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Long-Term Results of Mitral Valve Repair for Regurgitation Due to Leaflet Prolapse

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ABSTRACT

BACKGROUND Mitral valve (MV) repair has become the standard therapy for mitral regurgitation (MR) due to degenerative diseases, but information on late outcomes is limited.

OBJECTIVES The purpose of this study was to examine the late results of MV repair for MR in a large cohort of patients.

METHODS A total of 1,234 consecutive patients (median age 59 years; 70.4% men) had MV repair for MR due to leaflet prolapse and were followed prospectively for a median of 13 years (interquartile range: 8 to 34 years) with periodical echocardiographic studies. There were 163 patients still at risk at 20 years. Cumulative incidences of adverse events and associated factors were examined with death as a competing outcome.

RESULTS At 20 years, reoperation-free survival was 60.4% (95% confidence interval: 56.2% to 64.2%) and the cumulative incidence of cardiac and valve-related deaths was 12%, noncardiac deaths 21.3%, reoperation on the MV 4.6%, infective endocarditis 1.1%, thromboembolism 10.3%, and bleeding 6.4%. The probability of recurrent moderate or severe MR was 12.5%, persistent or new moderate or severe tricuspid regurgitation (TR) 20.8%, and new atrial fibrillation (AF) 32.4%. Multivariable analysis identified older age, complete heart block, MV repair without annuloplasty ring, and the degree of myxomatous degeneration of the MV to be associated with recurrent MR. The development of AF and TR was unrelated to recurrent MR.

CONCLUSIONS MV reoperation was uncommon after MV repair, but there was an increasing incidence of recurrent MR, TR, and new AF over time. (J Am Coll Cardiol 2019;74:1044-53) © 2019 by the American College of Cardiology Foundation.

Although there has been no randomized clinical trial on mitral valve (MV) repair versus MV replacement for the treatment of mitral regurgitation (MR) caused by leaflet prolapse secondary to degenerative diseases, numerous retrospective studies have shown that patients' survival and clinical outcomes are better with MV repair than with MV replacement (1-4). It is also believed that even mild degree of left ventricular dysfunction or the presence of symptoms of congestive heart failure (CHF) adversely affect late survival after MV repair (5,6). For this reason, it is generally accepted that asymptomatic patients with severe MR and normal left ventricular function should be considered for surgery if MV repair can be performed safely (7). Consequently, the clinical profile of patients who undergo MV repair has changed, and an increasing number of asymptomatic patients are now being subjected to surgery (8,9). This may be appropriate if MV repair corrects MR and MV function remains stable for a long time. Most studies on the efficacy of MV repair are based on clinical outcomes during the first decade of follow-up and have limited objective assessment of MV function (2-4). This study examined the long-term results of MV repair for MR due to leaflet prolapse in a large cohort of patients who have been followed prospectively with periodical clinical evaluations and echocardiographic assessment of MV function for >2 decades.

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METHODS

From 1981 to 2010, 1,234 consecutive patients had MV repair for MR due to degenerative diseases of the MV with leaflet prolapse and were followed prospectively with clinical assessments by the referring cardiologist (from our and other institutions) and periodical echocardiographic assessment of the MV function at our and other institutions. Patients and referring cardiologists were contacted every 2 to 3 years by our research personnel and the information was entered into a database. Late post-operative paroxysmal or persistent atrial fibrillation was recorded based on the patients' history and confirmed by the cardiologist's consult. In addition to transesophageal echocardiography during the operation (transepicardial before 1987), every patient had a transthoracic study before hospital discharge and a study every 2 to 5 years.

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All operations were performed by 1 surgeon and his residents. The probability of MV repair for MR due to degenerative diseases increased from 50% in 1981 to approximately 99% by 1991 and thereafter. The degree of myxomatous changes in the MV was graded at surgery as none or mild (e.g., fibroelastic deficiency or minimal myxomatous changes), moderate, and severe (5). Prolapse of the leaflets was recorded as isolated posterior leaflet prolapse, isolated anterior leaflet prolapse, or bileaflet prolapse. Surgery was performed through a partial or full median sternotomy, cardiopulmonary bypass, and aortic clamping with myocardial protection with a cardioplegic solution. Prolapse of the posterior leaflet was corrected by limited resection if its height exceeded 20 mm and with chordal replacement with fine Gore-Tex sutures (W.L. Gore & Associates, Inc, Elkton, Maryland) for shorter leaflet (10). Sliding plasty was used for large posterior leaflet involvement of 2 or more segments. Prolapse of the anterior leaflet and of the commissures was corrected mostly by chordal replacement with Gore-Tex sutures. All patients received warfarin sodium post-operatively during the first 3 months and permanently if they were in atrial fibrillation or flutter (AF). The maze procedure was introduced in 1994 in our practice and was performed in patients with persistent AF.

Adverse events were reported according to the guidelines set by cardiac surgical societies (11). The cause of death was determined by hospital charts review, death certificates, or information from the physician who was caring for the patient at that time. This study was approved by the Review Ethics Board of University Health Network, and a waiver of consent had been granted up to June 2016; thereafter, a written consent from patients has been required.

