内容の報告のため、委員長に運営委員会への出席を依頼する場合がある。

# JaSWAT-1 臨床評価委員会実施手順書

2003年5月1日 Ver.1.0

## 1．組織

臨床評価委員会は、主任研究者及び担当医師から独立した組織であり、本委員会が定める「イベント判定マニュアル」に基づき有効性及び安全性エンドポイントとなるイベントを盲検下で検討し、以下の委員により構成される。

| | |
|---|---|
| 祖父江　元 | 名古屋大学神経内科教授 |
| 井林雪郎 | 九州大学病態機能内科助教授 |
| 苅田典生 | 神戸大学神経内科講師 |
| 長束一行 | 国立循環器病センター脳血管内科医長 |

## 2．臨床評価委員会の役割

2.1 イベント判定

臨床評価委員会はエンドポイント（脳梗塞およびTIA、無症候性脳梗塞、心筋梗塞、全身性塞栓症、死亡、出血）に達した症例の記録用紙、CT、MRIなど評価に必要な資料をもとに、エンドポイントとしての判定が正しいかどうかを検討する。必要があればさらに各施設に追加資料を要求することができる。またその他の有害事象について、本研究との因果関係につき検討し判定結果をデータ安全性委員会に報告する。

2.2 判定結果の報告

臨床評価委員会は、京都大学 EBM 共同研究センターより提出されたエンドポイントに達した症例のリストおよびその他の有害事象リストに、判定結果を記入して京都大学EBM共同研究センターに提出する。

## 3．臨床評価委員会の開催

3.1 開催時期

臨床評価委員会は少なくとも半年に 1 度、または前回の委員会開催から新たに主要エンドポイントに達した症例数が20例を越えた時点で開催する。

3.2 出席者

臨床評価委員会には「1.組織」に挙げた委員のほか、臨床評価委員が委託した者および書記が出席できる。

The Journal of
Thoracic and Cardiovascular Surgery

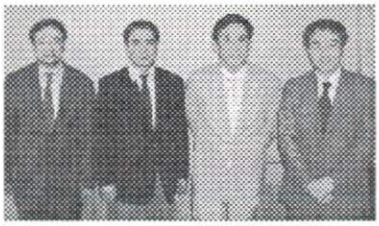
**Impact of preoperative and postoperative atrial fibrillation on outcome after mitral valvuloplasty for nonischemic mitral regurgitation**

Ko Bando, Hitoshi Kasegawa, Yukikatsu Okada, Junjiro Kobayashi, Akiko Kada, Tomoki Shimokawa, Michinori Nasu, Satoshi Nakatani, Kazuo Niwaya, Osamu Tagusari, Hiroyuki Nakajima, Mitsuhiro Hirata, Toshikatsu Yagihara and Soichiro Kitamura

*J Thorac Cardiovasc Surg* 2005;129:1032-1040

# Impact of preoperative and postoperative atrial fibrillation on outcome after mitral valvuloplasty for nonischemic mitral regurgitation

Ko Bando, MD,[a] Hitoshi Kasegawa, MD,[e] Yukikatsu Okada, MD,[d] Junjiro Kobayashi, MD,[a] Akiko Kada, MPH,[c] Tomoki Shimokawa, MD,[e] Michinori Nasu, MD,[d] Satoshi Nakatani, MD,[b] Kazuo Niwaya, MD,[a] Osamu Tagusari, MD,[a] Hiroyuki Nakajima, MD,[d] Mitsuhiro Hirata, MD,[f] Toshikatsu Yagihara, MD,[a] and Soichiro Kitamura, MD[a]



Kobayashi, Okada, Bando, Kasegawa
*(left to right)*

**Objective:** We sought to determine the impact of preoperative or postoperative atrial fibrillation on survival, stroke, and cardiac function after mitral valvuloplasty for mitral regurgitation.

**Methods:** Between 1991 and 2003, 1026 patients with nonischemic/noncardiomyopathy mitral valve regurgitation underwent mitral valve plasty in 3 centers; 663 patients remained in sinus rhythm (group A), and 363 patients had atrial fibrillation or flutter preoperatively (group B) with concomitant maze procedures (group BM, n = 163) or without maze procedures (group BN, n = 200).

**Results:** Eight-year freedom from cardiovascular-related death was better in group A (99.3%) than group B (BM: 96.9%, BN: 81.6%) ($P < .001$) and also better in group BM than group BN ($P = .007$). The adjusted hazard ratio of group B versus group A for preoperative differences was 5.1 (95% confidence interval: 1.8-14.8). Eight-year freedom from stroke was better in group A (99.2%) than group B (BM: 98.2%, BN: 82.6%) ($P < .001$) and also better in group BM than group BN ($P < .001$). Patients with preoperative atrial fibrillation had larger left atria and left ventricular systolic dimensions. The adjunct maze procedure improved left ventricular systolic dimensions over mitral repair alone (group A vs B: $P = .359$; group BM vs BN: $P = .001$).

**Conclusion:** Preoperative permanent/persistent atrial fibrillation was associated with a dilated left atrium and reduced left ventricular function in patients with mitral regurgitation. Including the maze procedure with mitral repair improved survival, late cardiac function, and freedom from late stroke.

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Read at the Eighty-fourth Annual Meeting of The American Association for Thoracic Surgery, Toronto, Ontario, Canada. April 25-28, 2004.

Received for publication May 11, 2004; revisions received Oct 17, 2004; accepted for publication Oct 28, 2004.

