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Impact of Mitral Valve Annuloplasty on Mortality Risk in Patients With Mitral Regurgitation and Left Ventricular Systolic Dysfunction

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OBJECTIVES This study was designed to assess effects of mitral valve annuloplasty (MVA) on mortality in patients with mitral regurgitation (MR) and left ventricular (LV) systolic dysfunction.

BACKGROUND Mitral valve annuloplasty improves hemodynamics and symptoms in these patients, but effects on long-term mortality are not well established.

METHODS We retrospectively analyzed consecutive patients with significant MR and LV systolic dysfunction on echocardiography between 1995 and 2002. Cox regression analysis, including MVA as a time-dependent covariate and propensity scoring to adjust for differing probabilities of undergoing MVA, was used to identify predictors of death, LV assist device implantation, or United Network for Organ Sharing-1 heart transplantation.

RESULTS Of 682 patients identified, 419 were deemed surgical candidates; 126 underwent MVA. Propensity score derivation identified age, ejection fraction, and LV dimension to be associated with undergoing MVA. End points were reached in 120 (41%) non-MVA and 62 (49%) MVA patients. Increased risk of end point was associated with coronary artery disease (hazard ratio [HR] 1.80, 95% confidence interval [CI] 1.30 to 2.49), blood urea nitrogen (HR 1.01, 95% CI 1.005 to 1.02), cancer (HR 2.77, 95% CI 1.45 to 5.30), and digoxin (HR 1.66, 95% CI 1.15 to 2.39). Reduced risk was associated with angiotensin-converting enzyme inhibitors (HR 0.65, 95% CI 0.44 to 0.95), beta-blockers (HR 0.59, 95% CI 0.42 to 0.83), mean arterial pressure (HR 0.98, 95% CI 0.97 to 0.99), and serum sodium (HR 0.93, 95% CI 0.90 to 0.96). Mitral valve annuloplasty did not predict clinical outcome.

CONCLUSIONS In this analysis, there is no clearly demonstrable mortality benefit conferred by MVA for significant MR with severe LV dysfunction. A prospective randomized control trial is warranted for further study of mortality with MVA in this population. (J Am Coll Cardiol 2005;45:381–7) © 2005 by the American College of Cardiology Foundation

Patients with heart failure (HF) due to left ventricular (LV) systolic dysfunction frequently develop mitral regurgitation (MR) because of unfavorable alterations in LV geometry resulting in deformation of the normal mitral valve apparatus and dilation of the ventricular chamber, which in turn lead to incomplete closure of the mitral valve leaflets (1–3).

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The presence of MR in the setting of LV dysfunction is associated with increased mortality (4–6). Previously, surgical treatment of MR was avoided in patients with severe LV systolic dysfunction owing to concern about operative risk and perioperative complications in patients. More recently, with improvements in surgical techniques and increased knowledge of the benefit of preserving the complete mitral valve apparatus for long-term preservation of LV function (7,8), surgical mitral valve annuloplasty (MVA) for MR in the setting of LV dysfunction has become a more popular treatment option. Several published series have shown that postoperative mortality in this population is low, HF symptoms are ameliorated, ventricular size and ejection fraction improve, and intermediate-term outcomes are favorable (9–12). What effect MVA has on long-term outcomes, specifically mortality, in patients with HF attributable to LV dysfunction is not well established. To assess the effect of MVA on mortality in this patient population, we retrospectively analyzed a consecutive series of patients with severe MR and LV systolic dysfunction who received care in the University of Michigan Health System.