STATISTICAL ANALYSES. Baseline clinical and surgical characteristics were summarized using descriptive statistics. Continuous variables were summarized in terms of mean ± SD or median (interquartile range [IQR]) as appropriate. Dichotomous and polytomous variables were summarized in terms of frequencies and proportions.

DESCRIPTIVE TIME-TO-EVENT ANALYSIS. Reoperation-free survival was described using Kaplan-Meier survival estimates. Patients without an event were censored at the end of their follow-up. Cumulative incidence functions were constructed using a competing risk model and were used to estimate the cumulative incidence of various outcomes in the presence of competing events (i.e., mortality) at specific time points.

REPEATED MEASURES ANALYSIS. Repeated measures logistic regression models were used to estimate the probability of recurrent moderate or severe MR over time. We used independent estimating equations with robust sandwich estimators for standard errors as described by Kurland and Heagerty (12). Moderate or severe MR was defined as MR grades 3 or 4, respectively. MR grade was assessed using post-operative echocardiograms. For subjects who had a valve reoperation, only echocardiograms that occurred after the original surgery and prior to the reoperation were included in the analysis. The same approach was also used to estimate probability of AF and pacing over time. In those cases, however, subjects with pre-operative history of AF or pacing were excluded from the analyses.

RISK FACTOR ANALYSIS. Imputation with lowest risk category was used for risk factors when required for modeling purposes. Single imputation was used because of the very low proportion of missing data (<0.1% in fewer than 5 variables) and because it is reasonable to assume that negative events are less likely to be reported. In some cases, categories were collapsed as required to model effects of risk factors on the outcomes. For time-to-event analyses, there were 2 subjects with confirmed death but unknown date of death. For those subjects, date of death was imputed as the date corresponding to the median survival time within the group of patients who had died. Candidate variables were screened using univariable models. Variables with significant association in univariable models were included in a full multivariable model. Variables that still showed significant association with outcome in the multivariable model were included in

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation/flutter
CD = cardiac death
CHF = congestive heart failure
MR = mitral regurgitation
MV = mitral valve
NCD = noncardiac death
TE = thromboembolism
TR = tricuspid regurgitation

TABLE 1 Pre-Operative Characteristics

Age at surgery, yrs	59 (50-68)
<45	207 (16.7)
45-60	453 (36.7)
61-75	500 (40.5)
>75	74 (5.9)
Male	871 (70.5)
Year of surgery	
1990 or earlier	111 (8.9)
1991-1995	181 (14.6)
1996-2000	290 (23.5)
2001-2005	327 (26.5)
2006-2010	325 (26.3)
Previous operations	
Coronary artery bypass grafting	4 (0.4)
Aortic valve repair	4 (0.3)
Mitral valve repair	6 (0.5)
Other cardiac surgery	13 (1.0)
Timing of surgery	
Elective	1,146 (92.8)
Urgent	88 (7.1)
Presenting symptoms	
Congestive heart failure	557 (45.1)
Angina pectoris	104 (8.4)
Other (fatigue, palpitations, endocarditis, and so on)	329 (26.6)
New York Heart Association functional class	
I	251 (20.3)
II	458 (37.1)
III	425 (34.4)
IV	100 (8.1)
Associated diseases	
Previous infective endocarditis	107 (8.6)
Diabetes	55 (4.4)
Hypertension	366 (29.6)
Hyperlipidemia	304 (24.6)
Chronic obstructive pulmonary disease	16 (1.3)
Previous stroke or transient ischemic attack	64 (5.2)
Peripheral vascular disease	9 (0.7)
Renal failure	3 (0.2)
Marfan syndrome	18 (1.5)
Electrocardiogram on admission	
Sinus rhythm	981 (79.5)
Atrial fibrillation or flutter	241 (19.5)
Complete heart block/pacemaker	12 (0.9)
Left ventricular ejection fraction	
≥60%	822 (66.4)
40%-59%	360 (29.1)
20%-39%	51 (4.1)
<20%	1 (0.1)
Coronary artery disease	175 (14.1)
Tricuspid valve regurgitation	
None, trace or mild	1,180 (95.6)
Moderate or severe	52 (4.3)

Values are median (interquartile range) or n (%). Pre-operative characteristics of 1,234 patients who had mitral valve repair from 1981 to 2010.

TABLE 2 Operative Data

Mitral valve prolapse	
Anterior leaflet	127 (10.3)
Posterior leaflet	572 (46.3)
Both leaflets	535 (43.3)
Degree of myxomatous changes	
None or mild	486 (39.4)
Moderate	463 (37.5)
Severe	285 (23.1)
Mitral annulus calcification	20 (1.6)
Mitral annuloplasty ring	
None	74 (5.9)
Carpentier ring	101 (8.2)
Duran ring	152 (12.3)
Cosgrove band	570 (46.2)
Simplici-T band	339 (27.4)
Chordal replacement with Gore-Tex sutures	851 (68.9)
Patch reconstruction of the mitral annulus	20 (1.6)
Other procedures	
Tricuspid valve repair	55 (4.4)
Replacement of the ascending aorta	11 (0.9)
Closure of atrial septal defect	33 (2.6)
Closure of ventricular septal defect	4 (0.3)
Coronary artery bypass grafting	175 (14.2)
Maze procedure for atrial fibrillation	144 (11.6)
Cardiopulmonary bypass time, min	78 (62-96)
Aortic clamping time, min	62 (47-77)