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J Thorac Cardiovasc Surg 2005;129:1032-40

0022-5223/$30.00



doi:10.1016/j.jtcvs.2004.10.037

Optimal timing of mitral valve repair for patients with chronic mitral regurgitation is critical and remains controversial.[1] Current American Heart Association/Americal College of Cardiology guidelines for surgery have focused on the onset of symptoms and left ventricular dysfunction.[2] However, waiting until a patient is in New York Heart Association (NYHA) class III or for a reduction of ventricular ejection fraction may result in increased postoperative morbidity and mortality.[3]

Atrial fibrillation (AF) commonly accompanies mitral regurgitation and has been identified as an independent predictor of overall survival and late stroke after surgery for mitral regurgitation.[4] However, there are conflicting reports regarding the impact of AF on late outcome after mitral valve surgery.[5,6] Moreover, little is known regarding the influence of preoperative and postoperative AF on survival and late cardiac function after mitral valve repair.

Recent studies indicated that combining the maze procedure and mitral valve repair reduces the incidence of late stroke,[7,8] but the impact of an adjunct maze procedure on

late survival and cardiac function remains unclear. The purpose of this study was to determine the impact of preoperative and postoperative AF on survival, cardiovascular-related deaths, stroke, and cardiac function after mitral valve repair for nonischemic mitral regurgitation.

## Patients and Methods

Between January 1991 and December 2003, 1026 consecutive patients underwent mitral valve repair at 3 centers: National Cardiovascular Center (n = 332), Sakakibara Heart Institute (n = 379), and Kobe Central City Hospital (n = 315). Thirty-three patients who were initially planned to undergo mitral valve repair but instead underwent mitral valve replacement at initial surgery were excluded from the study. We reviewed data from the operative notes, clinical case histories, and laboratory investigations, including electrocardiograms, echocardiograms, and cardiac catheterization reports. Institutional review board approval for this study was obtained in each institution. Follow-up data were collected from each institution's outpatient records and correspondence with referring physicians. Follow-up data for more than 6 months after operation were available in all patients. The mean follow-up period was 4.3 years, and 8 patients were lost to follow-up within 5 years. Morbid events were analyzed for both the early (in hospital) and late (after discharge) periods.

## Definitions

Preoperative AF was defined as permanent/persistent/paroxysmal AF according to American Heart Association/Americal College of Cardiology guidelines.[9] Preoperative stroke was defined as cerebral thromboembolism diagnosed by a neurologist and confirmed by computed tomography scan and was clearly differentiated from transient ischemic attack. Transient ischemic attacks were not counted as strokes in this study. Causes of death were divided as all cause of deaths and cardiovascular-related deaths. Cardiovascular-related deaths included death from congestive heart failure, arrhythmia, cerebral infarction, cerebral bleeding, and other cardiovascular-related events. We chose to analyze the recurrence of arrhythmia after the first 30 days because early postoperative AF might be caused by different mechanisms than those of permanent/persistent AF. Electrocardiography was performed in each patient within the first 30 days, 6 months after surgery, and at the annual clinic visit of referring physicians or surgeons.

## Patients

Demographic data and preoperative cardiac information are given in Table 1. The patients were divided into groups as follows: 663 patients in sinus rhythm (group A) and 363 patients in permanent AF (n = 310), persistent AF (n = 28), recurrent paroxysmal AF (n = 15), or atrial flutter (n = 10) preoperatively (group B). In group B, a concomitant maze procedure was performed in 163 patients (group BM), whereas the remaining 200 patients (group BN) did not undergo a maze procedure because of the surgeon's preference (eg, the maze procedure was omitted in complex mitral vale repair or severe congestive heart failure), documented duration of AF (>20 years), or emergency surgery.

**TABLE 1. Preoperative clinical characteristics**

| | A (n = 663) | BM (n = 163) | BN (n = 200) | *P* value |
|---|---|---|---|---|
| Gender (male/female) | 396/267 | 109/54 | 129/71 | .166 |
| Age (y) (range/median) | 18-82/56 | 22-79/60 | 19-78/62 | <.001 |
| Hypertension | 58 (9%) | 9 (6%) | 29 (15%) | .009 |
| Diabetes | 15 (2%) | 1 (1%) | 6 (3%) | .278 |
| Stroke history | 19 (3%) | 8 (5%) | 13 (7%) | .051 |
| Renal failure | 5 (1%) | 1 (1%) | 2 (1%) | .910 |
| LA thrombus | 8 (1%) | 5 (3%) | 0 (0%) | .033 |
| NYHA class | | | | |
| I | 69 (10%) | 10 (6%) | 14 (7%) | <.001 |
| II | 369 (56%) | 79 (49%) | 88 (44%) | |
| III | 160 (24%) | 54 (33%) | 77 (39%) | |
| IV | 36 (5%) | 13 (8%) | 15 (8%) | |
| Unknown | 29 (4%) | 7 (4%) | 6 (3%) | |
| LAD | | | | |
| <60 mm | 579 (87%) | 82 (50%) | 137 (69%) | <.001 |
| ≥60 mm | 16 (2%) | 72 (44%) | 58 (29%) | |
| Unknown | 68 (10%) | 9 (6%) | 5 (3%) | |
| LVDs | | | | |
| <40 mm | 439 (66%) | 76 (47%) | 108 (54%) | <.001 |
| ≥40 mm | 152 (23%) | 70 (43%) | 86 (43%) | |
| Unknown | 72 (11%) | 17 (10%) | 6 (3%) | |
| % FS | | | | |
| <25% | 24 (4%) | 24 (15%) | 31 (16%) | <.001 |
| ≥25% | 573 (86%) | 130 (80%) | 164 (82%) | |
| Unknown | 66 (10%) | 9 (6%) | 5 (3%) | |

*LA*, Left atrial; *NYHA*, New York Heart Association; *LAD*, left atrial dimension; *LVD*, left ventricular dimension; *FS*, fractional shortening.

