

# Sex Differences in Morphology and Outcomes of Mitral Valve Prolapse

Jean-François Avierinos, MD; Jocelyn Inamo, MD; Francesco Grigioni, MD; Bernard Gersh, MD; Clarence Shub, MD; and Maurice Enriquez-Sarano, MD

**Background:** Mitral valve prolapse is more common in women than in men, but men more often have surgery for severe regurgitation.

**Objective:** To compare morphology and outcomes of mitral valve prolapse in men and women.

**Design:** Retrospective cohort study.

**Setting:** The Mayo Clinic, Rochester, Minnesota.

**Patients:** 4461 women and 3768 men who received a diagnosis of mitral valve prolapse by echocardiography from 1989 to 1998 (896 Olmsted County residents and 7333 referred patients).

**Measurements:** Mitral prolapse characteristics (localization, leaflet thickening or flail, regurgitation), ventricular and atrial characteristics, cardiac surgery, and mortality.

**Results:** Compared with men, women had less posterior prolapse (22% vs. 31%), less flail (2% vs. 8%), more leaflet thickening (32% vs. 28%), and less frequent severe regurgitation (10% vs. 23%) ( $P < 0.001$  for all comparisons). Regardless of the severity of regurgitation, left ventricular and atrial diameters were smaller in

women than in men but were larger in women after normalization to body surface area. Among patients with severe regurgitation, women were less likely than men to undergo cardiac valve surgery (52% vs. 60%; adjusted risk ratio, 0.79 [95% CI, 0.74 to 0.84]). At 15 years, women with no or mild mitral regurgitation had better odds of survival than men (87% vs. 77%; adjusted risk ratio, 0.82 [CI, 0.76 to 0.89]), but those with severe regurgitation had worse survival than men (60% vs. 68%; adjusted risk ratio, 1.13 [CI, 1.01 to 1.26]). The survival rate 10 years after surgery was similar in women and men (77% vs. 79%;  $P = 0.14$ ). Observations in Olmsted County patients and referred patients were similar.

**Limitation:** Diagnoses were based on echocardiography, and clinical data at initial diagnosis, reason for index echocardiography, and cause of all deaths were lacking.

**Conclusion:** Morphology and severity of mitral valve prolapse differ according to sex. Among patients with severe regurgitation, women have higher mortality and lower surgery rates than men.

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For author affiliations, see end of text.

Mitral valve prolapse is estimated to affect more than 150 million persons worldwide, with an estimated prevalence of 2.5% of the population (1–3). The severity of mitral regurgitation, the major consequence of prolapse, is the main determinant of outcome and of left ventricular and atrial changes (4, 5). Mitral valve prolapse with severe regurgitation is currently treated with surgery (6), which can be life-saving (7).

Several studies have found important and potentially disturbing sex differences: More women than men have mitral valve prolapse (2, 4), but more men than women have mitral valve surgery (7, 8). The reasons for this discrepancy are unknown (9), and it is unclear whether it reflects differences in prolapse morphology (5) or physiologic differences (such as degree of regurgitation or potentially benign presentation in women) that are essential in influencing outcome (4). It is also unclear whether this difference is linked to differences in ventricular and atrial consequences of mitral valve prolapse, which usually guide surgical indication (6), or to sex-related management differences. Access to surgical management is essential in severe regurgitation to restore life expectancy (5, 7, 10). It is unclear whether women with mitral valve prolapse present with less serious symptoms than men (9, 11) and less often require surgery or whether, for similar severity of mitral valve prolapse and regurgitation, women have cardiac valve surgery less often than men. Finally, the potential survival differences after diagnosis in women versus men with mitral valve prolapse are unknown.

These questions are complex because tertiary care referral may distort apparent disease characteristics (12, 13), and it is essential to examine the consistency of findings in local versus referred patients (14). We identified patients with mitral valve prolapse in our institution according to current criteria (2) and attempted to ascertain sex-specific differences in baseline characteristics, management, and long-term outcome.

## METHODS

### Participants

We searched Mayo Clinic echocardiograms obtained between 1 January 1989 and 31 December 1998 to identify those by which mitral valve prolapse had been diagnosed. If more than 1 echocardiogram was available for a patient, we used only the first to establish the diagnosis (15, 16). The Mayo Clinic institutional review board approved our study. We excluded patients who declined con-

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**Context**

Mitral valve prolapse is more common in women than in men, but men more frequently undergo surgery for severe regurgitation, possibly because of sex differences in disease morphology.