Values are n (%) or median (interquartile range). Operative characteristics of patients, including mitral valve pathology and concurrent procedures.

the final model. Candidate variables were: age, sex, angina, prior surgery, mitral annulus calcification, cardiopulmonary bypass time, congestive heart failure, coronary artery disease, cross-clamp time, chronic obstructive pulmonary disease, degree of myxomatous changes, diabetes, endocarditis, use neo-chords of Gore-Tex, hyperlipidemia, hypertension, left ventricle grade, Marfan syndrome, mitral leaflet prolapse, mitral annuloplasty ring size, use of MV ring, New York Heart Association (NYHA) functional class, pre-operative AF, pre-operative complete heart block, concurrent maze procedure, previous stroke or transient ischemic attack, repair of congenital defect, tricuspid regurgitation, tricuspid annuloplasty, urgent status, and year of surgery. Time-to-event was modeled using competing risk models (Fine and Gray), and repeated measures data was modeled using independent estimating equations with robust sandwich estimators for standard errors.

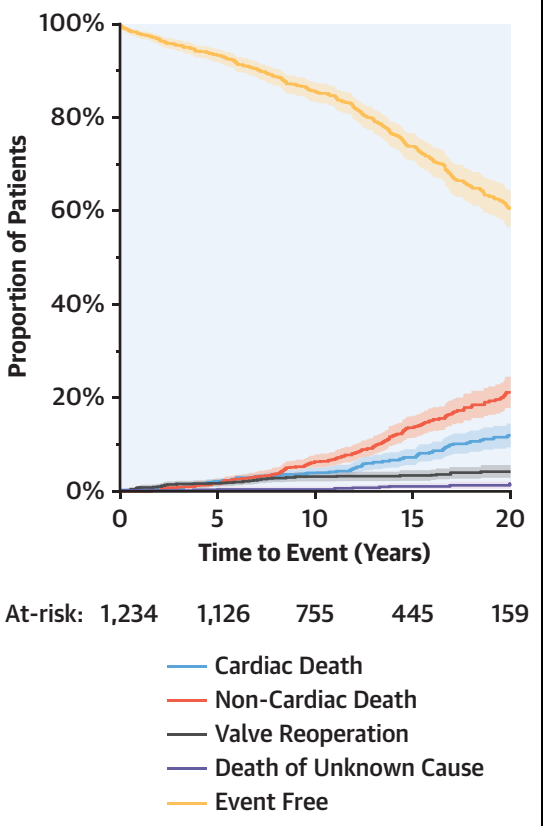
COMPETING RISK AND MULTISTATE MODELS ASSESSING THE ASSOCIATION BETWEEN AF, THROMBOEMBOLISM, CARDIAC DEATH, AND NONCARDIAC DEATH. Competing risk models were applied to assess the association of histories of the

TABLE 3 Rates of Adverse Events

	Number of Events	Incidence Rate (Per 100 Patient-Yrs of Follow-Up)
Death	324	0.203
Early deaths	7	0.004
Late deaths	317	0.198
Cardiac	115	0.072
Noncardiac	193	0.120
Unknown cause	9	0.006
Valve reoperation	48	0.030
Thromboembolic event	108	0.068
Stroke	58	0.036
TIA	49	0.031
Unspecified	1	0.001
Infective endocarditis	11	0.007
Anticoagulation-related hemorrhage	58	0.036
Myocardial infarct	26	0.016
Pacemaker insertion	77	0.048

Adverse events per 100 patient-years of follow-up. Total number of patient-years was 159,778. Late deaths were defined as deaths occurring 90 days or more post-operatively as opposed to in-hospital or early deaths.

FIGURE 1 Patient Survival and Competing Risk for Mortality and Mitral Valve Reoperation



Proportion of patients that remain event-free and cumulative proportion of competing events (cardiac death, noncardiac death, valve reoperation, and death of unknown cause) were calculated using a competing risk model.

post-repair AF and/or thromboembolism (TE) with terminal outcomes, namely, cardiac death (CD) and noncardiac death (NCD), in patients with normal sinus rhythm. The history of post-repair AF and TE was considered as time varying variables, indicating if a patient was ever diagnosed with AF or TE by a time point post-repair. The interaction between the 2 time-dependent variables was also considered. This model was formulated as a multistate model to estimate the cumulative incidence functions of CD with and without a prior history of post-repair AF and/or TE. In the data analysis, we implemented the competing risk model using cause specific hazard regression, estimated the association of AF with terminal events in terms of cause-specific hazard regression, and estimated the association of AF with the terminal events in terms of cause-specific hazard rations. The corresponding 95% confidence intervals (CIs) and p values were calculated using Wald's statistics. We presented the results of this competing risk analysis by graphically showing the estimated cumulative incidence functions for CD and NCD stratified by prior histories of AF and/or TE.