METHODS

This study was approved by the University of Michigan Institutional Review Board before data collection. Patients were included in the study population if they had undergone echocardiography in the adult echocardiography laboratory

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
CI = confidence interval
HF = heart failure
HR = hazard ratio
LV = left ventricular
MR = mitral regurgitation
MVA = mitral valve annuloplasty
OR = odds ratio
UNOS = United Network for Organ Sharing

between January 1, 1995, and December 31, 2002, and if they were found to have a LV ejection fraction ≤30% (severe impairment) and had at least moderate to severe MR. Patients were excluded from this analysis if they had undergone previous mitral valve surgery, had a history of complex congenital heart disease, received a cardiac support device as part of a clinical trial in conjunction with MVA, had mitral valve replacement rather than MVA, or had concomitant aortic valve surgery with MVA (patients who underwent concurrent tricuspid valve surgery were included). The study population represents a consecutive series of patients meeting these criteria. All patients undergoing MVA in this study did so in the University of Michigan Health System through the Section of Cardiac Surgery. The surgeries took place as part of clinical care and were performed by one of five different staff surgeons, with the vast majority performed by one of two surgeons (S.F.B. 75%, F.D.P. 15%). The surgical technique used has been previously described (10).

Patients' clinical characteristics at the time of echocardiography were recorded with respect to underlying cause of cardiomyopathy, medical comorbidities, physical examination findings, serum chemistries, medications, and findings on electrocardiography. Records were also reviewed independently by two cardiologists (T.K. and A.W.) and determination was made whether the patients would have a contraindication to referral for MVA. Determinations of surgical candidacy were performed in a manner blinded to the subsequent surgical decision. Conditions considered to be contraindications to surgery included metastatic cancer or any active diagnosis of cancer within five years preceding the index echocardiogram, recent stroke (within six months), severe chronic obstructive pulmonary disease, inoperable coronary disease, renal failure (serum creatinine >3.5 mg/dl, although hemodialysis was not considered a criterion for non-candidacy), inotrope dependency at the time of the index echocardiogram, arrhythmia (life-threatening, refractory to medical therapy necessitating urgent ablation procedure or mechanical support), peripheral vascular disease (accompanied by rest pain or ischemic ulcers requiring surgery or wound care strategies), other comorbidities likely to limit the survival of the patient, moribund state (imminently about to die from severe or multiple medical problems), and urgent transplant evaluation (defined as patient being listed United Network for Organ Sharing [UNOS] status 1A or 1B within 30 days after index echocardiogram). All echocardiograms were performed transthoracically, using standard windows. Quantitative analysis was performed by an experienced echocardiographer. Mitral regurgitation was assessed using color-flow Doppler as mild, mild-moderate, moderate, moderate-severe, or severe (6). Final quantitative and qualitative interpretation of echocardiographic and Doppler imaging was performed by an attending echocardiographer blinded to the subsequent clinical outcome of the patient and as part of usual care.

Statistical analysis. Statistical analyses were performed using SPSS Version 10.0 statistical software (SPSS Inc., Chicago, Illinois). Graphical display of event-free survival was produced using R Version 1.9.1 (R Foundation for Statistical Computing, Vienna, Austria). Results were considered to be statistically significant where $p < 0.05$. Analyses for three patient groups were performed: 1) patients determined to be non-candidates for MVA, 2) candidates for MVA who did not undergo MVA, and 3) candidates for MVA who underwent MVA. Baseline characteristics were determined for each patient group. Chi-square and Wilcoxon rank-sum tests were used to compare categorical and continuous variables, respectively. The primary clinical end point of interest was death, LV assist device implantation, or transplantation from UNOS status 1. Patients transplanted from UNOS status 2 were censored at the time of transplantation.

A propensity score was derived, reflecting the probability that a patient would undergo MVA. This was accomplished by performing a multivariable logistic regression analysis using MVA as the dependent outcome variable and entering all demographics, physical examination findings, electrocardiography and echocardiography measurements, and medications that clinically would likely affect the probability of undergoing MVA. These variables included age, male gender, whether hospitalized at time of index echocardiogram, diabetes, atrial fibrillation, chronic obstructive pulmonary disease, cancer, prior coronary bypass surgery, stroke, blood urea nitrogen, beta-blocker use, angiotensin-converting enzyme (ACE) inhibitor use, spironolactone use, digoxin use, inotrope use, heart rate, mean arterial pressure, presence of implantable cardioverter-defibrillator, LV ejection fraction, LV diastolic dimension, severity of tricuspid regurgitation, paced rhythm, and QRS interval. Stepwise backward elimination was employed and the resultant independent predictors of MVA were then used to calculate the probability of undergoing MVA (propensity score). Only patients felt to be candidates for MVA were included in the propensity score derivation and subsequent survival analysis.

