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PREVALENCE AND CLINICAL OUTCOME OF MITRAL-VALVE PROLAPSE

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ABSTRACT

Background Mitral-valve prolapse has been described as a common disease with frequent complications. To determine the prevalence of mitral-valve prolapse in the general population, as diagnosed with the use of current two-dimensional echocardiographic criteria, we examined the echocardiograms of 1845 women and 1646 men (mean [±SD] age, 54.7±10.0 years) who participated in the fifth examination of the offspring cohort of the Framingham Heart Study.

Methods Classic mitral-valve prolapse was defined as superior displacement of the mitral leaflets of more than 2 mm during systole and as a maximal leaflet thickness of at least 5 mm during diastasis, and nonclassic prolapse was defined as displacement of more than 2 mm, with a maximal thickness of less than 5 mm.

Results A total of 84 subjects (2.4 percent) had mitral-valve prolapse: 47 (1.3 percent) had classic prolapse, and 37 (1.1 percent) had nonclassic prolapse. Their age and sex distributions were similar to those of the subjects without prolapse. None of the subjects with prolapse had a history of heart failure, one (1.2 percent) had atrial fibrillation, one (1.2 percent) had cerebrovascular disease, and three (3.6 percent) had syncope, as compared with unadjusted prevalences of these findings in the subjects without prolapse of 0.7, 1.7, 1.5, and 3.0 percent, respectively. The frequencies of chest pain, dyspnea, and electrocardiographic abnormalities were similar among subjects with prolapse and those without prolapse. The subjects with prolapse were leaner ($P<0.001$) and had a greater degree of mitral regurgitation than those without prolapse, but on average the regurgitation was classified as trace or mild.

Conclusions In a community-based sample of the population, the prevalence of mitral-valve prolapse was lower than previously reported. The prevalence of adverse sequelae commonly associated with mitral-valve prolapse in studies of patients referred for that diagnosis was also low. (N Engl J Med 1999;341:1-7.)

MITRAL-VALVE prolapse has been described as a common disorder, with prevalence estimates generally ranging from 5 to 15 percent and up to 35 percent in some studies.[1-7] In addition, mitral-valve prolapse has often been portrayed as a disease with frequent and serious complications, including stroke, atrial fibrillation, heart failure, and mitral regurgitation requiring surgery.[8-13] However, previous studies examining the prevalence and epidemiology of prolapse have been limited by the use of hospital-based samples or highly selected patients referred because of mitral-valve prolapse, who are more likely to have clinical complications.[14,15] They have also relied on M-mode or two-dimensional echocardiographic views that are not specific for the diagnosis of mitral-valve prolapse.[2,7,16,17] The frequent diagnosis of prolapse and the emphasis on potential complications may have marked effects on young, otherwise healthy persons, including anxiety about the possibility of adverse events, ineligibility for insurance or increased insurance rates, and the need for antibiotic prophylaxis.[18,19]

Studies describing the three-dimensional shape of the mitral annulus[20,21] have allowed the two-dimensional echocardiographic characterization of prolapse to be refined, thus minimizing false positive diagnoses.[22-24] To our knowledge, however, no investigators have evaluated a community-based sample of subjects using current two-dimensional echocardio-

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graphic criteria to determine the prevalence and potential complications of mitral-valve prolapse. Therefore, in a study designed to be free of referral bias, we examined the prevalence of mitral-valve prolapse and its clinical associations in an unselected sample of outpatients.

METHODS

Subjects

The Framingham Heart Study was established in 1948 as a prospective epidemiologic investigation of a large cohort of men and women.[25] The offspring of the original subjects and the spouses of the offspring were enrolled in a prospective study in 1971.[26] Subjects who participated in the fifth examination of the offspring cohort, which began in January 1991 and was completed in January 1995, were the focus of this study. The examination protocol was approved by the institutional review board of Boston Medical Center, and all subjects gave informed consent.

A total of 3736 subjects who participated in the fifth examination were evaluated; 245 were excluded because of technically inadequate echocardiograms. Thus, the study group consisted of 3491 subjects (1845 women and 1646 men; mean [±SD] age, 54.7±10.0 years) for whom two-dimensional echocardiograms were available that were adequate for evaluating the mitral valve. Five of these subjects had a history of mitral-valve repair or replacement, only one of whom had undergone surgery for mitral-valve prolapse. The other four had undergone surgery for other abnormalities, such as mitral stenosis and ischemic regurgitation. These five subjects were included in the calculation of the prevalence of mitral-valve prolapse and associated clinical conditions, but they were excluded from all other analyses of the mitral valve and clinical characteristics because of the surgical intervention.

To ensure that no cases of mitral-valve prolapse were missed, we examined the echocardiograms of all subjects who had previously been identified as possibly having leaflet displacement suggesting prolapse in any two-dimensional view or on M-mode echocardiography at any examination of the offspring cohort. This broad approach identified 518 subjects. First, we assessed the echocardiograms obtained at the fifth examination of these subjects to identify those in whom qualitative superior displacement of the mitral leaflets during systole warranted a quantitative evaluation to determine whether prolapse was actually present. The 151 case subjects identified in this way were paired with controls matched for age and sex who were drawn from the fifth examination and who were initially coded as having no evidence of prolapse. The echocardiograms of these two subgroups were then examined for mitral-valve prolapse by cardiologists who were unaware of the subjects' status.

Echocardiographic Methods

All subjects underwent standard two-dimensional echocardiography with a commercially available system (Sonos 1000, Hewlett–Packard, Andover, Mass.) that used a 2.5-MHz transducer. Images were recorded on videotape, including complete parasternal, apical, and subcostal views and color Doppler assessment of valvular regurgitation. All measurements were performed with a Sony Off-line Cardiac Analysis System (Sum 1010, Sony, Park Ridge, N.J.).