**Contribution**

Among 4461 women and 3768 men with an echocardiogram showing mitral valve prolapse at the Mayo Clinic, Rochester, Minnesota, from 1989 to 1998, women had less frequent severe regurgitation. However, women with severe regurgitation were less likely to have surgery and had worse survival than men. Survival did not differ between men and women who had surgery.

**Implication**

Although women generally have less severe mitral valve prolapse than men, those who do have severe disease have worse survival, possibly because they receive less aggressive therapy.

—The Editors

sent, prisoners, and those who had had mitral valve surgery before the index echocardiogram. We identified patients as being from the local community (Olmsted County, Minnesota, residents) or as being referred from a distance. Because Olmsted County residents are cared for by a few providers linked by the Rochester Epidemiology project, we considered them to be nonreferred patients (14). The Mayo Clinic provides all cardiovascular consultative services and echocardiographic services to county residents, which allowed us to identify those with a diagnosis of mitral valve prolapse.

**Clinical Variables**

We collected information on clinical characteristics at the time of index echocardiography from the electronic summary of inpatient and outpatient medical records established by each patient's personal physician. We reviewed electronic medical and surgical indexes up to the time of mitral valve prolapse and used the Charlson Comorbidity Index to assess comorbid conditions (17). We also electronically collected baseline blood pressure and criteria for severe presentation (congestive heart failure, atrial fibrillation, or ischemic neurologic event before the index echocardiogram) (4, 18).

**Echocardiographic Methods**

All patients uniformly had comprehensive 2-dimensional, M-mode, color and Doppler echocardiographic study during a routine examination. Mitral valve prolapse was diagnosed according to criteria that are current and were also recommended throughout the study period (2, 15): annular overshoot of mitral leaflets greater than 2 mm in long-axis views. Flail leaflets (19) or thickened leaflets (2) were diagnosed on the basis of previously recom-

mended criteria. Measurement of M-mode left ventricular diameter, ejection fraction (20), and left atrial diameter was guided by 2-dimensional echocardiography (21). We categorized the degree of regurgitation (when present) as mild, moderate, or severe on the basis of comprehensive assessment (22), in keeping with American Society of Echocardiography guidelines (23). All Doppler echocardiographic data were those measured originally, obtained by direct electronic transfer from the echocardiographic database without alteration.

For methodological assessment, echocardiograms were reinterpreted in a blinded manner for diagnosis of valve prolapse and thickening in 50 randomly selected study patients and 20 nonstudy patients. Agreement between the initial and reinterpreted echocardiograms was 97% for prolapse ( $\kappa$ , 0.93; mean valve displacement, 3.1 mm [SD, 1.0]) and 93% for leaflet thickening greater than 5 mm ( $\kappa$ , 0.85; mean thickness, 5.6 mm [SD, 1.1] vs. 3.5 mm [SD, 1.0];  $P < 0.001$ ). To assess the consistency of qualitative mitral regurgitation grading, we compared simultaneously obtained regurgitant volume in 89 patients with mild regurgitation, 241 patients with moderate regurgitation, and 441 patients with severe regurgitation (mean degree of regurgitation, 21 mL/beat [SD, 16] vs. 35 mL/beat [SD, 15] vs. 83 mL/beat [SD, 45], respectively;  $P < 0.001$ ), thus demonstrating the general appropriateness of the original qualitative grading.

**Clinical Outcome and Management**

The clinical outcome measure was total mortality. Information on vital status was obtained by using questionnaires, institutional death records, and the National Death Index and was complete for 99.9% of our sample in 2006. Patients' personal physicians conducted clinical management, which we assessed by performance of cardiac valve surgery during follow-up as ascertained from institutional computerized indexes.