A Cox proportional-hazards model to analyze the effect of MVA on event-free survival was used, treating MVA as a time-dependent covariate. Variables entered into the initial model included demographics, physical examination findings, electrocardiography and echocardiography mea-

surements, and medications. With the propensity score forced into the model, the remaining variables were selected using a backward elimination method. All analyses were performed on the entire dataset and then repeated on the cohort of patients without coronary disease (nonischemic cohort). Coronary artery disease was defined as presence of any coronary stenosis ≥70% diameter, history of myocardial infarction, or history of revascularization.

The graphical display of event-free survival based on the time-dependent covariate of mitral valve annuloplasty was performed according to the method described by Venables and Ripley (13). Using this method, the survival time for the medically treated patients was taken from the time of echocardiogram to the time of event or last follow-up. Each MVA-treated patient was treated as two records. The first record created for the MVA patients represented the pre-MVA treated survival time from the time of the echocardiogram to the time of the MVA. For these records, the MVA coding variable indicated non-MVA and the status variable indicated survival free of event. The second record created for the MVA patients represented the post-MVA treated survival time from the time of MVA to the time of event or last follow-up. In these records, the MVA coding variable indicated MVA, and the status variable was based on the individual patient's event status. The plot of event-free survival based on MVA as a time-dependent covariate was adjusted for the independent predictors identified in the Cox proportional hazards analysis, setting each covariate at the average value for the patient population.

RESULTS

Of the 682 total patients in the study, 419 were felt to be candidates for MVA, and 126 of these underwent MVA. Decisions for candidacy were concordant between the two reviews on 675 of 682 subjects (99%). Survival analysis repeated with either reviewer's candidate decisions did not result in different findings in the study. The reasons for patients determined not to be candidates for MVA included cardiogenic shock (n = 34, 12.9%), metastatic/recent cancer (n = 31, 11.8%), renal failure (n = 30, 11.4%), significant valvular lesion other than MR (n = 30, 11.4%), felt to be too frail to undergo MVA after evaluation by cardiac surgeon or cardiologist (n = 21, 8.0%), severe chronic obstructive pulmonary disease (n = 13, 4.9%), infection (n = 13, 4.9%), delirium or dementia (n = 13, 4.9%), acute myocardial infarction (n = 12, 4.6%), intracranial hemorrhage or recent stroke (n = 12, 4.6%), urgent transplant evaluation (n = 11, 4.2%), cardiac arrest (n = 10, 3.8%), inoperable coronary disease (n = 10, 3.8%), peripheral vascular disease (n = 8, 3.0%), or other reasons (n = 26, 9.9%) (many patients had more than one reason). Other reasons included primarily the coexistence of conditions that increased risk of cardiac surgery (such as dehisced aortic root replacement, pulmonary hypertension, and ventricular septal defect), or medical conditions that limited survival independent of surgery (such as giant cell myocarditis, end-stage liver disease, pulmonary sarcoid, and systemic lupus erythematosus). Baseline characteristics are shown in Table 1. Patients who did not have MVA were as a group significantly younger, were less likely to have coronary artery disease, were more likely to have an implantable cardioverter-defibrillator, and had higher heart rate than patients who did have MVA.