## Surgical Indications and Techniques

Table 2 summarizes the surgical pathology of the mitral valve. Ischemic mitral regurgitation and dilatated cardiomyopathy were excluded from this study. Although combined tricuspid valve surgery and atrial or ventricular septal defect closure were included, patients who underwent combined coronary artery bypass, aortic valve surgery, or aortic surgery were excluded from the study.

Repair of the mitral valve was performed by techniques described by Carpentier[10] and David and colleagues.[11] Prolapse of the mid-scallop of the posterior leaflet was corrected by resection; prolapse of the anterior leaflet was corrected by chordal replacement with polytetrafluoroethylene (Gore-Tex; W. L. Gore and Associates, Inc, Flagstaff, Ariz) sutures.[10,11] Commissural prolapse was repaired by resection and sutures with or without the Kay technique. Patients with longstanding mitral regurgitation and dilated mitral annulus underwent annuloplasty with Carpentier, Duran, or Cosgrove rings, or a handmade ring made by autologous pericardium.[12] In patients undergoing the maze procedure, 3 different techniques were used: Cox maze III (n = 18), Kosakai maze (n = 47), and cryo-maze procedure (n = 98); 5 patients in atrial flutter underwent only the right side of the cryo-maze procedure. The cryo-maze procedure was modified from the Kosakai maze procedure to use cryoablation around the left pulmonary veins, avoiding the incision encircling all 4 orifices of the pulmonary veins.[8,13]

**TABLE 2. Surgical pathology and concomitant surgery**

| | A (n = 663) | BM (n = 163) | BN (n = 200) | P value |
|---|---|---|---|---|
| Cause | | | | |
| Degenerative | 492 (74%) | 111 (68%) | 161 (81%) | <.001 |
| Infective endocarditis | 127 (19%) | 8 (5%) | 18 (9%) | |
| Rheumatic | 24 (4%) | 30 (18%) | 18 (9%) | |
| Congenital | 20 (3%) | 14 (9%) | 3 (2%) | |
| Anterior leaflet involved | | | | |
| Yes | 265 (40%) | 49 (30%) | 97 (49%) | .002 |
| No | 398 (60%) | 114 (70%) | 103 (52%) | |
| Concomitant surgery | | | | |
| TAP | 48 (7%) | 48 (29%) | 59 (30%) | <.001 |
| ASD/VSD repair | 17 (3%) | 13 (8%) | 3 (2%) | .001 |
| Year of operation | | | | |
| 1991-1995 | 170 (26%) | 42 (26%) | 49 (25%) | .263 |
| 1996-2000 | 287 (43%) | 73 (45%) | 110 (55%) | |
| 2001-2003 | 206 (31%) | 48 (29%) | 41 (21%) | |

*TAP*, tricuspid annuloplasty; *ASD*, atrial septal defect; *VSD*, ventricular septal defect.

ACD

## Preoperative and Postoperative Echocardiograph Evaluation

Transthoracic echocardiograms were performed before surgery, at discharge, and annually thereafter. In the majority of the patients, intraoperative echocardiography was performed at the completion of the surgery. Successful mitral valve repair was defined as a maximal mitral regurgitant area less than 2 cm.[2,14] Postoperative echocardiographic examinations were performed during a follow-up period of 4.3 ± 3.2 years after operation. For those patients who died or underwent reoperation during the follow-up period, the last echocardiographic data before death or the secondary surgical intervention were used.[13]

## Postoperative Anticoagulation

All patients were given warfarin sodium for the first 3 postoperative months. Permanent anticoagulation was recommended if AF persisted after operation. In case autologous pericardium was used as a ring annuloplasty, systemic anticoagulation was not performed for patients in sinus rhythm.

## Statistics

All values were expressed as mean ± SD or percentages. The $\chi^2$ or Kruskal-Wallis test was used for comparison. The adjusted hazard ratio (HR) of group B versus group A for death and stroke was estimated by using a Cox proportional hazard model with variables: gender; age; hypertension; diabetes; stroke history; NYHA class; preoperative left atrial dimension (LAD) (<60 mm/≥60 mm); preoperative left ventricular dimension (LVD) (<40 mm/≥40 mm); years of operation; rheumatic, degenerative, infective endocarditis; anterior leaflet involved; and institution. To estimate the adjusted HR of group BN against BM, the propensity score[15] was used in the Cox proportional hazard model. The propensity score (the probability of the maze procedure was combined with that of mitral valve repair in patients with AF) was estimated by multivariable logistic regression by use of the same variables in the Cox proportional hazard model. Survival and freedom from stroke and AF were estimated by using the Kaplan-Meier method. Survival curves were compared with the log-rank test. Echocardiographic variables were compared by $t$ test as percentage changes from preoperation to last follow-up.

## Results

### Patient Background and Surgical Techniques

Patient characteristics among the 3 cohorts are shown in Table 1. Patients in group A were younger and had better NYHA functional class, smaller LAD, and smaller left ventricular systolic dimension (LVDs) when compared with those with preoperative AF (groups BN and BM). Furthermore, patients with infective endocarditis were more likely to be in sinus rhythm, whereas rheumatic patients had a higher incidence of AF before surgery. Among patients with preoperative AF, the use of a concomitant maze procedure was significantly less when anterior leaflet repair was involved. Finally, concomitant tricuspid valve surgery was required more frequently in groups BN and BM than group A (Table 2).