**Statistical Analysis**

Baseline characteristics are expressed as means (SDs) or percentages. For direct comparisons between men and women, we used the *t* test or Wilcoxon rank-sum test for continuous variables and the chi-square test for categorical variables without imputations for missing values. Because of age differences, we stratified comparisons by age and tested by analysis of variance (continuous variables) or logistic regression (categorical variables). To examine the effect of potential referral bias on comparisons between men and women, we also stratified those comparisons by geographic origin of patients (local versus referred). We estimated survival and cardiac surgery rates by using the Kaplan–Meier method and compared them between men and women by using the log-rank test and, for multivariate analysis, Cox proportional hazard analysis. Interaction terms between sex and regurgitation severity, geographic origin, or severity of presentation were forced into multi-

variate models and tested. *P* values less than 0.05 were considered significant.

### Role of the Funding Source

The study was funded by the Mayo Clinic, which had no role in the design or conduct of the study or data analysis.

## RESULTS

From 1989 to 1998, 8229 patients had an index echocardiogram that documented mitral valve prolapse. Among these, 896 were Olmsted County residents (who formed our local mitral valve prolapse sample) and 7333 patients were distantly referred.

### Mitral Valve Prolapse in Women with or without Regurgitation

The calendar year of diagnosis was the same in men and women (1993 [SD, 2.9 years] vs. 1993 [SD, 3.0 years]; *P* = 0.120); **Table 1** shows baseline participant characteristics. Anatomically, women had fewer flail leaflets but more anterior and bileaflet prolapse and more leaflet thickening than men. Physiologically, women had lower regurgitation grades, smaller left atrial and ventricular dimensions, and higher ejection fractions than men. Clinically, women had a severe clinical presentation (congestive heart failure, atrial fibrillation, or ischemic neurologic events) less frequently than men. When we stratified patients by age (comparing women and men at age <50 years, 50 to 70 years, and >70 years to account for the younger age of women at diagnosis) and by regurgitation grade, we found that the morphologic sex differences noted in **Table 1** persisted (*P* < 0.001 for all stratified compari-

sons). After excluding flail leaflets, we confirmed these morphologic differences between women and men (*P* < 0.001 for all comparisons).

Thus, sex-specific differences in mitral valve prolapse are not age- or flail-related. Moreover, women represented 39% of referred patients and 49% of local patients with moderate or severe regurgitation who were candidates for surgery, justifying analysis of this specific subset.

### Mitral Valve Prolapse in Women with Moderate or Severe Regurgitation

**Table 2** compares women and men with moderate regurgitation or severe regurgitation. Among these subsets, women and men were of similar mean age (67.1 years [SD, 16] vs. 67.2 years [SD, 13]; *P* = 0.82), and women with moderate regurgitation were slightly younger and those with severe regurgitation were slightly older than men; thus, age plays little role in this regard. Blood pressure also differed little between men and women. Echocardiographically, after stratification for regurgitation severity, women had smaller absolute left ventricular and atrial cavity size than men. The difference between women and men was large: 4 to 5 mm for end-diastolic diameter. Only 5.7% of women reached the classic surgical threshold of left ventricular end-systolic diameter 45 mm or greater, compared with 9.6% of men (*P* < 0.010). However, women tend to be smaller than men, and normalization to body surface area demonstrates greater ventricular and atrial enlargement at the same severity of regurgitation in women compared with men (**Table 2**). Ejection fraction was slightly higher in women than men.

**Table 1. Clinical and Echocardiographic Characteristics at Diagnosis**

Characteristic	Women (n = 4461)	Men (n = 3768)	P Value
<b>Clinical</b>			
Mean age (SD), y	57 (19)	62 (17)	<0.001
Mean body surface area (SD), m <sup>2</sup>	1.7 (0.2)	1.9 (0.2)	<0.001
Mean systolic blood pressure (SD), mm Hg	130 (22)	133 (20)	<0.001
Mean diastolic blood pressure (SD), mm Hg	74 (11)	76 (11)	<0.001
Severe clinical presentation, n (%)*	550 (12)	792 (21)	<0.001
<b>Echocardiographic</b>			
Mean left ventricular ejection fraction (SD), %	63 (8)	60 (9)	<0.001
Mean left ventricular end-systolic diameter (SD), mm	29 (5)	34 (6)	<0.001
Mean left ventricular end-diastolic diameter (SD), mm	48 (6)	54 (7)	<0.001
Mean left atrial diameter (SD), mm	38 (8)	45 (9)	<0.001
Mitral regurgitation, n (%)			<0.001
None	1614 (36)	910 (24)	
Mild	1711 (38)	1131 (30)	
Moderate	690 (16)	854 (23)	
Severe	446 (10)	873 (23)	
Flail leaflet, n (%)	96 (2)	301 (8)	<0.001
Thickened valve, n (%)	1438 (32)	1067 (28)	<0.001
Leaflet localization, n (%)			<0.001
Anterior	832 (18)	511 (13)	
Posterior	1017 (23)	1191 (32)	
Bileaflet	2612 (59)	2066 (55)	

\* Congestive heart failure, atrial fibrillation, or ischemic stroke.