Echocardiography and medication data are shown in Tables 2 and 3, respectively. Compared with the patients who underwent MVA, patients who did not have MVA had

Table 1. Baseline Characteristics

	Candidate Had MVA (n = 126)	Not Candidate (n = 263)	p*	Candidate but No MVA (n = 293)	p†
Male	80 (63%)	152 (58%)	NS	171 (58%)	NS
Age (yrs)	65.5 ± 9.6	65.4 ± 15.1	NS	60.9 ± 15.3	0.006
Hospitalized at time of echocardiogram	61 (48%)	186 (71%)	<0.0001	142 (48%)	NS
Months followed before echocardiogram	7.2 ± 14.1	11.4 ± 18.4	NS	13.2 ± 19.1	0.03
Coronary artery disease	89 (71%)	167 (64%)	NS	150 (51%)	0.0002
Diabetes	33 (26%)	72 (27%)	NS	81 (28%)	NS
Chronic obstructive pulmonary disease	12 (10%)	47 (18%)	0.03	28 (10%)	NS
Stroke	4 (3%)	22 (8%)	NS	17 (6%)	NS
Recent myocardial infarction	10 (8%)	46 (17%)	0.01	11 (4%)	NS
Implantable cardioverter-defibrillator	23 (18%)	60 (23%)	NS	88 (30%)	0.01
Cancer	4 (3%)	24 (9%)	0.03	9 (3%)	NS
Prior coronary bypass surgery	34 (27%)	74 (28%)	NS	70 (24%)	NS
Mean arterial pressure (mm Hg)	85 ± 14	83 ± 17	NS	86 ± 16	NS
Heart rate (beats/min)	80 ± 16	89 ± 20	<0.0001	85 ± 19	0.03
Sodium (mmol/l)	138 ± 4	136 ± 5	0.0002	138 ± 4	NS
Blood urea nitrogen (mg/dl)	29 ± 20	39 ± 24	<0.0001	28 ± 17	NS
Creatinine (mg/dl)	1.4 ± 0.9	2.0 ± 1.7	<0.0001	1.5 ± 1.2	NS
Atrial fibrillation	33 (26%)	80 (30%)	NS	68 (23%)	NS
Paced	11 (9%)	38 (14%)	NS	42 (14%)	NS
QRS interval (ms)	131 ± 37	126 ± 36	NS	128 ± 36	NS

*Had MVA vs. not candidate; †Candidate/had MVA vs. candidate/no MVA.
MVA = mitral valve annuloplasty; NS = not significant (p ≥ 0.05).

Table 2. Echocardiogram Characteristics

	Had MVA (n = 126)	Not Candidate (n = 263)	p*	Candidate but No MVA (n = 293)	p†
Left atrial size (mm)	51 ± 7	48 ± 8	0.001	50 ± 8	NS
Left ventricular diastolic diameter (mm)	65 ± 8	62 ± 10	0.001	65 ± 10	NS
Left ventricular systolic diameter (mm)	54 ± 12	53 ± 12	NS	57 ± 12	0.04
Left ventricular ejection fraction (%)	23 ± 7	20 ± 7	0.0003	19 ± 7	<0.0001
Tricuspid regurgitation			0.0008		NS
None–mild	67 (53%)	91 (35%)		121 (41%)	
Mild/moderate–moderate	38 (30%)	91 (35%)		99 (34%)	
Moderate/severe–severe	21 (17%)	81 (31%)		73 (25%)	

*Had MVA vs. not candidate; †candidate/had MVA vs. candidate/no MVA.
MVA = mitral valve annuloplasty; NS = not significant (p ≥ 0.05).

larger LV systolic dimension and lower LV ejection fraction. The non-MVA group was more likely to be treated with spironolactone when compared to the MVA group. Other medical treatments, such as ACE inhibitors, beta-blockers, digoxin, and intravenous inotropes, did not differ significantly between the MVA and non-MVA groups.

The variables that were significant in the final multivariable logistic regression model defining the propensity scoring included age (per 1 year older, odds ratio [OR] 1.03, 95% confidence interval [CI] 1.008 to 1.05), LV ejection fraction (per 1% point increase, OR 1.09, 95% CI 1.05 to 1.13), and LV diastolic dimension (per 1 mm increase, OR 1.04, 95% CI 1.01 to 1.07). These variables indicate clinical characteristics associated with significantly increased baseline probability to undergo MVA: older age, higher LV ejection fraction, and larger LV dimension. The propensity scores for the non-MVA patients and MVA patients were 0.29 ± 0.13 and 0.37 ± 0.13, respectively ($p < 0.0001$). These results are consistent with the differences seen in baseline characteristics between the MVA and non-MVA groups.