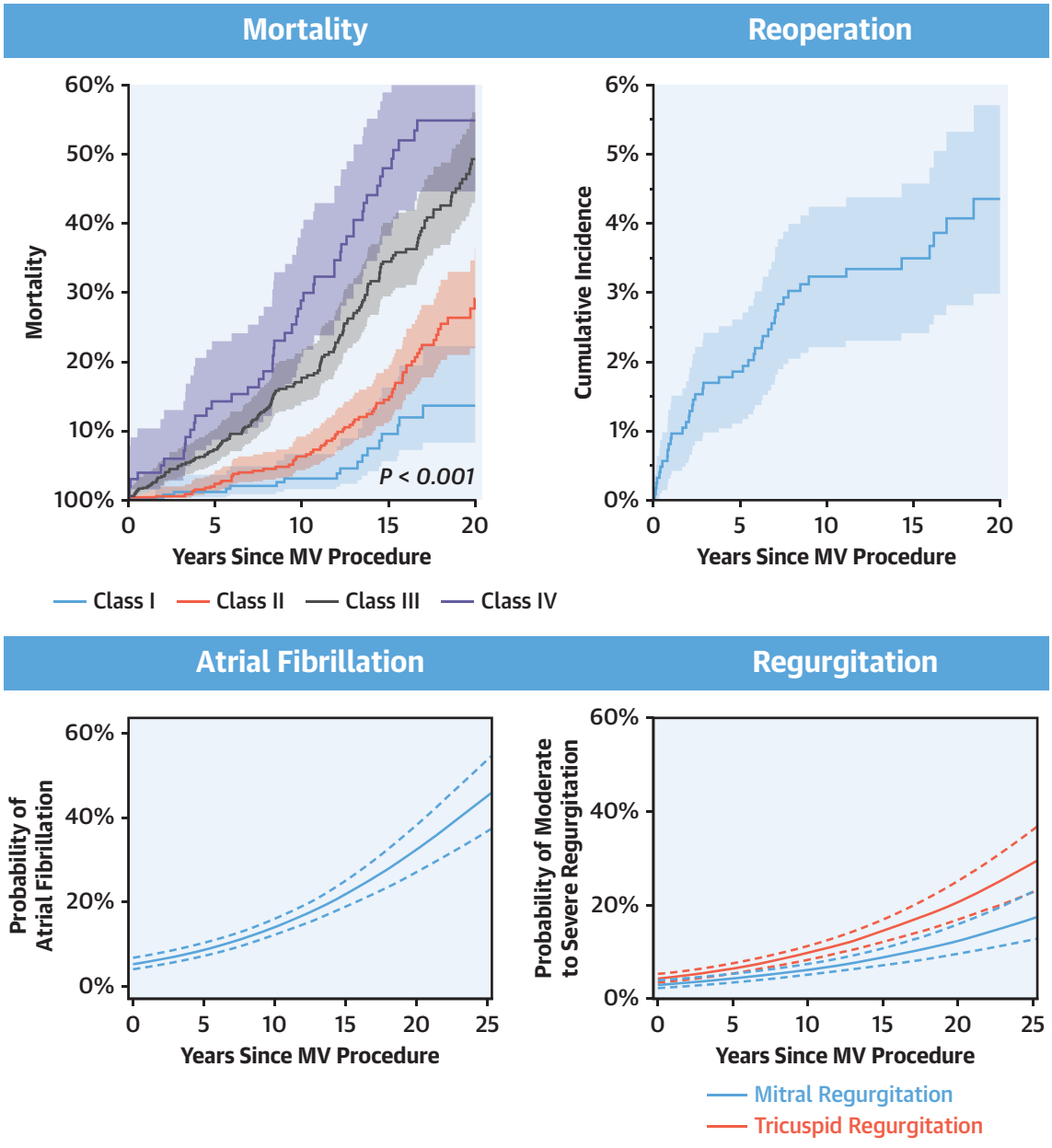
All statistical analyses were performed using either SAS version 9.4 (SAS Statistical Software, Cary, North Carolina) or R version 3.4.1 (R Foundation, Vienna, Austria).

RESULTS

There were 1,234 patients, of which 871 (70.5%) were men. The median age at surgery was 59 years (IQR: 50 to 68 years). Table 1 summarizes the patient characteristics and Table 2 the operative data for all patients. The follow-up for this study was closed on June 30, 2018, and extended from 0 to 34 years, with a median of 13 years (IQR: 8 to 17 years), and 85% complete within the most recent 3 years. The echocardiographic follow-up extended from 0 to 34 years, median 11 years (IQR: 6 to 16 years), and it was 65% complete within the most recent 3 years. The proportion of patients who had echocardiography at 5 to 10 years was 97% and 10 to 20 years was 94%.

MORTALITY AND MORBIDITY. Table 3 shows the rates of adverse events per 100 patient-years of follow-up. The cause of death could not be verified in 9 patients. Figure 1 shows the proportion of patients alive and reoperation-free and the cumulative proportion of competing events, namely CD, NCD, death of unknown cause, and MV reoperations.

