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Sex Differences in the Morphology and Outcomes of Mitral Valve Prolapse: A Cohort study

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Abstract

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 prolapse in men and women

Design—Retrospective cohort study

Setting—Mayo Clinic

Patients—4461 women and 3768 men diagnosed with mitral valve prolapse on echocardiogram 1989–98 (896 Olmsted County residents and 7,333 referred patients)

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

Results—Compared to 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%; all $p < 0.001$). At each level of regurgitation, left ventricular and atrial diameters were smaller in women than in men but were larger after normalization to body-surface-area in women than in men. Among patients with severe regurgitation women were less likely than men to undergo cardiac valve surgery (52% vs. 60%, adjusted RR 0.79[0.74–0.84]). At 15-years, women with no/mild mitral regurgitation had better survival than men (87% vs. 77%, adjusted RR 0.82[0.76–0.89]) but those with severe regurgitation had worse survival than men (60% vs. 68%, adjusted RR 1.13[1.01–1.26]). Survival 10-years after surgery was similar in women and men (77% vs. 79%, $p = 0.14$). Our observations were similar in Olmsted County and referred patients.

Limitations—Diagnosis based on echocardiogram, absence of clinical data at previous initial diagnosis, reason for index echocardiogram and cause of death.

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Availability of data: The dataset and statistical code cannot be made available.

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Conclusion—There are sex differences in the morphology and severity of mitral valve prolapse. Among patients with severe regurgitation, women have higher mortality and lower surgery rates than men.

Introduction

Mitral valve prolapse with prevalence estimated around 2.5% of the population,(1–3) is estimated to affect in excess of 150 million subjects worldwide. Mitral regurgitation is prolapse's major consequence and its severity (from absent to severe) is the main determinant of outcome and of left ventricular and atrial alterations.(4,5) Current treatment of mitral prolapse with severe regurgitation is surgery,(6) which can be life saving.(7) In that regard, important and potentially disturbing gender differences are observed: Women predominate among subjects with mitral prolapse in the population(2,4) but men predominate among those undergoing mitral surgery.(7,8) The tenants of this discrepancy are undefined long after its seminal observation.(9) It is unclear whether this discrepancy reflects differences in prolapse morphology(5) or physiologic differences (degree of regurgitation and potentially benign presentation in women) essential in influencing outcome.(4) It is also unclear if this discrepancy is linked to differences in ventricular and atrial consequences of mitral prolapse, which usually guide surgical indication,(6) or due to sex-related management differences. Access to surgical management is essential in severe regurgitation to restore life expectancy.(5,7,10) Hence, for transition from diagnosis to surgery, it is unclear whether women with mitral prolapse present less seriously,(9,11) and require less surgery or if for similar mitral prolapse and regurgitation, women undergo less cardiac valve surgery than men. Finally, potential survival differences after diagnosis in women vs. men with mitral prolapse are unknown.

These questions are complex because tertiary-care referral may distort apparent disease characteristics,(12,13) and examining consistency of local (14) and referred patients findings is essential. Thus, we identified patients diagnosed with mitral prolapse in our institution using current criteria,(2) and aimed at ascertaining sex-differences regarding baseline characteristics, management and long-term outcome.

Methods

Study Subjects

We searched Mayo Clinic echocardiographic records between January 1st 1989 and December 31st 1998 to identify those studies that reported diagnosis of mitral prolapse. If patients had more than one echocardiogram, we used only the first to provide diagnosis during that period of stable and current diagnostic criteria.(15,16) The study was approved by the Mayo Institutional review board. We excluded patients who denied research authorization, who were prisoners or who had mitral surgery prior to index echocardiogram. We identified patients as being from the local community (Olmsted County residents) or as being referred from a distance. Olmsted County, MN, residents are cared for by few providers linked by the Rochester Epidemiology project, so we consider them to be non-referred patients.(14) Mayo Clinic provides all cardiovascular consultative services and echocardiographic services to county residents allowing identification of those diagnosed with mitral valve prolapse.