### Postoperative Morbidity and Mortality

Hospital death occurred in 15 patients (1.5%); the causes of deaths included respiratory failure (n = 6), congestive heart failure (n = 4), multisystem organ failure (n = 3), and others (n = 2). Postoperative complications included bleeding (15), respiratory failure (13), renal failure (6), infection (5), low output syndrome (5), cerebral infarction (4), myocardial infarction (3), left ventricular rupture (3), and liver failure (1).

### Freedom from Reoperation and Durability of Mitral Valve Repair

Only 22 patients (3.3%) in group A, 9 patients (4.5%) in group BN, and 7 patients (4.3%) in group BM required reoperation (Appendix 1). Moreover, only 4% to 9% of patients had more than moderate regurgitation in the latest follow-up over 2 years after surgery (Appendix 2).

### Survival and Late Mortality

All patients were followed for at least 6 months after operation. Actuarial survival of group B was significantly lower than group A, and survival of group BN was significantly lower than group BM (Figure 1). Eight-year survivals were 99.3% (A), 96.9% (BM), and 81.6% (BN). Similar trends were observed in freedom from cardiovascular-related deaths (Figure 2).

There were 46 late deaths. The causes of late deaths included cerebral infarction (14), congestive heart failure (8), malignancy (8), cerebral bleeding (4), respiratory failure (2), multisystem organ failure (n = 1), and others (9). Of note, 12 patients remained in AF or had frequent paroxysmal AF after surgery and died of thromboembolic events.

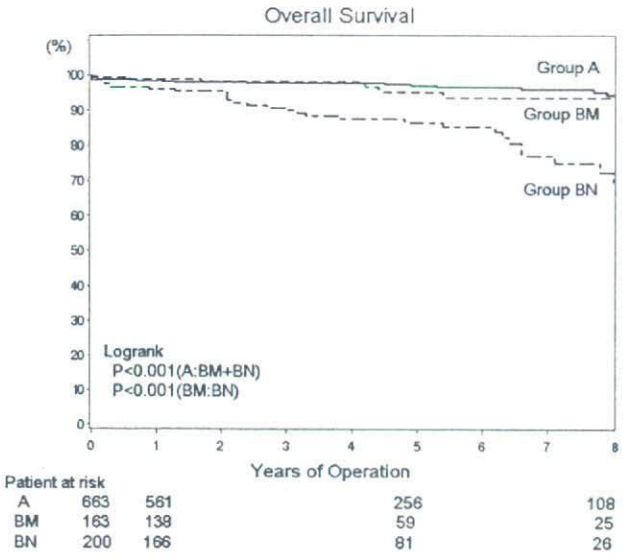


**Figure 1. Overall survival.**

Because significant background variability was observed among the groups, the Cox hazard model was applied to analyze the independent risk factors. The adjusted HR of cardiovascular-related deaths for group B versus group A was 5.1 (95% confidence interval [CI]: 1.8-14.8). The risk for late mortality increased with advanced age (HR: 2.5, 95% CI: 1.4-4.3, 10-year unit) and a preoperative enlarged LAD (HR: 3.3, 95% CI: 1.2-9.0) (Table 3), although the adjusted HR of group BN versus group BM did not reach a significant level (HR: 2.7, 95% CI: 0.4-18.0).

**TABLE 3. Results of Cox analysis for cardiac-related death**

| Variables* | Hazard ratio | 95% CI | *P* value |
|---|---|---|---|
| Group B vs A | 5.12 | 1.77-14.80 | .003 |
| Age | 2.48 | 1.44-4.27 | .001 |
| NYHA (I, II/III, IV) | 2.10 | 0.84-5.23 | .114 |
| Preoperative LAD (<60 mm/≥60 mm) | 3.34 | 1.24-8.99 | .017 |
| Infective endocarditis | 3.03 | 0.58-15.78 | .189 |
| Institution A vs C | 3.48 | 1.01-11.97 | .049 |
| B vs C | 3.33 | 1.01-11.03 | .049 |
| Group BN vs BM† | 2.73 | 0.41-18.01 | .298 |

*CI*, Confidence interval; *NYHA*, New York Heart Association; *LAD*, left atrial dimension. *Variables with *P* value < .20 were presented. †Adjusted by propensity score for maze procedure.

### Incidence of Stroke After Mitral Valve Repair

Twenty-six patients had a late stroke, 23 of whom were aged more than 60 years. Eight-year freedom from stroke was better in group A (99.2%) compared with group B (BM: 98.2%, BN: 82.6%, $P < .001$) (Figure 3).

The adjusted HR of stroke incidence for group B versus group A was 8.7 (95% CI: 2.7-27.9). Risk for late mortality increased with advanced age (HR: 3.4, 95% CI: 1.9-6.4, 10-year unit) (Table 4). For group BN versus group BM, the HR was significantly higher at 7.6 (95% CI: 1.2-47.7).

### Recurrence of AF

We chose to analyze recurrence of arrhythmia after the first 30 days because early postoperative AF might be caused by different mechanisms than those of permanent/persistent AF. In patients with preoperative sinus rhythm (group A), 94.2% (92.4%-96.1%) of patients maintained sinus rhythm