CENTRAL ILLUSTRATION **Long-Term Outcomes After Mitral Valve Repair for Leaflet Prolapse**



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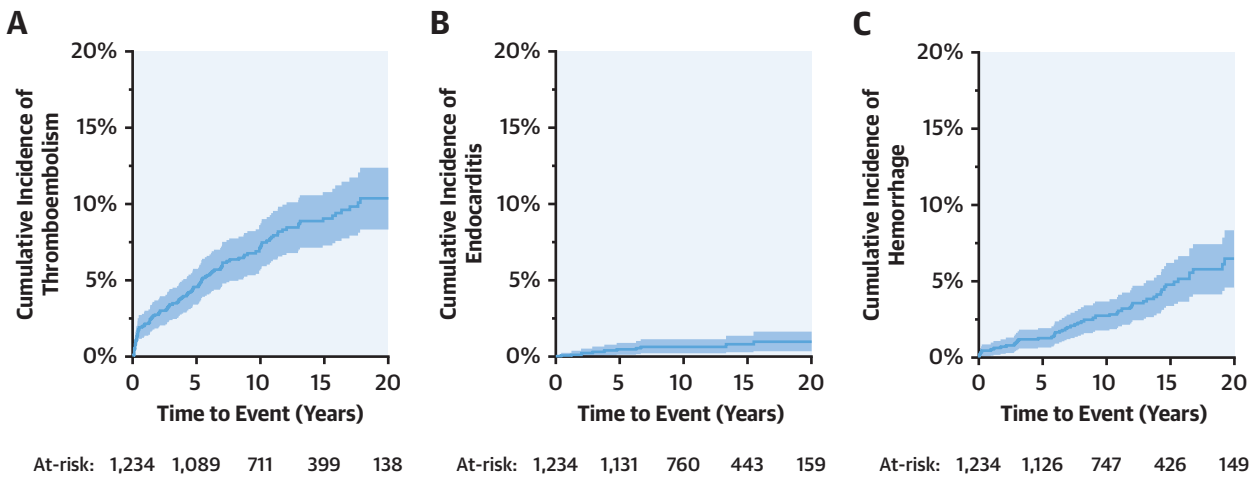
Mortality according to pre-operative functional class and incidences of reoperation on the mitral valve, development of new atrial fibrillation, and moderate or severe mitral and tricuspid regurgitation over the years.

The **Central Illustration** shows patients' survival stratified by pre-operative NYHA functional class. **Figure 2** shows the cumulative proportion of TE, endocarditis, and anticoagulation-related major bleeding with death of any cause as a competing risk. **Table 4** provides the rates of event-free survival and cumulative proportion of competing outcomes at various time intervals. **Table 5** shows the cumulative proportion or estimated probability of other adverse events at various time intervals. **Table 6** shows the results of multivariable analysis to identify risk factors associated with various endpoints.

FIGURE 2 Cumulative Proportions of Adverse Events



Cumulative proportion of **(A)** thromboembolism, **(B)** endocarditis, and **(C)** hemorrhage were calculated using competing risk models with death of any cause as the competing risk. The shaded area represents the 95% confidence interval.

REOPERATION ON THE MV. A total of 48 patients had MV reoperation: 31 for recurrent MR, 5 for hemolysis with MR, 2 for systolic motion of the anterior leaflet of the MV, 5 for endocarditis, and 5 for mitral stenosis due to pannus. Two patients died at reoperation. The MV was re-repaired in 9 patients and replaced in 39. The Central Illustration shows the cumulative incidence of reoperations on the MV.

ENDOCARDITIS. A total of 11 patients developed MV endocarditis: 5 required reoperation and 6 were successfully treated with antibiotics alone. Two patients died.

THROMBOEMBOLIC EVENTS. A total of 109 patients had ≥1 TE events: 58 strokes and 51 transient ischemic attacks. Fourteen patients died following a stroke.

ANTICOAGULATION-RELATED HEMORRHAGE. A total of 58 patients had 1 or more major bleeding episodes, and 11 patients died.

RECURRENT MITRAL REGURGITATION. During the follow-up, 18 patients developed severe MR and 147 moderate MR. The Central Illustration shows the estimated probability of recurrent moderate/severe MR over time, and Table 5 gives the values at various time intervals. Table 7 shows the results of the multivariable analysis on variables associated with recurrent MR.

TRICUSPID REGURGITATION. During the follow-up, 31 patients developed severe tricuspid regurgitation (TR) and 195 had persistent or new moderate TR. Three patients required tricuspid valve repair because of heart failure, and 1 patient died. The Central Illustration shows the estimated probability of moderate/severe TR over time, and Table 5 gives the values at various time intervals. Table 7 shows the results of the multivariable analysis on variables associated with the development of TR.

TABLE 4 Survival Estimates and Cumulative Proportions of Competing Events at Specific Timepoints

	1 Yr	5 Yrs	10 Yrs	15 Yrs	20 Yrs
Event-free survival	98.0 (97.0-98.6)	93.4 (91.9-94.7)	85.5 (83.3-87.5)	74.0 (70.9-76.7)	60.4 (56.2-64.2)
Cardiac death	0.6 (0.1-1.0)	2.1 (1.3-2.9)	4.0 (2.8-5.1)	7.4 (5.7-9.1)	12.0 (9.4-14.5)
Noncardiac death	0.2 (0.0-0.4)	1.9 (1.2-2.7)	6.7 (5.2-8.2)	13.9 (11.5-16.2)	21.3 (17.9-24.5)
Death unknown causes	0.4 (0.0-0.8)	0.6 (0.2-1.1)	0.6 (0.2-1.1)	1.2 (0.5-1.8)	1.7 (0.7-2.8)
Mitral valve reoperation	0.9 (0.4-1.4)	1.9 (1.1-2.6)	3.2 (2.2-4.2)	3.5 (2.4-4.6)	4.6 (3.1-6.0)

Values are % (95% confidence interval). Event-free survival and cumulative proportion of competing events were estimated using a competing risk model.