Clinical variables

Clinical characteristics concomitant to index echocardiography, were collected from electronic summary of inpatient and outpatient medical records established by the patients' personal physicians. Up-to-diagnosis electronic medical and surgical indexes were reviewed to assess comorbidity using Charlson index(17). Baseline blood pressure and criteria for severe

presentation (congestive heart failure, atrial fibrillation or ischemic neurologic event before the index echocardiogram) were electronically collected.(4,18)

Echocardiographic methods

All patients uniformly underwent comprehensive two-dimensional, M-mode, color and Doppler echocardiographic study during a routine examination. Mitral prolapse was diagnosed with criteria recommended currently and throughout the study period,(2,15) based on an annular overshoot of mitral leaflets >2 mm in long axis views. The diagnosis of flail leaflet, (19) or of thickened leaflets,(2) was based on previously recommended criteria. M-mode left ventricular diameters and ejection fraction,(20) and left atrial diameter measurements were guided by two-dimensional echocardiography.(21) Degree of regurgitation when present was categorized as mild, moderate or severe based on comprehensive assessment,(22) coherently with American Society of Echocardiography guidelines.(23) All study Doppler-echocardiographic data were those measured originally, obtained by direct electronic transfer (from the echocardiographic database) without alteration.

Methodological assessment used blind reinterpretation of echocardiograms for diagnosis of valve prolapse and thickening in randomly selected study ($n=50$) and non-study ($n=20$) patients. Agreement between initial and reinterpreted echocardiograms was 97 percent for prolapse diagnosis (kappa 0.93; valve displacement 3.1 ± 1.0 mm) and 93 percent for leaflet thickening >5 mm (kappa 0.85, thickness 5.6 ± 1.1 vs. 3.5 ± 1.0 mm, $P<0.001$). To assess consistency of qualitative mitral regurgitation grading, simultaneously obtained regurgitant volume in 781 patients was compared in patients with mild (21 ± 16 mL/beat, $n=89$), moderate (35 ± 15 mL/beat, $n=248$) or severe regurgitation (83 ± 45 mL/beat, $n=444$, $p<0.001$), demonstrating general appropriateness of original qualitative grading.

Clinical outcome and management

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

Statistical analysis

Baseline characteristics are summarized as mean $\pm$ SD or percentages. Direct comparison between men and women used t test or Wilcoxon rank-sum test for continuous variables, or chi-square test for categorical variables without imputations for missing values. Because of age differences, comparisons were stratified by age and tested by analysis of variance (continuous variables) or logistic regression (categorical variables). To examine potential referral bias impact on comparisons between men and women, those were also stratified by geographical origin (local Olmsted County residents and referred patients). Survival and cardiac surgery rates were estimated using Kaplan-Meier method and compared between men and women using log-rank test and in multivariate analysis with Cox-proportional Hazards analysis. Interaction terms between sex and regurgitation severity, geographical origin or severity of presentation were forced into multivariate models and tested. $P<0.05$ was considered significant.

Results

In 1989–1998, 8,229 patients had an index echocardiogram that documented mitral valve prolapse. Among these, 896 were Olmsted County, MN, residents and formed our local mitral prolapse population and 7,333 patients were distantly referred.

Women with mitral valve prolapse with and without regurgitation

Diagnosis in men and women was simultaneous (1993 ± 2.9 vs. 1993 ± 3 , $p=0.12$) and baseline characteristics comparison is shown Table 1.

Anatomically, women vs. men showed less flail leaflets, more anterior and bileaflet prolapse and more leaflet thickening. Physiologically, women compared to men had lower regurgitation grades, smaller left atrial and ventricular dimensions and higher ejection fraction. Clinically, women displayed less frequently than men severe clinical presentation (congestive heart failure, atrial fibrillation or ischemic neurologic events). Stratifying patients by age (comparison women vs. men for age strata <50 , 50 to 70 and >70), to account for younger age of women at diagnosis, and stratifying for regurgitation grade demonstrated persistence of morphologic sex-differences noted in Table 1 (all stratified $p<0.001$). Excluding flail leaflets, morphologic differences between women and men were confirmed (all $p<0.001$).

Thus, sex-differences are not age-, flail-related and reveal specific sex-differences for mitral prolapse. Despite these differences, women represent a large part, 39% of referred and 49% of local patients with moderate or severe regurgitation that are candidates for surgery, justifying analysis of this specific subset.