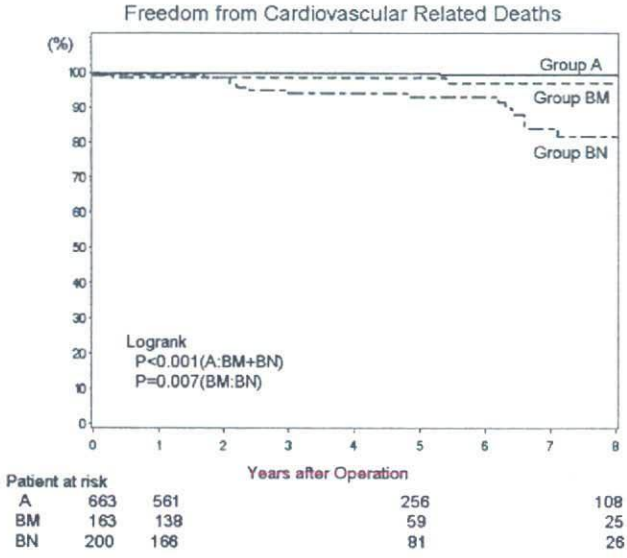


**Figure 2. Freedom from cardiovascular-related deaths.**

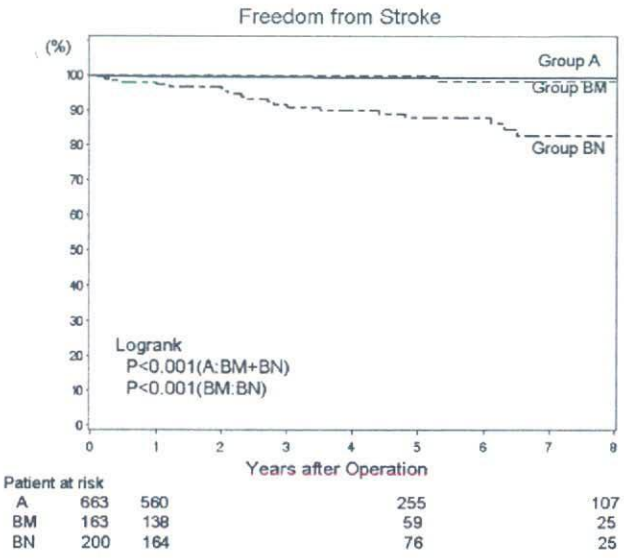


**Figure 3. Freedom from stroke.**

**TABLE 4. Results of Cox analysis for stroke**

| Variables* | Hazard ratio | 95% CI | *P* value |
|---|---|---|---|
| Group B vs A | 8.69 | 2.71-27.89 | <.001 |
| Age | 3.37 | 1.85-6.13 | <.001 |
| Preoperative LAD (<60 mm/≥60 mm) | 2.24 | 0.79-6.34 | .129 |
| Preoperative LVDs (<40 mm/≥40 mm) | 0.47 | 0.17-1.25 | .129 |
| Institution A vs C | 1.27 | 0.32-5.11 | .736 |
| B vs C | 2.84 | 0.88-9.18 | .082 |
| Group BN vs BM† | 7.63 | 1.22-47.66 | .030 |

*CI,* Confidence interval; *LAD,* left atrial dimension; *LVD,* left ventricular dimension. *Variables with *P* value < .20 were presented. †Adjusted by propensity score for maze procedure.

8 years after surgery. In patients who underwent a concomitant maze procedure for preoperative AF (group BM), freedom from AF at 8 years was 80.4% (72.4%-88.3%). Freedom from AF in the group undergoing mitral valvuloplasty alone (group BN) at 8 years was 24.3% (18.1%-30.5%) (Figure 4).

### Impact of Postoperative AF on Late Mortality and Stroke

Because the incidence of postoperative AF was different among the 3 groups, freedom from cardiac-related death and stroke was analyzed separately by postoperative rhythm 1 month after surgery.

In regard to the impact of postoperative rhythm, freedom from cardiac-related death in patients with postoperative regular rhythm was 98.9% (97.9%-100%) compared with 82.1% in those with permanent/persistent AF (73.5%-90.7%) (Figure 5). Freedom from stroke in patients with postoperative regular rhythm was 99.4% (98.7%-100%) compared with 81.0% (73.2%-88.7%) in those withpba permanent/persistent AF after surgery (Figure 6). The summary of stroke- and cardiac-related deaths stratified by postoperative AF is depicted in Appendix 3.