TABLE 5 Cumulative Proportion or Estimated Probability of Adverse Events

Adverse Outcome	1 Yr	5 Yrs	10 Yrs	15 Yrs	20 Yrs
Endocarditis	0.1 (0.0-0.2)	0.5 (0.1-0.9)	0.8 (0.3-1.3)	0.9 (0.3-1.5)	1.1 (0.4-1.7)
Thromboembolism	2.2 (1.4-3.0)	4.6 (3.4-5.7)	7.2 (5.7-8.7)	9.0 (7.2-10.7)	10.3 (8.3-12.3)
Anticoagulation-related bleeding	0.6 (0.1-1.0)	1.3 (0.7-1.9)	2.7 (1.8-3.7)	4.8 (3.4-6.2)	6.4 (4.5-8.3)
Mitral regurgitation					
Moderate or severe (≥3)	3.3 (2.5-4.2)	4.4 (3.6-5.4)	6.3 (5.2-7.5)	8.9 (7.2-10.8)	12.5 (9.7-15.9)
Severe only (≥4)	0.4 (0.2-0.7)	0.4 (0.3-0.7)	0.5 (0.3-0.8)	0.6 (0.3-1.1)	0.6 (0.3-1.5)
Tricuspid regurgitation					
Moderate or severe (≥3)	4.6 (3.8-5.7)	6.5 (5.5-7.7)	9.8 (8.4-11.3)	14.4 (12.2-17.0)	20.8 (16.9-25.2)
Severe only (≥4)	0.4 (0.2-0.6)	0.5 (0.4-0.9)	0.9 (0.6-1.3)	1.5 (1.0-2.3)	2.5 (1.5-4.2)
New atrial fibrillation	5.8 (4.5-7.4)	8.6 (7.2-10.4)	14.0 (12.2-16.0)	21.8 (18.9-25.1)	32.4 (27.1-38.3)
Permanent pacemaker	1.3 (0.7-2.2)	1.4 (0.9-2.2)	1.6 (1.0-2.3)	1.7 (1.1-2.8)	1.9 (1.0-3.7)

Values are % (95% confidence interval). Cumulative proportion of thromboembolism and endocarditis were estimated using competing risk models with death of any cause as the competing risk. Probability of recurrent moderate to severe mitral regurgitation, atrial fibrillation, or pacing was estimated using independent estimating equations. Subjects with pre-operative arrhythmia were excluded from the estimation of the probability of post-operative atrial fibrillation and pacing.

ATRIAL FIBRILLATION. A total of 232 patients who had sinus rhythm prior to MV repair developed new-onset paroxysmal or permanent AF during the follow-up. The **Central Illustration** shows the estimated probability of new AF over time, and **Table 5** shows the estimated probability of AF at various time intervals. **Table 7** shows the multivariable analysis on factors associated with the development of AF. AF was associated with CD (hazard ratio [HR]: 4.144; 95% CI: 2.361 to 7.271; $p < 0.001$) and NCD (HR: 2.105; 95% CI: 1.456 to 3.044; $p < 0.001$), but it was not associated with thromboembolism (HR: 1.429; 95% CI: 0.909 to 2.248; $p = 0.121$). All patients who developed AF were treated with an oral anticoagulant.

DISCUSSION

MV repair for correction of MR due to degenerative diseases is believed to be superior to MV replacement, but successful repair does not guarantee freedom from cardiac and valve-related morbid events. CHF due to ventricular dysfunction with or without recurrent MR was the principal cause of CDs in this series. Because of the nature of this study, it was sometimes difficult to distinguish CD due to myocardial or valvular disease, so we reported them jointly. This study showed that even mild impairment in left ventricular ejection fraction and the development of symptoms of CHF adversely affected late survival. CHF with or without recurrent MR was the leading cause of CD, and most of these patients could not be helped with further cardiac surgery because of severe ventricular dysfunction. Sudden CD was responsible for 25 deaths in our series. Basso et al. (13) from Italy established a relationship between sudden CD in young patients and MV prolapse (70% had bileaflet prolapse) and fibrosis of the papillary muscles and inferobasal left ventricular wall. We have seen papillary muscle fibrosis during surgery, but we did not document this finding in the operative reports until we read the study by Basso et al. (13). Contrary to the findings of Basso et al. (13), in our series of MV repair, bileaflet prolapse had a protective effect against sudden CD. It has been our impression that MV repair reduces but does not prevent sudden CD in patients with MV prolapse (5). Thus, in the light of the observations by Basso et al. (13), in addition to MV repair, ablation of the possibly arrhythmogenic area may be needed to prevent sudden CD in this subgroup of patients; this can be clarified only through large prospective studies (14).