Mitral prolapse in women with moderate or with severe regurgitation

Table 2 compares women and men with moderate regurgitation (left panel) or severe regurgitation (right panel). Among these patients, women were of similar age than men ($p>0.10$, slightly younger with moderate regurgitation and slightly older with severe regurgitation) so that age plays little role in women vs. men differences in this segment. Blood pressure showed also little difference between men and women. Echocardiographically, stratifying for regurgitation severity, women displayed smaller absolute left ventricular and atrial cavity size than men did. The difference is large, between 4 and 5 mm for end-diastolic diameter. Only 5.7% of women reached the classic surgical threshold of LV end-systolic diameter ≥ 45 mm vs. 9.6% in men ($p<0.01$). However, women vs. men have smaller bodies than men and normalization to body-surface-area demonstrates, for the same regurgitation severity, actually greater ventricular and atrial enlargement (diameters in mm/m²) in women vs. men (Table 2). Ejection fraction was slightly higher in women than men.

Outcome of mitral valve prolapse in Women vs. Men

Clinical management with cardiac valve surgery was performed in 1185 patients during follow-up (mitral surgery in 97%). Incidence of cardiac valve surgery 15-year after diagnosis according to baseline regurgitation severity was $5.7 \pm 3.6\%$ with no/mild regurgitation, $18 \pm 1\%$ with moderate regurgitation and $57 \pm 1\%$ with severe regurgitation ($p<0.001$). Cardiac valve surgery performance at 15-years in women vs. men was 15 ± 1 vs. $22 \pm 2\%$ ($p<0.01$) with baseline moderate regurgitation and were 52 ± 3 vs. $60 \pm 2\%$ ($p=0.03$) with severe regurgitation. Adjusting for age, ejection fraction and regurgitation severity, referral to cardiac valve surgery was less likely in women vs. men (adjusted risk-ratio 0.79[0.74–0.84], $p<0.001$). When the model including multiple imputations for the 599 (7.3%) missing ejection fraction the magnitude and significance of sex differences were not affected. Cardiac valve surgery was more likely with larger left ventricular absolute diastolic diameter (adjusted risk-ratio 1.06[1.05–1.07] per mm, $p<0.001$) which superseded body-surface-area-normalized diameter ($p=0.34$). Surgery was also more likely with larger absolute atrial diameter (1.02[1.01–1.03] per mm, $p<0.001$) which superseded body-surface-area-normalized diameter ($p=0.74$). Lower incidence of cardiac valve surgery in women was confirmed adjusting for presentation severity (0.78[0.73–0.83], $p<0.001$), diastolic LV diameter (0.89[0.82–0.96], $p=0.002$) or LA diameter (0.81[0.75–0.87], $p<0.001$).

Survival: Follow-up was 11.7 ± 4.4 years (2229 patients remaining at risk at 15 years) during which 1690 patients died. Survival was 90 ± 0.4 , 83 ± 0.4 and $78 \pm 0.5\%$ respectively at 5, 10 and 15 years. In multivariate models predicting survival, there was strong interaction between sex and regurgitation severity ($p < 0.001$) unaffected by presentation severity ($p = 0.60$). Survival at 15 years (Fig. 1) was higher in women with no/mild regurgitation (87 ± 0.7 vs. $77 \pm 1\%$, $p < 0.001$), slightly higher with moderate regurgitation (71 ± 2 vs. $66 \pm 2\%$, $p = 0.02$) but significantly lower in women vs. men with severe regurgitation (60 ± 3 vs. $68 \pm 2\%$, $p = 0.049$). Adjusting for age, ejection fraction, presentation severity and comorbidity, women mortality-risk vs. men was lower with no/mild regurgitation ($0.82[0.76-0.89]$, $p < 0.001$), comparable with moderate regurgitation ($0.93[0.84-1.03]$, $p = 0.15$) and was excessive in women with severe regurgitation ($1.13[1.01-1.26]$, $p = 0.026$) (Fig. 1). Multiple imputations for the missing ejection fraction, magnitude and significance of sex differences were not affected. Cause of death was blindly analyzed in 750 Minnesotans (deaths certificates obtainable). In 363 with no/mild regurgitation, cardiovascular cause was similar in women and men (35 vs. 37%, $p = 0.75$). In 211 with moderate regurgitation, cardiovascular cause trended higher in women (60.7% vs. 47.2%, $p = 0.054$). In 176 with severe regurgitation, similar cardiovascular cause in women and men (62% vs. 61%, $p = 0.89$). Lower comorbidity (Charlson index) was noted in women with no/mild regurgitation (0.40 ± 1.2 vs. 0.65 ± 1.6 , $p < 0.001$), with moderate regurgitation (0.56 ± 1.4 vs. 0.85 ± 1.8 , $p < 0.001$) and with severe regurgitation (0.41 ± 1.1 vs. 0.55 ± 1.5 , $p = 0.09$), confirming the lack of other cause to the excess mortality of women with severe regurgitation. Cardiac surgery was performed at the same age in women vs. men (61 ± 20 vs. 61 ± 17 yrs, $p = 0.69$) and was followed by the same survival (at 10 years post-operatively 77 ± 2 vs. $79 \pm 2\%$, $p = 0.14$). Cardiac valve surgery was associated with no significant survival improvement with moderate regurgitation ($0.88[0.65-1.18]$, $p = 0.39$) but with improved survival with severe regurgitation ($0.79[0.63-0.98]$, $p = 0.03$).