**Outcome of Mitral Valve Prolapse in Women versus Men**

Cardiac valve surgery was performed in 1185 patients during follow-up (mitral valve surgery in 97%). Incidence of cardiac valve surgery 15 years after diagnosis was 5.7% (SD, 3.6) for patients with no or mild regurgitation, 18% (SD, 1) for those with moderate regurgitation, and 57% (SD, 1) for those with severe regurgitation ( $P < 0.001$ ). At 15 years, 15% (SD, 1) of women and 2% (SD, 2) of men ( $P = 0.82$ ) with baseline moderate regurgitation and 52% (SD, 3) of women and 60% (SD, 2) of men ( $P = 0.031$ ) with severe regurgitation had had cardiac valve surgery. After we adjusted for age, ejection fraction, and regurgitation severity, women were less likely than men to be referred for cardiac valve surgery (adjusted risk ratio, 0.79 [CI, 0.74 to 0.84];  $P < 0.001$ ). Multiple imputations in the model for the 599 (7.3%) patients with missing ejection fraction data did not change the magnitude or significance of sex-specific differences.

Cardiac valve surgery was more likely to be done in patients with greater left ventricular absolute diastolic diameter (adjusted risk ratio, 1.06 [CI, 1.05 to 1.07] per mm;  $P < 0.001$ ), which was a better predictor than the body surface area–normalized diameter ( $P = 0.34$ ). Surgery was also more likely to be done in patients with greater absolute atrial diameter (adjusted risk ratio, 1.02 [CI, 1.01 to 1.03] per mm;  $P < 0.001$ ), which again was a better predictor than the body surface area–normalized diameter ( $P = 0.74$ ). Women had cardiac valve surgery less often than men even after adjustment for severity of presentation (adjusted risk ratio, 0.78 [CI, 0.73 to 0.83];  $P < 0.001$ ), diastolic left ventricular diameter (adjusted risk ratio, 0.89 [CI, 0.82 to 0.96];  $P = 0.002$ ), or left atrial diameter (adjusted risk ratio, 0.81 [CI, 0.75 to 0.87];  $P < 0.001$ ).

**Survival**

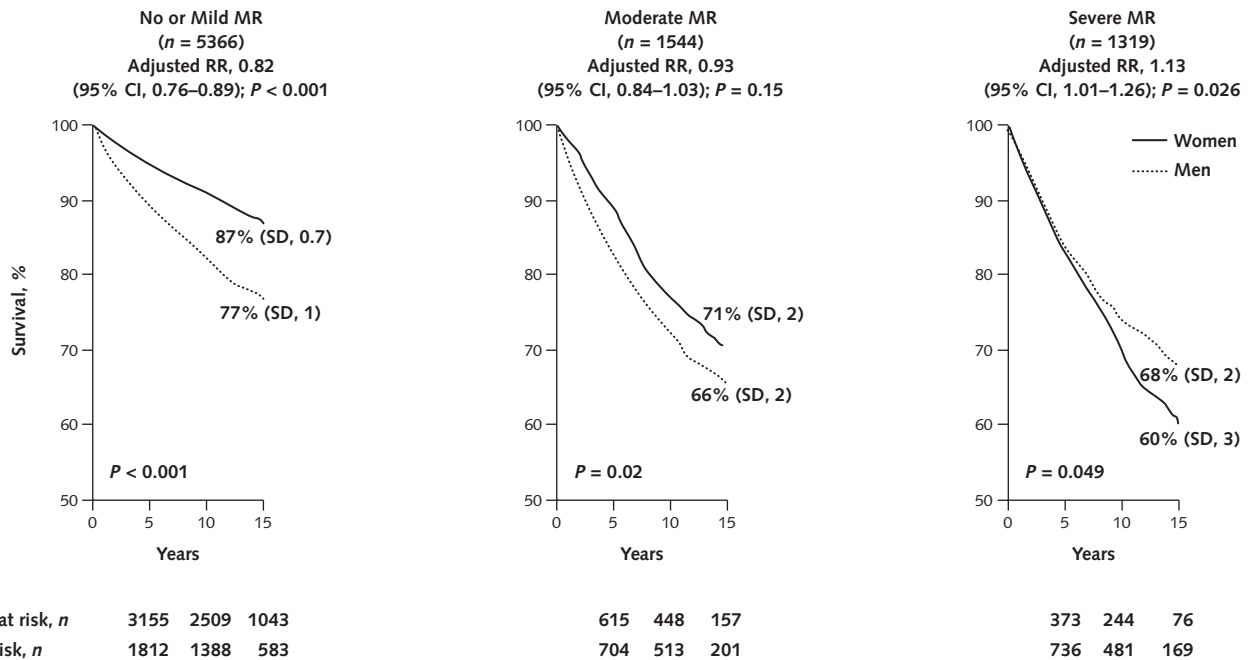
During the mean follow-up of 11.7 years (SD, 4.4), 1690 patients died (2229 patients remained at risk at 15