A total of 177 (67%) patients determined not to be candidates for MVA died during the follow-up period. Of those determined to be candidates for surgery, 112 patients (38%) who did not have MVA died versus 61 (48%) of those who had MVA (p = NS). Thirty-day mortality for the MVA group (postsurgical mortality) was 4.8% (6 patients). The combined end point of death, implantation of a LV assist device, or transplantation from UNOS status 1 was reached by 62 (49%) patients who underwent MVA versus 120 (41%) patients who did not have MVA (p = NS).

Results of multivariable Cox regression analysis are shown in Table 4. Factors associated with increased risk of the combined outcome include presence of coronary artery disease (hazard ratio [HR] 1.80, 95% CI 1.30 to 2.49), blood urea nitrogen (per 1 mg/dl increase, HR 1.01, 95% CI 1.005 to 1.02), history of cancer (HR 2.77, 95% CI 1.45 to 5.30), and digoxin use (HR 1.66, 95% CI 1.15 to 2.39). Reduced risk of the combined outcome was associated with ACE inhibitor use (HR 0.65, 95% CI 0.44 to 0.95), beta-blocker use (HR 0.59, 95% CI 0.42 to 0.83), higher mean arterial pressure (per 1 mm Hg increase, HR 0.98, 95% CI 0.97 to 0.99), and higher serum sodium (per 1 mmol/l increase, HR 0.93, 95% CI 0.90 to 0.96). Whether the propensity score was allowed to be removed or was forced into the model did not influence the final prediction model significantly. Mitral valve annuloplasty status, treated as a time-dependent covariate, was not an independent predictor of clinical outcome in this analysis. The event-free survival based on MVA as a time-dependent covariate, adjusted for the independent predictors identified in the Cox proportional hazards analysis, is shown in Figure 1.

After exclusion of subjects with coronary artery disease, the study sample consisted of 276 patients: 96 (35%) patients were determined not to be candidates for surgery, and of the remaining 180 who were believed to be surgical candidates, 37 (21%) underwent MVA. Comparisons of the baseline characteristics of the MVA and the non-MVA

Table 3. Medications

	Had MVA (n = 126)	Not Candidate (n = 263)	p*	Candidate but No MVA (n = 293)	p†
ACE inhibitor	98 (78%)	170 (65%)	0.009	235 (80%)	NS
Beta-blocker	41 (33%)	94 (36%)	NS	125 (43%)	NS
Digoxin	81 (64%)	146 (56%)	NS	190 (65%)	NS
Loop diuretic	99 (79%)	202 (77%)	NS	244 (83%)	NS
Spironolactone	19 (15%)	45 (17%)	NS	81 (28%)	0.006
Nitrate	33 (26%)	77 (29%)	NS	57 (19%)	NS
Hydralazine	5 (4%)	22 (8%)	NS	9 (3%)	NS
Aspirin	73 (58%)	132 (50%)	NS	150 (51%)	NS
Calcium-channel blocker	15 (12%)	24 (9%)	NS	25 (9%)	NS
Inotropes	6 (5%)	40 (15%)	0.003	9 (3%)	NS

*Had MVA vs. not candidate; †candidate/had MVA vs. candidate/no MVA.
ACE = angiotensin-converting enzyme; MVA = mitral valve annuloplasty; NS = not significant (p ≥ 0.05).