Local versus referred subsets

Referred vs. local mitral prolapse displayed an expected shift towards older patients (63 ± 17 vs. 56 ± 20 years in men, 58 ± 18 vs. 50 ± 22 in women, $p < 0.001$) with more severe regurgitation (24% vs. 16% in men, 10% vs. 6% in women, $p < 0.001$) and larger ventricle and atrium (45 ± 9 vs. 41 ± 9 mm in men, 39 ± 9 vs. 36 ± 7 in women, $p < 0.001$) and lesser women predominance (53 vs. 63%, $p < 0.001$). Nevertheless, anatomic and physiologic sex-differences were similar in local and referred populations with women vs. men having less regurgitation, flail or posterior leaflet prolapse and more valve thickening (data not shown). Likewise, sex-differences in absolute and normalized ventricular diameters were observed in local and referred populations with similar magnitude (all $p > 0.10$). Geographical origin (Local vs. Referred) did not affect the association between sex and surgery performance (interaction $p = 0.34$) or survival (interaction $p = 0.86$).

Discussion

This study in our community(14) and large referral practice, analyzes the elusive issue of morphological and outcome differences in women vs. men with mitral prolapse. Coherence of local and referred patients data strongly supports genuine differences between men and women, independently of referral bias: Women are diagnosed with mitral prolapse more often than men and at a younger age. Women present with anatomical (more anterior and bileaflet prolapse, more thickened leaflets, less flail leaflets) and physiological (less regurgitation) differences vs. men. Thus, women present more frequently than men with benign forms of prolapse. However, women represent a large proportion of patients with moderate or severe regurgitation. In these severe forms, assessment of ventricular enlargement in women is problematic because of body size differences and women undergo mitral surgery less frequently than men with similar regurgitation severity. Concomitantly, women with severe

regurgitation exhibit excess long-term mortality compared to men while survival after surgery is similar to men. Therefore, there are important sex-differences in morphology and outcome of mitral valve prolapse.

Characteristics of mitral valve prolapse in women

Mitral prolapse observed in men and women is not identical, a coherent observation in local and referral practice. Women have more valve thickening reflecting generalized myxomatous degeneration(24) a chemically active matrix-remodeling process(25) while flail leaflets, structurally different from diffusely myxomatous valves(24) predominate in men. These sex-differences are not age-related or attributable to sex-specific screening(4) and represent sex-differences in disease mechanisms supported by recently suggested X-linked genetic mitral prolapse determination.(26) Moderate/severe regurgitation affect 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 management and outcome differences. Valve thickening affects stroke risk,(18) but only modestly and it does not affect survival of patients with mitral prolapse(4) which is highly dependent on regurgitation severity.(4) Women are more often diagnosed with a benign form of mitral prolapse irrespective of age,(9) which appears to agree with predominance of men in surgical series(7,8) and with smaller ventricular and atrial size in women. This may affect management as cardiac enlargement, considered to reflect regurgitation severity, is recommended to guide surgical indications.(6) For similar regurgitation severity, women reach less often diameter-based surgical guideline-criteria,(9, 11) which were essentially established in men.(27,28) However, with smaller bodies, women have at least 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 in women with similar regurgitation severity than men (11) even after adjustment for ventricular size and clinical severity. It is not possible to separate respective roles of surgical referral, patient preference and associated conditions completely, but it is an important observation because surgery affects outcome. Mitral surgery has been consistently linked to reduced mortality(10) and restored life-expectancy(7) and similar post-operative survival in men and women(30) suggests similar benefit of surgery irrespective of sex. Thus, differences in valve surgery performance may not be inconsequential.