years). The mean survival rate was 90% (SD, 0.4) at 5 years, 83% (SD, 0.4) at 10 years, and 78% (SD, 0.5) at 15 years. In multivariate models predicting survival, sex and regurgitation severity strongly interacted ( $P < 0.001$ ) and were unaffected by presentation severity ( $P = 0.60$ ). Compared with men, survival at 15 years (Figure) was higher in women with no or mild regurgitation (87% [SD, 0.7] vs. 77% [SD, 1];  $P < 0.001$ ) and slightly higher in women with moderate regurgitation (71% [SD, 2] vs. 66% [SD, 2];  $P = 0.02$ ) but significantly lower for women with severe regurgitation (60% [SD, 3] vs. 68% [SD, 2];  $P = 0.049$ ). After adjustment for age, ejection fraction, presentation severity, and comorbid conditions, women had a lower risk for death than men among patients with no or mild regurgitation (adjusted risk ratio, 0.82 [CI, 0.76 to 0.89];  $P < 0.001$ ), a similar risk among patients with moderate regurgitation (adjusted risk ratio, 0.93 [CI, 0.84 to 1.03];  $P = 0.150$ ), and an excessive risk among patients with severe regurgitation (adjusted risk ratio, 1.13 [CI, 1.01 to 1.26];  $P = 0.026$ ) (Figure). Multiple imputations for missing ejection fraction did not affect the magnitude and significance of sex-specific differences.

We analyzed cause of death in a blinded manner for 750 Minnesotans for whom death certificates were available. For men and women, the rate of cardiovascular causes of death was similar (35% vs. 37%;  $P = 0.75$ ) among the 363 deceased patients with no or mild regurgitation, showed a trend toward being greater in women among the 211 deceased patients with moderate regurgitation (60.7% vs. 47.2%;  $P = 0.054$ ), and was similar among the 176 deceased patients with severe regurgitation (62% vs. 61%;  $P = 0.89$ ). Compared with men, women with all grades of regurgitation had fewer comorbid conditions; mean Charlson Comorbidity Index scores were 0.40 (SD, 1.2) versus 0.65 (SD, 1.6) for those with no or mild regurgitation ( $P < 0.001$ ), 0.56 (SD, 1.4) versus 0.85 (SD, 1.8) for those with moderate regurgitation ( $P < 0.001$ ), and 0.41 (SD, 1.1) versus 0.55 (SD, 1.5) for those with severe re-