Flameng et al. (15) were some of the first investigators to show the fallibility of MV repair for leaflet prolapse assessed by echocardiography, and documented a freedom from recurrent moderate or severe MR of only 71% at 7 years. That study was an eyeopener for cardiac surgeons, because previous reports on the success of MV repair were largely expressed by freedom from reoperation on the MV instead of recurrent MR (16). In addition, given the broad spectrum of degenerative diseases that cause MR, certain pathologies are more suitable for MV repair than others and may be associated with higher failure rates (17,18). Castillo et al. (8) reported a 100% MV repair rate in a series of 744 consecutive patients, with more than one-half of patients with complex pathology over a 9-year interval (8). Freedom from recurrent moderate or severe MR at 7 years was 96% in that study (8). These outstanding results can only be

obtained in centers of excellence where large volumes of MV repair are done. In a report by Gammie et al. (19) on the STS Database, the rate of MV repair for leaflet prolapse was 82.7% in a series of 36,554 patients operated on from 2011 through 2016 (19). These differences in MV repair rates have important implications when recommending surgery in asymptomatic patients with MR due to leaflet prolapse (7). MV repair does not cure the underlying degenerative process, and late recurrent MR remains a potential problem (5). The probability of recurrent moderate or severe MR was 12.5% at 20 years in our experience. In a report from the Cleveland Clinic on 6,153 patients who had MV repair, the probability of reoperation on the MV at 18 years was 6.3% for simple MV pathology and 11% for complex MV pathology (18). After decades of experience with MV repair, we still need a second and even a third pump run after completion of the repair because of residual MR, systolic anterior motion of the MV, or other technical error. Imperfect repairs must be addressed intra-operatively if we are to attain a higher standard in late outcomes (20,21).

We were surprised to find a relatively high rate of new AF over time in our patients. Excluding those with pre-operative AF, there was an increase in the probability of new AF over time, which reached 32.4% at 20 years after surgery. AF was associated with CD and NCD by multivariable analysis but not with thromboembolism. However, patients with AF were treated with an oral anticoagulant, and 58 patients experienced serious hemorrhagic complications, with resulting death in 11 patients. In addition, we closed the left atrial appendage orifice at the time of surgery in most of our patients. The development of AF was puzzling and unexplained by the progressive deterioration in MV function over time. Advancing age, the development of moderate or severe TR, advanced pre-operative NYHA functional class, and reduced left ventricular ejection fraction were associated with the development of new AF (**Table 7**). A recent report by Ma et al. (22) from China suggested that a post-operative mean transvalvular gradient >4.5 mm Hg increased the risk of AF after MV repair. Only a few of our patients developed gradients higher than 4.5 mm Hg, possibly because we used mostly posterior annuloplasty bands as opposed to complete rings.

The development of new TR was also puzzling, but severe TR was uncommon after MV repair in a previous analysis of our experience (23). Newer guidelines for the management of TR at the time of left-side valve operations suggest that tricuspid annuloplasty should be performed even if the absence of moderate or severe TR if the tricuspid annulus diameter is ≥40 mm (7). Several centers have adopted this guideline and have performed tricuspid annuloplasty in up to 65% of all patients undergoing MV repair for leaflet prolapse (24). However, 2 recent studies on MV repair challenged this guideline, but both had follow-up duration of less than a decade (25,26). It is possible that much longer follow-up is needed to observe changes in tricuspid annulus diameter. In addition, it has been our experience that dilated right ventricle is probably more important in predicting the development of post-operative TR than a dilated tricuspid

TABLE 6 Final Multivariable Models of Mortality, Cardiac Death, Sudden Cardiac Death, Valve Reoperation and Thromboembolism

	Hazard Ratio (95% CI)	p Value
All-cause mortality		
Age (5-yr increment)	1.576 (1.476–1.681)	<0.001
Diabetes	1.719 (1.131–2.615)	0.011
Hypertension	1.515 (1.206–1.904)	<0.001
Left ventricular ejection fraction (ref: >60%)		
40%–59%	1.711 (1.357–2.157)	<0.001
<40%	4.571 (3.049–6.853)	<0.001
Cardiac death		
Age (5-yr increment)	1.300 (1.168–1.448)	<0.001
LV grade (ref: >60%)		
40%–59%	1.666 (1.113–2.492)	0.013
<40%	3.197 (1.663–6.146)	<0.001
NYHA functional class (ref: I)		
II	2.469 (0.884–6.899)	0.085
III	2.877 (1.025–8.073)	0.045
IV	5.827 (1.997–16.998)	0.001
Leaflet prolapse (ref: posterior leaflet only)		
Anterior leaflet only	1.276 (0.739–2.206)	0.38
Both leaflets	0.638 (0.411–0.991)	0.045
Sudden cardiac death		
Left ventricular ejection fraction (ref: >60%)		
40%–59%	4.015 (1.705–9.454)	0.002
<40%*	–	–
Leaflet prolapse (ref: posterior leaflet only)		
Anterior leaflet only	0.737 (0.219–2.478)	0.62
Both leaflets	0.188 (0.056–0.635)	0.007
Valve reoperation		
Any previous cardiac surgery	3.729 (1.374–10.122)	0.010
Leaflet prolapse (ref: posterior leaflet only)		
Anterior leaflet only	3.790 (1.933–7.432)	<0.001
Both leaflets	1.372 (0.676–2.786)	0.38
Mitral annuloplasty ring (ref: posterior band)		
No ring	0.416 (0.051–3.423)	0.42
Carpentier	2.148 (0.851–5.426)	0.11
Duran	4.181 (2.251–7.767)	<0.001
Thromboembolism		
Age (5-yr increment)	1.114 (1.031–1.204)	0.006
Surgery year (5-yr increment)	0.802 (0.700–0.918)	0.001