We observe a pattern of changing relative long-term survival of women vs. men depending on regurgitation severity. Survival is higher in women with no/mild regurgitation (known longer life expectancy), is similar with moderate regurgitation and is worse in women with severe regurgitation. Predominantly cardiovascular mortality in men and women with severe regurgitation, and low comorbidity in women minimizes potential non-cardiac responsibility in the excess mortality of women with severe regurgitation. These outcome differences are disturbing and challenging and should lead to carefully review of clinical management practices.

Previously published data on sex-differences in mitral prolapse

(English-language MEDLINE, national library of medicine search to January 2007)
Morphological differences between women and men with mitral prolapse were suggested previously,(9) but were difficult to ascertain for important reasons. First, stricter diagnostic criteria for mitral prolapse were implemented in the late 1980's,(16) preventing interpretation of previous reports for comparison of men and women. Another limitation was the relatively low number of cases identified in population-based studies,(1,2,31) preventing morphological characteristics' comparison. Indeed, inference that male sex could be a risk factor for

complications,(9,11,32) originated from men predominance among patients hospitalized for severe MR due to mitral prolapse in tertiary-care.(5,7,8) Hence, it remained uncertain whether observed gender-linked differences were real or related to differential referral, particularly surgical referral in severe MR.(33–35) With regard to outcome after diagnosis, there is no previous data analyzing surgical referral, but similarity of postoperative survival(30) and mitral surgery benefit(10) between men and women is consistent with previous data.

Study limitations

Data on sex-differences regarding mitral prolapse in the general population are lacking, leaving the pending question of bias due to echocardiography referral. Analysis of our community is relevant in that all in- and outpatient cases diagnosed in this geographically defined area are gathered. Thus, it provides a benchmark, remarkably coherent regarding sex-differences with tertiary-referred patients, making it unlikely that these differences are due to referral bias. Our study was based on first diagnosis at our institution of mitral valve prolapse with current criteria, as previous diagnostic criteria were non-specific,(15,16) but, thereby, lacks certainty on baseline characteristics at the time of a potentially first mitral prolapse observation. Reliability of routine echocardiography was addressed in two ways: first, the high agreement between initial report and blinded reinterpretation for diagnosis of mitral valve prolapse and leaflet thickening is reassuring; Second, quantitative parameters could not be obtained in all patients since regurgitation quantification emerged during the study period. However, high correlation between qualitative grading and regurgitant volume supports overall reliability or regurgitation grading in the study. Knowledge of direct responsibility of mitral-related events in outcome sex-differences 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 is suggestive of such a link.

Future research directions

Attributing with certainty the cause of differences between men and women with mitral valve prolapse and severe regurgitation regarding valve surgery performance and survival is not possible. Pointing out these yet unclear morphological and outcome differences is an essential step in improving clinical management of men and women with mitral prolapse and in planning future research. Potential causal link between underestimation of mitral prolapse and regurgitation severity, because of lower unadjusted cavities size, leading to lesser cardiac valve surgery referral and to excess mortality of women with severe regurgitation would be disturbing. Such link, possible but hypothetical, is essential to address in future studies. Despite its massive size and considerable follow-up, our study cannot replace a clinical trial in testing valve surgery benefit for outcome in men and women with mitral prolapse.

Clinical implications

Women with mitral prolapse, more often than men, present benignly but should not be regarded as uniformly benign. Those with moderate or severe MR incur outcome similar or worse than that of men, so that women require, similarly to men, careful risk stratification, watchful attention and consideration of operative management.

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

Conclusion

Women vs. men with mitral prolapse display important morphological and outcome differences. Women present more often with thick leaflets and less often with flail, posterior leaflet prolapse or severe regurgitation. Despite often-benign presentation, women with mitral prolapse represent a clinical challenge. In women, assessment of cardiac enlargement is problematic. Women undergo mitral surgery less often than men and those with severe regurgitation incur excess long-term mortality vs. men. These sex-differences are disturbing and should be addressed in future studies aimed at improving management and outcome of mitral prolapse and regurgitation.