**Table 2. Clinical, Left Atrial, and Left Ventricular Characteristics at Diagnosis**

Characteristic	Moderate Mitral Regurgitation (n = 1544)			Severe Mitral Regurgitation (n = 1319)		
	Women	Men	P Value	Women	Men	P Value
Patients, n (%)	690 (45)	854 (55)	–	446 (34)	873 (66)	–
Mean age (SD), y	66 (17)	68 (13)	0.020	68 (15)	66 (14)	0.040
Mean body surface area (SD), m <sup>2</sup>	1.6 (0.2)	1.9 (0.2)	<0.001	1.6 (0.2)	1.9 (0.2)	<0.001
Mean systolic blood pressure (SD), mm Hg	137 (23)	136 (19)	0.40	133 (23)	134 (20)	0.50
Mean diastolic blood pressure (SD), mm Hg	76 (11)	77 (11)	0.20	74 (11)	76 (11)	0.003
Echocardiographic characteristics						
Mean left ventricular ejection fraction (SD), %	62 (9)	59 (10)	<0.001	63 (10)	61 (9)	0.010
Mean left ventricular end-systolic diameter (SD), mm	30 (6)	34 (7)	<0.001	33 (8)	36 (7)	<0.001
Mean left ventricular end-systolic diameter/body surface area (SD), mm/m <sup>2</sup>	19 (5)	18 (4)	<0.001	20 (6)	19 (4)	<0.001
Mean left ventricular end-diastolic diameter (SD), mm	49 (6)	54 (7)	<0.001	55 (8)	59 (7)	<0.001
Mean left ventricular end-diastolic diameter/body surface area (SD), mm/m <sup>2</sup>	30 (6)	28 (5)	<0.001	34 (7)	30 (5)	<0.001
Mean left atrial diameter (SD), mm	43 (8)	46 (8)	<0.001	50 (10)	52 (9)	0.010
Mean left atrial diameter/body surface area (SD), mm/m <sup>2</sup>	26 (5)	24 (5)	<0.001	31 (7)	27 (5)	<0.001

**Figure. Sex-specific differences in survival after diagnosis of mitral valve prolapse.**

$P$  values are for the log-rank direct comparison of survival between women and men. MR = mitral regurgitation; RR = risk ratio.

gurgitation ( $P = 0.09$ ), confirming the lack of other cause of excess mortality in women with severe regurgitation. Cardiac surgery was performed at the same mean age in women and men (61 years [SD, 20] vs. 61 years [SD, 17];  $P = 0.69$ ), and women and men had the same mean post-operative survival rate at 10 years (77% [SD, 2] vs. 79% [SD, 2],  $P = 0.14$ ). Cardiac valve surgery was not associated with significant survival improvement for patients with moderate regurgitation (adjusted risk ratio, 0.88 [CI, 0.65 to 1.18];  $P = 0.39$ ) but did improve survival for patients with severe regurgitation (adjusted risk ratio, 0.79 [CI, 0.63 to 0.98];  $P = 0.030$ ).

#### Local versus Referred Patients

Compared with local patients, referred patients with mitral valve prolapse were older (63 years [SD, 17] vs. 56 years [SD, 20] in men and 58 years [SD, 18] vs. 50 years [SD, 22] in women;  $P < 0.001$ ), had more severe regurgitation (24% vs. 16% in men, 10% vs. 6% in women;  $P < 0.001$ ), had larger ventricular and atrial diameter (45 mm [SD, 9] vs. 41 mm [SD, 9] in men, 39 mm [SD, 9] vs. 36 mm [SD, 7] in women;  $P < 0.001$ ), and were less likely to be women (53% vs. 63%;  $P < 0.001$ ). Nevertheless, anatomical and physiologic sex-specific differences were similar in local and referred populations: Women had less regurgitation, flail, or posterior leaflet prolapse and more valve thickening than men (data not shown). Likewise, we observed sex-specific differences in absolute and normalized ventricular diameters of similar magnitude among local and referred samples (all  $P > 0.100$ ). Geographic origin

did not affect the association between sex and surgery performance ( $P = 0.34$  for interaction) or survival ( $P = 0.86$  for interaction).

#### DISCUSSION

This study in our community (14) and large referral practice analyzes the elusive issue of morphologic and outcome differences in women and men with mitral valve prolapse. The consistency of data from local and referred patients strongly supports genuine differences between men and women, independent of referral bias. Women receive a diagnosis of mitral valve prolapse more often than men, and at a younger age. Women also present with anatomical (more anterior and bileaflet prolapse, more thickened leaflets, fewer flail leaflets) and physiologic (less regurgitation) differences. Thus, women present with benign forms of prolapse more frequently than men. However, women represent a large proportion of patients with moderate or severe regurgitation. In these severe cases, assessment of ventricular enlargement in women is problematic because of body size differences, and women have mitral valve surgery less frequently than men with similar severity of regurgitation. Women with severe regurgitation have greater long-term mortality than men, whereas their survival after surgery is similar to that of men. Therefore, the morphology and outcome of mitral valve prolapse differs by sex. This observation was sustained across local and referred patients.