Table 4. Results of Multivariable Cox Regression Model Using Backward Stepwise Selection, for Combined End Point of Death, Ventricular Assist Device Implantation, or United Network for Organ Sharing-1 Transplantation

	HR (95% CI)	Chi-Square	p
ACE inhibitor	0.65 (0.44, 0.95)	4.86	0.03
Beta-blocker	0.59 (0.42, 0.83)	9.08	0.003
Blood urea nitrogen (per 1 mg/dl increase)	1.01 (1.005, 1.02)	11.00	0.0009
Cancer	2.77 (1.45, 5.30)	9.43	0.002
Coronary artery disease	1.80 (1.30, 2.49)	12.37	0.0004
Digoxin	1.66 (1.15, 2.39)	7.26	0.007
Mean arterial pressure (per 1 mm Hg increase)	0.98 (0.97, 0.99)	11.87	0.0006
Sodium (per 1 mmol/l increase)	0.93 (0.90, 0.96)	17.47	<0.0001

Variables removed: mitral valve annuloplasty (time-dependent covariate), MVA propensity score, diabetes, age, atrial fibrillation, paced rhythm, hospitalized at time of index echocardiogram, male gender, creatinine, severity of tricuspid regurgitation, chronic obstructive lung disease, spironolactone, heart rate, implantable cardioverter-defibrillator, LV ejection fraction, inotrope, history of stroke, QRS interval, prior coronary bypass surgery, LV diastolic dimension.

ACE = angiotensin-converting enzyme; CI = confidence interval; HR = hazard ratio; LV = left ventricular; other abbreviations as in Table 3.

patients revealed the same differences shown in the larger dataset described earlier. The MVA and non-MVA subjects differed with respect to age (63.4 ± 11.0 years vs. 54.6 ± 16.4 years, p = 0.002), heart rate (81 ± 16 beats/min vs. 90 ± 21 beats/min, p = 0.02), serum sodium (139 ± 5 mmol/l vs. 137 ± 4 mmol/l, p = 0.006), LV ejection fraction (21 ± 6% vs. 17 ± 7%, p < 0.0001), and spironolactone use (19% vs. 36%, p = 0.04). The derived propensity score for the no-coronary-disease cohort consisted of the same variables defined by the all-inclusive cohort: age, LV ejection fraction, and LV diastolic dimension. The Cox proportional hazards analysis, treating MVA as a time-dependent covariate, selected ACE inhibitor use (HR 0.40, 95% CI 0.21 to 0.76, p = 0.005), digoxin use (HR 2.86, 95% CI 1.25 to 6.58, p = 0.01), serum sodium (per 1 mmol/l increase, HR 0.92, 95% CI 0.87 to 0.97, p = 0.001), and QRS interval (per 1 ms increase, HR 1.01, 95% CI 1.00 to 1.02, p = 0.04), but not the time-dependent covariate, as independent predictors of event-free survival. The event-free survival based on MVA as a time-dependent covariate for the patients without coronary artery disease, adjusted for the independent predictors identified in the Cox proportional hazards analysis, is shown in Figure 2.

DISCUSSION

Mitral valve repair, or annuloplasty, is the preferred surgical treatment of functional mitral regurgitation compared to mitral replacement (14,15). Whereas previous studies have demonstrated that MVA is associated with low surgical mortality and leads to improvement of heart failure symptoms in patients with MR and severe LV systolic dysfunction, studies comparing the outcomes of these patients with patients treated medically are not available (9,11,12,16,17). Previous studies of MVA in the setting of ischemic MR have shown that it does not appear to be associated with improved survival compared to coronary artery bypass grafting surgery alone in patients with relatively preserved systolic function (18). Our study does not demonstrate a survival advantage conferred by MVA compared to medical therapy in patients with mitral regurgitation and LV systolic dysfunction. After excluding patients who were not surgical candidates and controlling for potentially confounding clinical factors, the event-free survival was not significantly different between medically and surgically treated patients.

The similar outcomes between the two groups cannot be readily explained by intergroup differences, as baseline characteristics and medical therapy of candidate patients who underwent MVA versus those who did not were largely similar. There were no differences in the use of ACE inhibitors, beta-blockers, digoxin, or loop diuretics. It is likely that the higher use of spironolactone in the non-MVA group is related to care practice differences between University of Michigan Health System cardiologists and cardiologists referring patients for surgical intervention.