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Figure 1.

Gender differences in survival after diagnosis among patients with mitral valve prolapse. Survival is compared between women (thick line) and men (thin line) with no or mild regurgitation (No-mild MR, left panel), with moderate regurgitation (moderate MR, central panel) and with severe regurgitation (severe MR, right panel). The p value in each panel corresponds to the log-rank direct comparison of survival between women and men. Above each panel is presented the risk-ratio [95% confidence interval] of mortality of women vs. men in multivariate Cox proportional-hazards analysis. Below each panel are presented the number (N at risk) of women (W) and men (M) at risk for the intervals of 5, 10 and 15 years. Note that with no or mild regurgitation women have higher survival than men do. Conversely, with moderate regurgitation the small survival advantage of women in direct comparison becomes insignificant after adjustment, while with severe regurgitation survival of women is coherently lower than that of men by direct comparison or after adjustment.

Comparison of clinical and echocardiographic characteristics at diagnosis between women and men with mitral valve prolapse:

Table 1

	Women N=4,461	Men N=3,768	p
Baseline Clinical characteristics			
Age (years)	57±19	62±17	<0.001
Body Surface Area, (m ²)	1.7±0.2	1.9±0.2	<0.001
Systolic blood pressure (mmHg)	130±22	133±20	<0.001
Diastolic blood pressure (mmHg)	74±11	76±11	<0.001
Severe clinical presentation [†] n, %	550 (12)	792 (21)	<0.001
Echocardiographic Characteristics			
LV EF (percent)	63±8	60±9	<0.001
LV-ESD (mm)	29±5	34±6	<0.001
LV-EDD (mm)	48±6	54±7	<0.001
LA diameter (mm)	38±8	45±9	<0.001
MR (n, %)	1,614(36)	910(24)	<0.001
	Mild	1,131(30)	
	Moderate	854(23)	
	Severe	873 (23)	
Flail leaflet (n, %)	96(2)	301(8)	<0.001
Thickened valve (n, %)	1,438(32)	1,067(28)	<0.001
Leaflet Localization			
(n, %)	Anterior	511 (13)	<0.001
	Posterior	1,191 (32)	
	Bileaflet	2,066 (55)	

Abbreviations: LV: Left ventricle; EF: ejection fraction; ESD: end-systolic diameter; EDD: end-diastolic diameter; LA: left atrium; MR: mitral regurgitation.

[†] presentation with either congestive heart failure, atrial fibrillation or ischemic stroke.

* comparison of men vs. women;

Table 2

Comparison of clinical, left atrial and ventricular characteristics at diagnosis between women and men with mitral valve prolapse and mitral regurgitation moderate (left) or severe (right) in the entire population

		Moderate MR, N=1,544		Severe MR, N=1,319		P*
		Women	Men	Women	Men	
N		690 (45%)	854 (55%)	446 (34%)	873 (66%)	
Age, years		66±17	68±13	68±15	66±14	0.04
BSA, m ²		1.6±0.2	1.9±0.2	1.6±0.2	1.9±0.2	<0.001
Systolic blood pressure		137±23	136±19	133±23	134±20	0.5
Diastolic blood pressure		76±11	77±11	74±11	76±11	0.003
Echocardiographic Characteristics						
LVEF (percent)		62±9	59±10	63±10	61±9	0.01
LV-ESD (mm)		30±6	34±7	33±8	36±7	<0.001
LV-ESD/BSA mm/m ²		19±5	18±4	20±6	19±4	<0.001
LV-EDD (mm)		49±6	54±7	55±8	59±7	<0.001
LV-EDD/BSA (mm/m ²)		30±6	28±5	34±7	30±5	<0.001
LA diameter (mm)		43±8	46±8	50±10	52±9	0.01
LA diameter/BSA (mm/m ²)		26±5	24±5	31±7	27±5	<0.001

Abbreviations: BSA: body surface area; LV: Left ventricle; EF: ejection fraction; ESD: end-systolic diameter; EDD: end-diastolic diameter; LA: left atrium; MR: mitral regurgitation.

* comparison of men vs. women;