Women have more valve thickening, which reflects generalized myxomatous degeneration (24) (a chemically active matrix-remodeling process [25]), whereas flail leaflets, which differ structurally from diffusely myxomatous valves (24), predominate in men. These differences are not age-related or attributable to sex-specific screening (4) and represent sex-specific differences in disease mechanisms, as supported by recently suggested X-linked genetic mitral valve prolapse determination (26). Moderate or severe regurgitation affects lower proportions of women than men, but women represent a sizable proportion of patients with such clinically significant regurgitation.

These baseline characteristics may result in differences in management and outcome. Valve thickening affects stroke risk (18), but only modestly, and it does not affect survival of patients with mitral valve prolapse (4), which is highly dependent on regurgitation severity (4). A benign form of mitral valve prolapse is more often diagnosed in women regardless of age (9), a finding that seems to be supported by the predominance of men in surgical series (7, 8) and by smaller ventricular and atrial size in women. This may affect management because cardiac enlargement, considered to reflect regurgitation severity, is recommended to guide surgical indications (6). At a similar severity of regurgitation to men, women less often meet diameter-based surgical guideline criteria (9, 11), which were essentially established in men (27, 28). However, with smaller bodies, women have equal or greater volume overload and ventricular enlargement than men (29). Thus, assessment of left ventricular and atrial enlargement is problematic in women.

Cardiac valve surgery is performed less often in women than men with similar regurgitation severity (11), even after adjustment for ventricular size and clinical severity. The respective roles of surgical referral, patient preference, and associated conditions cannot be separated completely, but this is an important observation because surgery affects outcome. Mitral valve surgery has been consistently linked to reduced mortality (10) and restored life expectancy (7), and similar postoperative survival rates in men and women (30) suggest a similar benefit of surgery regardless of sex. Thus, differences in valve surgery performance may not be inconsequential.

We observed a pattern of changing relative long-term survival of women compared with men depending on regurgitation severity: Survival is greater in women with no or mild regurgitation (known longer life expectancy), similar in those with moderate regurgitation, and worse in those with severe regurgitation. Predominantly cardiovascular mortality in men and women with severe regurgitation, and few comorbid conditions in women minimize potential noncardiac causes of the excess mortality of women with severe regurgitation. These outcome differences are disturbing and challenging and should lead to a careful review of clinical management practices.

Another study (9) suggested morphologic differences

between women and men with mitral valve prolapse, but such differences were difficult to ascertain for important reasons. Stricter diagnostic criteria for mitral valve prolapse were implemented in the late 1980s (16), preventing interpretation of previous reports for comparison of men and women. In addition, the relatively few cases identified in population-based studies (1, 2, 31) prevented comparison of morphologic characteristics. The inference that male sex could be a risk factor for complications (9, 11, 32) originated from a male predominance among patients hospitalized for severe mitral regurgitation due to mitral valve prolapse in tertiary care (5, 7, 8). Hence, it remained uncertain whether observed sex-linked differences were real or related to differential referral, particularly surgical referral, in severe mitral regurgitation (33–35). For outcome after diagnosis, no previous data on surgical referral are available, but the similarity of postoperative survival (30) and mitral valve surgery benefit (10) between men and women is consistent with previous data.

Our study has limitations. Data on sex differences in mitral valve prolapse in the general population are lacking, leaving the question of bias due to echocardiography referral. Analysis of our community is relevant in that all inpatient and outpatient cases were diagnosed in a geographically defined area. Thus, our data provide a consistent benchmark for sex differences in patients referred from tertiary care, decreasing the likelihood that these differences are due to referral bias. We based our study on initial diagnoses of mitral valve prolapse according to current criteria, because previous diagnostic criteria were nonspecific (15, 16); however, we lack information about baseline patient characteristics at the time that mitral valve prolapse may have first been observed. The high agreement between the initial reading of echocardiograms and blinded reinterpretation for diagnosis of mitral valve prolapse and leaflet thickening is reassuring, and although quantitative data could not be obtained in all patients because quantification of regurgitation began during the study period, the high correlation between qualitative grading and regurgitant volume supports the overall reliability of regurgitation grading in the study. Knowledge of direct responsibility of mitral valve–related events in sex-specific differences in outcome would be desirable, but such information cannot be extracted from routine clinical follow-up or certificates of death. High and similar cardiac mortality in men and women with severe regurgitation suggests such a link.