There were some differences in baseline characteristics between the two groups that warrant discussion. Most of these differences, including higher heart rate and lower LV ejection fraction, indicate poorer prognosis for the non-MVA group, whereas two—younger age and less coronary

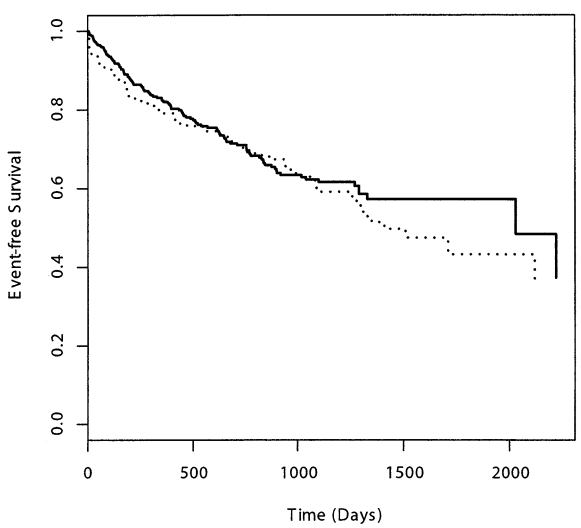

Figure 1. Event-free survival for non-mitral-valve annuloplasty (MVA) group **(solid line)** and MVA group **(dotted line)**.

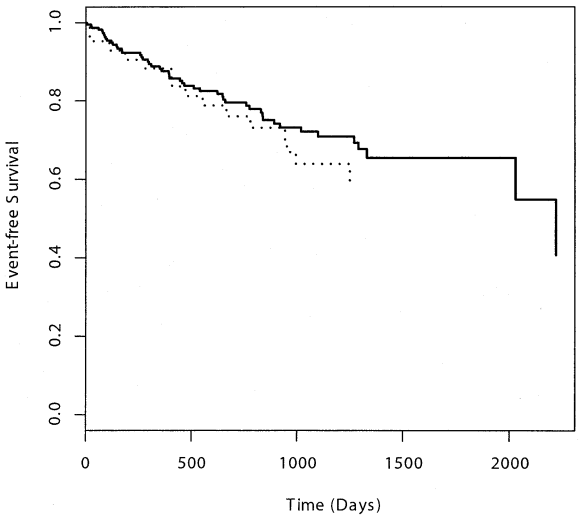

Figure 2. Event-free survival for patients without coronary artery disease in non-mitral-valve annuloplasty (MVA) group **(solid line)** and MVA group **(dotted line)**.

artery disease—would be expected to be associated with better prognosis. Older age has been shown to be associated with poorer survival after mitral valve replacement (19), and may have contributed to worse outcomes after MVA, but in our analysis, age was not associated with mortality, LV assist device implantation, or UNOS status 1 transplantation. Coronary disease was found to be an independent predictor of mortality in this study and represents a key difference in the MVA and non-MVA subjects. After exclusion of patients with coronary disease from the analysis, however, the conclusion regarding the lack of association between mitral surgery and clinical outcomes does not change. The other differences in baseline characteristics would be expected to make prognosis appear worse in the non-MVA group. The presence of lower LV ejection fraction and higher heart rate has been shown to be associated with poor prognosis in HF (20,21).

The surgically and medically treated groups also differed with respect to defibrillator use and spironolactone use. Although each of these therapies has been shown to reduce mortality in patients with systolic heart failure (22–24), neither of these variables was associated with improved survival in our analysis. As these treatments are more likely to be applied to patients with more severe disease, in a retrospective analysis the perceived impact on mortality risk may be diminished. We repeated the multivariable analysis forcing each of these variables into the model and found no change in the predictive value of the MVA time-dependent covariate.