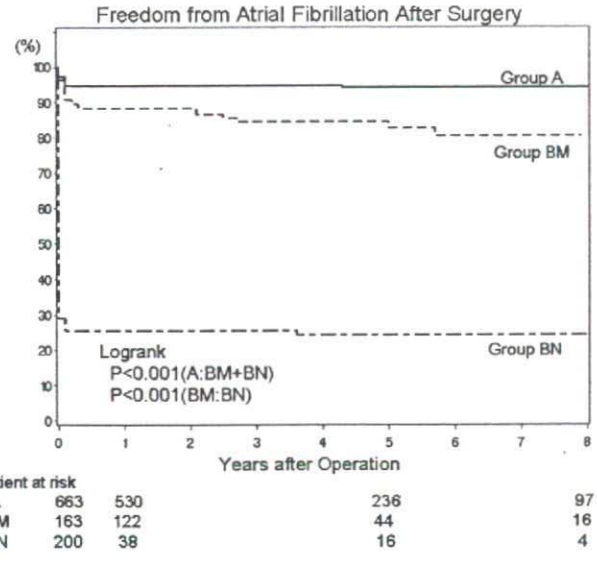


**Figure 4. Freedom from atrial fibrillation after surgery.**

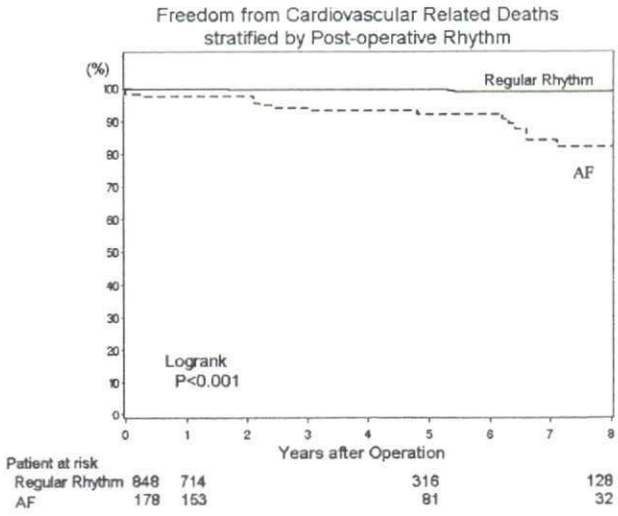


**Figure 5. Freedom from cardiovascular-related deaths stratified by postoperative rhythm. *AF,* Atrial fibrillation.**

### Comparison of Preoperative and Postoperative Echocardiographic Variables

Before surgery, patients with permanent/persistent AF had a larger LAD than patients in sinus rhythm (group A: 45.7 ±

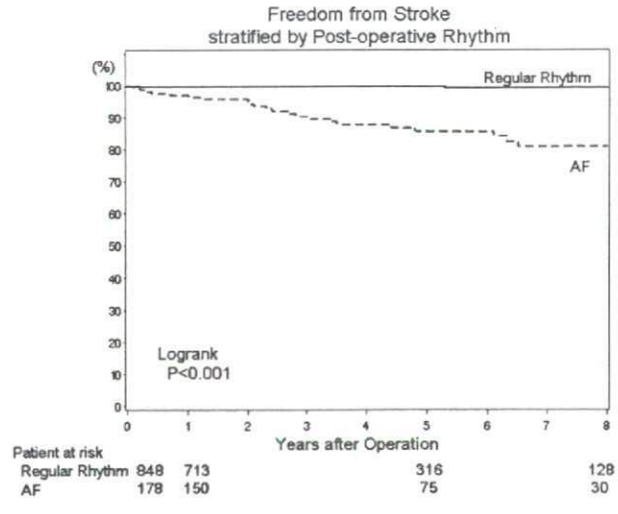


**Figure 6. Freedom from stroke stratified by postoperative rhythm. *AF,* Atrial fibrillation.**

**TABLE 5. Echocardiographic variables**

| Variables | Preoperative | Discharge percentage change | Last follow-up percentage change | *P* value A:BM+BN | *P* value BM:BN |
|---|---|---|---|---|---|
| LAD (mm) | | | | | |
| Group A | 45.7 ± 7.2 (595) | −17.0 ± 14.0 (470) | −11.3 ± 15.3 (313) | .001 | |
| Group BM | 57.8 ± 8.2 (154) | −20.9 ± 11.4 (79) | −23.3 ± 12.6 (122) | | <.001 |
| Group BN | 53.9 ± 10.7 (195) | −18.8 ± 14.6 (178) | −7.1 ± 127.8 (105) | | |
| LVDd (mm) | | | | | |
| Group A | 57.3 ± 7.5 (596) | −17.7 ± 10.5 (492) | −15.5 ± 13.7 (311) | .006 | |
| Group BM | 58.6 ± 9.5 (146) | −12.6 ± 12.7 (75) | −11.5 ± 16.0 (102) | | .574 |
| Group BN | 58.9 ± 7.6 (194) | −14.2 ± 12.2 (180) | −12.6 ± 12.4 (102) | | |
| LVDs (mm) | | | | | |
| Group A | 36.0 ± 6.9 (591) | −7.0 ± 17.4 (485) | −15.0 ± 17.1 (310) | .359 | |
| Group BM | 39.1 ± 7.8 (146) | −4.3 ± 16.3 (73) | −17.9 ± 17.8 (102) | | .001 |
| Group BN | 39.1 ± 7.8 (194) | −6.2 ± 19.8 (178) | −9.1 ± 19.6 (102) | | |

Number of patients is given in parentheses. *LAD,* Left atrial dimension; *LVDd,* Left ventricular end-diastolic dimension; *LVDs,* Left ventricular end-systolic dimension.

7.2 mm; group BM: 57.8 ± 8.2 mm; group BN: 53.9 ± 10.7 mm). After surgical intervention, the LAD size decreased but enlarged again in patients with permanent/persistent AF after surgery (Table 5). Similarly, left ventricular end-diastolic dimension and LVDs decreased after mitral repair in all groups. However, in patients who did not undergo a maze procedure (group BN), late recurrent enlargement of LAD was observed, whereas LAD remained small in groups A and BM late after surgery (>2 years). Furthermore, a significant improvement of LVDs was observed in group BM compared with BN.

## Discussion

In the current study, we elucidated the impact of preoperative and postoperative AF and an adjunct maze procedure on late survival, stroke, and change in echocardiographic indices after mitral valvuloplasty.

This multicenter retrospective study suggests that mitral valve repair before development of AF may have a significantly positive impact on survival and freedom from stroke and improved late cardiac function after surgical intervention. Before surgery, patients in group A generally had smaller LAD and LVDs compared with group B. Accordingly, patients in group A had excellent 8-year freedom from cardiovascular-related death (99.3%) and freedom from stroke (99.2%). In contrast, patients with preoperative AF (group B) had significantly lower freedom from cardiovascular-related deaths (BM: 96.9%, BN: 81.6%) and stroke (BM: 98.2%, BN: 82.6%) 8 years after surgery. Group BM (with adjunct maze procedure) showed similar high freedom from cardiovascular-related death (96.9%) and stroke (98.2%) compared with group A. Thus, the maze procedure may help to improve survival and reduce the incidence of stroke when combined with mitral valve repair as previously reported.[16,17]

Because significant differences were observed in patient demographics and clinical history, the risk factors for late death and stroke were analyzed with the Cox hazard model. Preoperative AF, advanced age, and larger LAD predicted cardiovascular-related mortality late after surgery (Table 3). When groups BM and BN were compared, however, the effect of the maze procedure on survival was not significant when the propensity score was used (Table 3). Preoperative AF and older age were the significant risk factors for late stroke after mitral valve repair. The effect of the maze procedure in reducing the incidence of stroke was confirmed by the Cox hazard model with the propensity score (Table 4). These results suggest that advanced age and omission of the maze procedure in patients with AF are the independent risk factors for stroke after mitral valve repair.