We cannot state with certainty the cause of differences in valve surgery performance and survival between men and women with mitral valve prolapse and severe regurgitation. However, defining morphologic and outcome differences between men and women is an essential step toward improving the clinical management of all patients with mitral valve prolapse and in planning future research. A potential causal link between underestimation of mitral valve prolapse and regurgitation severity because of lower unadjusted cavity size, leading to less cardiac valve surgery

referral and excess mortality among women with severe regurgitation, would be disturbing. Studies are needed to examine this hypothetical link. Although our study was large, it cannot replace a clinical trial of the benefits of valve surgery in men and women with mitral valve prolapse.

The presentation of mitral valve prolapse is more often benign in women than in men, but not uniformly so. Because women with moderate or severe mitral regurgitation incur outcomes similar to or worse than those of men, women also require careful risk stratification, watchful attention, and consideration for surgical management.

Use of absolute ventricular diameter as an indirect measure of volume overload due to mitral regurgitation is problematic in women because of their smaller body size. An analogous phenomenon in aortic regurgitation (29) led to an emphasis on the use of ventricular dimensions normalized to body size (36). Normalization of cardiac size to body size should be strongly considered for mitral regurgitation as well (37). Another important approach to avoiding underestimation of regurgitation requires the quantitative assessment recommended by the American Society of Echocardiography (23) for baseline risk stratification independent of sex (10).

In conclusion, women with mitral valve prolapse have important differences in morphologic characteristics and outcome compared with men. Women present more often with thick leaflets and less often with flail leaflet, posterior leaflet prolapse, or severe regurgitation. Although the presentation of mitral valve prolapse is more often benign in women, this setting represents a clinical challenge. In women, assessment of cardiac enlargement is problematic. Women have mitral valve surgery less often than men, and women with severe regurgitation incur greater long-term mortality than men. These sex-specific differences should be addressed in studies aimed at improving management and outcome of mitral valve prolapse and regurgitation.

From Hôpital La Timone, Marseille, France; Ospedale de l'Università di Bologna, Bologna, Italy; and the Mayo Clinic, Rochester, Minnesota.

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**Requests for Single Reprints:** Maurice Enriquez-Sarano, MD, Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905; e-mail, sarano.maurice@mayo.edu.

Current author addresses and author contributions are available at [www.annals.org](http://www.annals.org).

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**Current Author Addresses:** Dr. Avierinos: Service de Cardiologie, Hôpital La Timone, Marseille, France.

Dr. Inamo: Service de Cardiologie, Centre Hospitalo-Universitaire Fort-de-France, Fort-de-France, France.

Dr. Grigioni: Clinica de Cardiologia, Ospedale de l'Università di Bologna, Bologna, Italy.

Drs. Gersh, Shub, and Enriquez-Sarano: Mayo Clinic, 200 First Street SW, Rochester, MN 55905.

**Author Contributions:** Conception and design: J.F. Avierinos, M. Enriquez-Sarano.

Analysis and interpretation of the data: J.F. Avierinos, F. Grigioni, C. Shub, M. Enriquez-Sarano.

Drafting of the article: J.F. Avierinos, F. Grigioni, C. Shub, M. Enriquez-Sarano.

Critical revision of the article for important intellectual content: J.F. Avierinos, J. Inamo, F. Grigioni, C. Shub, M. Enriquez-Sarano.

Final approval of the article: J. Inamo, C. Shub, M. Enriquez-Sarano.

Provision of study materials or patients: M. Enriquez-Sarano.

Statistical expertise: J.F. Avierinos, M. Enriquez-Sarano.

Obtaining of funding: M. Enriquez-Sarano.

Administrative, technical, or logical support: B. Gersh.

Collection and assembly of data: J.F. Avierinos, J. Inamo, M. Enriquez-Sarano.