In our multivariable analysis, many of the predictors of clinical outcome (coronary artery disease, serum sodium, blood urea nitrogen, beta-blocker therapy, mean arterial pressure, and ACE inhibitor therapy) are consistent with those factors previously established to have prognostic importance in HF in general. Indicative of an activated renin-angiotensin-aldosterone system, low serum sodium was clearly established as a prognostic indicator in heart failure more than 20 years ago and remains an important marker of disease severity (25). Serum sodium, presence of coronary artery disease, mean arterial pressure, and QRS interval are components of the Heart Failure Survival Score, a multivariable model used to risk stratify ambulatory patients with heart failure (21). The adjusted HRs we obtained for these variables are remarkably similar to those obtained for the Heart Failure Survival Score. Beta-blocker therapy clearly improves mortality in chronic heart failure. Recent meta-analyses have also shown that beta-blocker therapy for heart failure reduces all-cause mortality, cardiovascular mortality, and mortality due to pump failure and sudden death by roughly 31% to 39% (26,27). Consistent with these findings, we found a protective adjusted hazard ratio of 0.59 (95% CI 0.42 to 0.83) imparted by beta-blocker therapy. Our finding that a history of cancer was associated with greater risk of adverse outcome was not surprising, given the increased mortality associated with cancer.

Study limitations. The data presented in this study represent our clinical experience with a consecutive series of patients with MR and severe LV systolic dysfunction rather than a prospective randomized clinical trial. The adverse outcomes assessed in this population of patients may be influenced by factors that could not be assessed in our review of the data (i.e., functional status). Given the complex decision making involved in the determination of surgical candidacy, it is critical that preexisting influences of comorbidities on clinical outcomes be considered. Not measured in our study are the factors that make a patient willing to agree to surgery. We cannot comment on whether these unmeasured factors either made the MVA group higher risk at baseline, the medical group lower risk at baseline, or both, and whether MVA improved clinical outcomes to a degree comparable to that of the medical group. Given the different outcomes of clinical series versus randomized controlled trials, the influence of unmeasured confounding factors is important to consider. The results of the study should be taken in the context of the relatively small sample size included in the analysis, particularly in the noncoronary disease cohort.

There is potential for lead-time bias in this retrospective analysis. We do not know the initial time of diagnosis for each patient. It is possible that patients with severe MR and LV systolic dysfunction referred for surgery from outside the University of Michigan Health System had significant unaccounted survival time before undergoing echocardiography in our clinics or hospital. Candidates for MVA who did not undergo MVA were followed for a longer time period in the University of Michigan Health System before the index echocardiogram compared with candidates who did undergo MVA. We attempted to examine the issue of lead-time bias by comparing whether the patient was hospitalized at the time of echocardiography. There were no differences in the proportion

of patients hospitalized at the time of the index echocardiogram in the MVA or no-MVA groups.

This study analyzes clinical outcomes of patients with treatment initiating from the years 1995 to 2002. Changes in medical treatment and surgical techniques may have improved over this time period, leading to lower mortality rates. Similarly, changes in surgical techniques (i.e., use of rigid, rather than flexible, mitral annuloplasty rings) may lead to a more durable repair and lessen the chance of residual MR postoperatively. Changes in other aspects of perioperative and postoperative medical care of the surgically treated patients may also lead to improved clinical outcomes in more recently treated patients. Furthermore, these data do not include routine postoperative echocardiographic assessment to determine the influence of residual MR on subsequent long-term outcomes.

Conclusions. Despite previous evidence demonstrating hemodynamic and symptomatic improvement with good intermediate-term outcomes, and current low surgical mortality, retrospective analysis of this large cohort of patients with LV dysfunction and significant MR demonstrates no mortality benefit conferred by undergoing MVA. Prognosis in this group of patients is associated with several clinical factors that have been shown previously to be predictive in HF patients in general, whereas undergoing MVA was not associated with the combined end point of death, LV assist device implantation, or UNOS status 1 heart transplantation. Further study with a prospective randomized control trial will be needed to clarify which HF patients will benefit from MVA.

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