Because 27 patients in group BM had permanent/persistent AF after the maze procedure and mitral valve repair, the impact of postoperative rhythm on survival and stroke was analyzed separately. As shown in Figures 5 and 6, freedom from cardiovascular-related death and stroke was significantly lower in patients with postoperative AF compared with those in sinus rhythm 1 month after surgery.[18] Overall, 26 patients had stroke after mitral valve repair. Twenty of those patients were in group BM and had AF both before and after surgery. Of note, 11 (11/20 = 55%) of those patients were not anticoagulated or were inadequately anticoagulated (international normalized ratio < 1.8) with warfarin at the time of their strokes. The importance of maintaining adequate anticoagulation and ensuring compliance with warfarin in patients with AF deserves reemphasis.[19]

This study was also designed to examine the effect of preoperative rhythm and the maze procedure on late cardiac function. In all groups, LAD decreased after mitral valve repair. However, in patients who did not undergo a maze

procedure (group BN), late recurrent enlargement of LAD was observed, whereas LAD remained small in groups A and BM late after surgery (>2 years). Furthermore, significant improvement of LVDs was observed in group BM when compared with group BN. Thus, left ventricular function may be improved by restoring sinus rhythm after the maze procedure. Although a positive impact of sinus rhythm on cardiac function was observed, we believe these findings are still preliminary because all of the echocardiography indices were load-dependent. Thus, these data may be directly influenced by the alterations in preload and afterload, and the vagaries of medical management. Obviously, further study is necessary to precisely analyze the impact of preoperative and postoperative AF on cardiac function before and after mitral valve repair.

This retrospective multi-institutional study has several limitations. First, the significant number of differences in preoperative background made comparisons difficult among the groups. Patients in sinus rhythm were younger, had better NYHA functional class, and had smaller LAD and LVDs when compared with those with preoperative AF. Thus, it is difficult to precisely blame AF for the decreased survival, reduced freedom from stroke, and inadequate recovery of late cardiac function.

Second, the decision to perform an adjunct maze procedure was primarily according to surgeon preference. Because the Cox maze procedure prolongs cardiopulmonary bypass time, the maze procedure was omitted when patients had complex mitral regurgitation or severe left ventricular dysfunction. However, the cryo-maze technique requires only 20 to 25 minutes of additional aortic crossclamp time, so the adjunct maze procedure is currently performed in the majority of mitral repair cases.[20] The development of easier "mini-maze" or pulmonary vein isolation techniques with better energy sources may further improve the adaptability of this technique.[21] Third, although the length of AF before surgery may have a significant impact on preoperative cardiac function, these indices were not examined because the period of AF before surgery was not clear in 40% of the patients. Fourth, information on left atrial contraction before and after surgery was available in only a few of the patients who underwent maze procedures; thus this information was also not incorporated in this study.[22]

## Conclusion

Preoperative AF was associated with reduced survival and freedom from late stroke after surgery.[23] The addition of a maze procedure improved late cardiac function, survival, and freedom from late stroke. The development of easier "mini-maze" or pulmonary vein isolation techniques with other energy sources may benefit a significant number of patients with AF who require extensive and complex mitral valve surgery.[24]

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## Appendix 1. Freedom from reoperation

| | Freedom from reoperation | | | Reoperation |
|---|---|---|---|---|
| | Year 1 | Year 5 | Year 8 | n (%) |
| Group A | 98.3% (97.3-99.3%) | 96.3% (94.4-98.2%) | 93.5% (90.2-96.3%) | 22/663 (3.3) |
| Group BM | 98.1% (96.0-100%) | 94.3% (89.5-99.1) | 91.7% (84.9-98.5%) | 7/163 (4.3) |
| Group BN | 99.5% (98.5-100%) | 96.3% (93.0-99.5%) | 86.7% (76.6-96.7%) | 9/200 (4.5) |

## Appendix 2. Mitral regurgitation at last follow-up

| | MR, n (%) | | | | |
|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 |
| Group A (n = 325) | 143 (44.0) | 130 (40.0) | 36 (11.1) | 13 (4.0) | 3 (0.9) |
| Group BM (n = 120) | 37 (30.8) | 61 (50.8) | 17 (14.2) | 3 (2.5) | 2 (1.7) |
| Group BN (n = 102) | 42 (41.2) | 30 (29.4) | 21 (20.6) | 6 (5.9) | 3 (2.9) |

*MR,* Mllitral regurgitation.

## Appendix 3. Stroke and cardiac-related deaths stratified by postoperative atrial fibrillation and group

| | Postoperative AF: No | | Postoperative AF: Yes | |
|---|---|---|---|---|
| | Stroke | Cardiac-related deaths | Stroke | Cardiac-related deaths |
| Group A (n = 663) | 2/626 (0.3%) | 5/626 (0.8%) | 2/37 (5.4%) | 1/37 (2.7%) |
| Group BM (n = 163) | 0/137 (0%) | 1/137 (0.7%) | 2/26 (7.7%) | 2/26 (7.7%) |
| Group BN (n = 200) | 0/50 (0%) | 0/50 (0%) | 20/150 (13.3%) | 17/150 (11.3%) |

*AF,* Atrial fibrillation.