Candidate variables were first screened using univariable models. Variables significantly associated with the outcome in univariable models were used to build a full multivariable model. Variables that remained significantly associated in the multivariable model were retained into the final multivariable model. Hazard ratios are reported along with their 95% confidence intervals (CIs) and p value. Models of cardiac death and sudden cardiac death included death of other causes as a competing risk. Models of valve reoperation and thromboembolism included death of any cause as a competing risk. *There were no patients with left ventricular ejection fraction <40% who had sudden cardiac death.

TABLE 7 Final Multivariable Repeated Measures Models of Moderate/Severe Mitral Regurgitation, and Atrial Fibrillation

	OR (95% CI)	p Value
Moderate or severe mitral regurgitation		
Time (1-yr increment)	1.087 (1.064–1.112)	<0.001
Age (5-yr increment)	1.210 (1.100–1.329)	<0.001
Pre-operative complete heart block	4.403 (1.852–10.471)	<0.001
Mitral annuloplasty ring (ref: posterior band)		
No ring	2.168 (1.225–3.836)	0.008
Carpentier	1.146 (0.631–2.080)	0.65
Duran	1.609 (0.959–2.699)	0.072
Degree of myxomatous degeneration (ref: mild)		
Moderate	1.258 (0.821–1.927)	0.292
Severe	2.885 (1.732–4.806)	<0.001
Moderate or severe TR (≥3)		
Time (1-yr increment)	1.101 (1.077–1.191)	<0.001
Age (5-yr increment)	1.272 (1.148–1.409)	<0.001
Pre-operative atrial fibrillation	2.020 (1.383–2.950)	<0.001
Pre-operative complete heart block	5.745 (2.107–15.669)	<0.001
NYHA functional class (ref: class I)		
II	3.732 (1.879–7.412)	<0.001
III	4.558 (2.345–8.861)	<0.001
IV	4.420 (2.107–9.274)	<0.001
Atrial fibrillation		
Time (1-yr increment)	1.149 (1.122–1.177)	<0.001
Age (5-yr increment)	1.475 (1.369–1.590)	<0.001
Tricuspid regurgitation greater than mild	3.473 (1.277–9.447)	0.015
NYHA functional class (ref: class I)		
II	1.370 (0.844–2.226)	0.20
III	1.857 (1.123–3.071)	0.016
IV	1.394 (0.704–2.760)	0.34
Left ventricular ejection fraction (ref: ≥60%)		
40%–59%	1.474 (1.043–2.084)	0.028
<40%	3.452 (1.346–8.855)	0.010

Candidate variables were screened with univariable models and those that were significantly associated with the outcome in univariable models were used to build a full multivariable model. Variables that remained significantly associated in the multivariable model were retained into the final multivariable model. A full multivariable model was constructed with all variables with a significant association in univariable models. Only variables that remained significantly associated with the outcome in the full multivariable model were included in the final model. Odds ratios with 95% confidence intervals (CIs) are reported along with p value.

NYHA = New York Heart Association.

annulus. Yiu et al. (27) found that right ventricular mid-cavity diameter and tricuspid valve tethering area were associated with recurrent TR after tricuspid annuloplasty for functional TR.

STUDY LIMITATIONS. Although our patients were followed prospectively during the past 3 decades, this study has numerous limitations. The clinical evolution of patients was acquired prospectively from patients' information and referring cardiologists' consultations. Assessment of post-operative MV function was performed by echocardiography, and the images were interpreted by various cardiologists as opposed to a central core laboratory. Data on left and right atria, ventricular dimensions, and pulmonary artery pressure were incomplete for more detailed analysis of ventricular function and its effects on outcomes. The causes of death could not be verified in all patients. In addition, certain time-dependent adverse events, such as recurrent MR, and AF developed over time, and we may have underestimated the speed of increase in the cumulative incidence.

CONCLUSIONS

This study documented the late outcomes of MV repair for correction of MR using established operative techniques, including a median-sternotomy, cardiopulmonary bypass with cardioplegic arrest and correction of leaflet prolapse, and annular dilatation. Reoperations on the MV were infrequent, and the probability of recurrent MR was low, but there was a progressive risk of new AF and TR. These results may serve as a benchmark for comparison with newer approaches to correct MR such as minimally invasive surgery and catheter-based techniques.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: MV repair for degenerative diseases associated with MR is generally durable, but ongoing surveillance is needed because of a risk of deterioration of valve function and development of AF in the decades after surgery.

TRANSLATIONAL OUTLOOK: Long-term prospective studies are needed to elucidate the full range of adverse events that may occur following MV repair for MR due to degenerative diseases and define the incidence of heart failure and sudden death.

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