## Discussion

**Dr Kevin Accola** *(Orlando, Fla).* I appreciated the opportunity to review your article beforehand. Dr Bando and his colleagues have extensive database experience relative to mitral surgical procedures. They have contributed other reports to this association regarding mitral valve procedures, associated stroke risk, and atrial arrhythmias. Dr Bando now adds to this very informative retrospective review of the impact on treatment of AF with concomitant mitral valvuloplasty using various forms of the maze procedure.

Basically, Dr Bando's data demonstrate the statistically significant survival improvement at 8 years in patients remaining in sinus rhythm compared with those patients who remain in AF after mitral valvuloplasty, therefore demonstrating a definitive benefit in patients in whom a concomitant maze procedure was performed. Also, freedom from cerebrovascular events was significant at 8 years if the patient was in sinus rhythm preoperatively or if a concomitant maze procedure was performed, compared with those patients who remained in AF regardless of anticoagulation status. Patients who underwent maze procedures demonstrated improved LVD and subsequent left ventricular function compared with those patients who remained in AF after mitral valvuloplasty.

Dr Bando, I have 4 questions for you. In your article you differentiated between patients in group B as those in preoperative AF or atrial flutter. How many of these patients were in atrial flutter? Because it is often considered a right-sided phenomenon, did this alter your approach to these patients and does this alter your results?

**Dr Bando.** Question number 1 related to AF versus flutter. We performed maze procedures in 163 patients; 10 of those were in atrial flutter and 5 of those underwent a right-sided maze procedure, but the remaining 158 patients underwent a full maze procedure.

**Dr Accola.** Have you evaluated newer technologies and energy sources, and what are your experiences with these? Have you incorporated these into your mitral valvuloplasty procedures?

**Dr Bando.** In this series, we did not include any of these new devices, but we did have experience with a unipolar radiofrequency catheter in approximately 50 patients. Right now we still have a question about the transmurality of these devices. A good deal of laboratory data is now available to determine the efficacy

of the new devices, such as from Dr Damiano's laboratory. So our policy is just to sit tight and wait and see which device will be the best fit for us.

However, I totally agree with you. For this type of complex mitral valve repair, the easier mini-maze or pulmonary vein isolation with a better source will certainly increase the adaptability of this technique and further benefit a significant number of patients.

**Dr Accola.** Dr Bando, in follow-up of the left ventricle dimensional and functional improvement, did you recognize a decrease in LAD, as you have stated, as well as improved atrial contractility? Did you see increasing atrial function when you went back and reevaluated these patients with follow-up echocardiograms?

**Dr Bando.** There are certain limitations of this large retrospective study, especially, as you pointed out, only part of the patients' data are available in terms of left atrial contractility, and newer techniques, such as the radial approach described by Dr Nitta, certainly will facilitate the contraction of the left atrium. However, we do not have enough information from this retrospective large-scale data.

**Dr Accola.** Last, Dr Bando, regarding anticoagulation, in your article some of the patients who underwent the maze procedure were not anticoagulated postoperatively if they remained in sinus rhythm. Did any of these patients experience cerebrovascular events, and if so, do you think differently now about anticoagulating these patients, considering the numerous left atrial and intra-atrial suture lines present? Would it be safer, possibly, to anticoagulate these patients for a brief period of time postoperatively?

**Dr Bando.** Because we use rings in most patients, we continue the anticoagulation for 3 months, and with the combined maze procedure, those 3 months are the time we see the various types of arrhythmia. If you do not see any types of arrhythmia, we stop the anticoagulation at 3 months after surgery.

However, we did see 2 patients who underwent a failed maze procedure and had a stroke. At that time there was no left atrial contraction confirmed by serial echocardiography. I think it is important to follow these patients with serial echocardiography whether there is left atrial contraction or not. If there is not, I would recommend to continue anticoagulation.

**Dr Eugene H. Blackstone** *(Cleveland, Ohio).* Two concerns. First, I believe that your data are consistent with many other pieces of data that are coming out, so I do not have a concern about that, but I have some concern about an apples and oranges comparison.

Is AF in your case a marker or a risk factor? Your groups are all very different: You have large ventricles in group B, large atria in group B, and older age in group B. All of these are factors that are related to the outcomes that you have mentioned, and yet there seems to be very little that you have done to try to make these groups comparable.

I think the differences you are seeing are probably much larger than real, and I wonder if you have tried to properly adjust the analysis so we know much more truthfully what the differences are?

**Dr Bando.** Maybe I should have sent you the article beforehand, Dr Blackstone. I did mention in my presentation that we performed a multivariate analysis, a Cox hazard model using a propensity score. So any possibility of risk factors or predictors such as hypertension, stroke experience, diabetes, or AF was put into the Cox hazard model, and then we analyzed the data. I would not say we simply divided 3 different groups according to whether this is in AF or not, but we did perform the Cox hazard model.

**Dr David H. Adams** *(New York, NY).* Can you just tell us about your strategy for the left atrial appendage? Did you ligate it and did you consider a reduction atrioplasty in selected patients?

**Dr Bando.** That is a very good point. These are 3 different institutional studies, and I would say that the left atrial appendage was ligated and closed in 65% of patients. However, in some of those different institutions, they do not perform ligation. We would especially not ligate patients in sinus rhythm.

**Impact of preoperative and postoperative atrial fibrillation on outcome after mitral valvuloplasty for nonischemic mitral regurgitation**

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*J Thorac Cardiovasc Surg* 2005;129:1032-1040



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