We used current two-dimensional echocardiographic criteria based on the three-dimensional shape of the annulus and clinical correlations[12,20-24] to diagnose mitral-valve prolapse according to the maximal superior displacement of the mitral leaflets during systole relative to the line connecting the annular-hinge points. We measured the displacement of the anterior and posterior mitral leaflets in the parasternal and apical long-axis views, which were scanned by tilting the transducer to visualize all three scallops of the posterior leaflet.[12,20-23] Because the lateral scallop of the posterior leaflet is most difficult to evaluate from these views, we also measured the displacement of this leaflet in the apical four-chamber view[22,27]; however, the degree of displacement was always confirmed by examination of the long-axis scans. The thickness of the mitral leaflets during diastasis was measured from the leading to the trailing edge of the thickest area of the midportion of the leaflet, excluding focal areas of thickness and

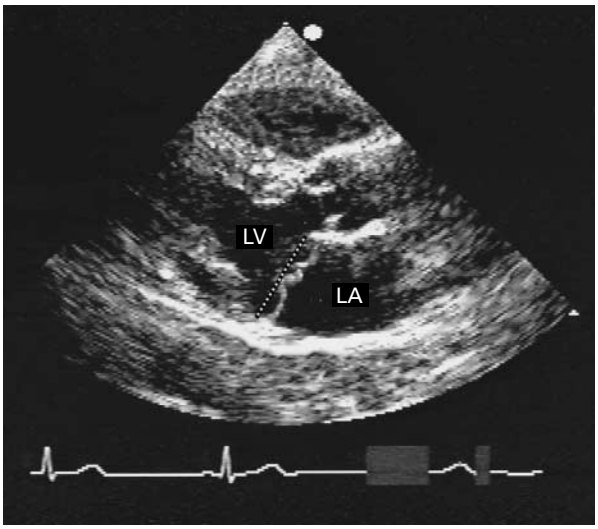

Figure 1. Classic Mitral-Valve Prolapse during Systole.

The parasternal long-axis view shows the mitral leaflets prolapsing (>2 mm), as indicated by the dotted line, into the left atrium during systole. LA denotes left atrium, and LV left ventricle.

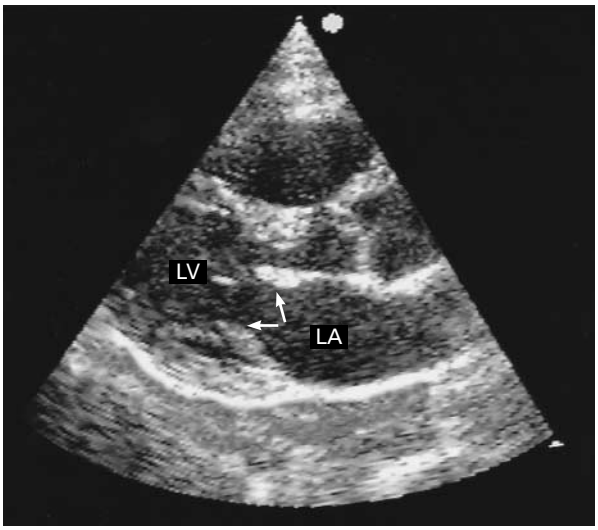

Figure 2. Classic Mitral-Valve Prolapse with Leaflet Thickening (Arrows) during Diastole.

The parasternal long-axis view demonstrates mitral-leaflet thickening (≥5 mm) during diastole. LA denotes left atrium, and LV left ventricle.

chordae.[12,22,24,28-30] Each leaflet was measured and categorized according to the maximal thickness.

On the basis of prior clinical and prognostic studies, subjects were classified as having classic prolapse if displacement exceeded 2 mm and maximal thickness was at least 5 mm (Fig. 1 and 2) and as having nonclassic prolapse if displacement exceeded 2 mm but the maximal thickness was less than 5 mm.[8,12,22-24,28] Borderline degrees of displacement (≤2 mm) are not associated with increased leaflet thickness, mitral regurgitation, left atrial enlargement, valve-related complications, or progression over a period of 10 years and were not included in the definition of prolapse.[22,24,31] The degree of mitral regurgitation was assessed as the ratio of the maximal regurgitant jet area to the area of the left atrium in the parasternal and apical long-axis and apical four-chamber views.[32] The degree of regurgitation was considered to be trace, mild, moderate, or severe on the basis of ratios of >0 to 10, >10 to 20, >20 to 40, and >40 percent, respectively.[32]

Clinical Variables

Clinical variables were derived from assessments of the subjects' histories and physical examinations performed by Framingham Heart Study physicians. Diagnoses of cardiovascular end points were made by a committee of three physicians who evaluated records from the Framingham Heart Study clinic examinations, interim hospitalizations, and visits to personal physicians in accordance with published criteria.[33,34] The clinical variables that we compared in subjects with mitral-valve prolapse and those without prolapse were age, sex, symptoms of chest pain or dyspnea, history of hypertension (defined as a systolic blood pressure of at least 140 mm Hg or a diastolic blood pressure of at least 90 mm Hg on each of two successive readings obtained by the clinic physician or as current use of antihypertensive medication), presence of coronary heart disease (defined as angina pectoris, coronary insufficiency, or myocardial infarction), presence of diabetes mellitus (glucose level of at least 140 mg per deciliter [7.7 mmol per liter] after a 12-hour fast or the use of insulin or an oral hypoglycemic agent), current cigarette smoking, and presence of hypercholesterolemia (defined as a serum total cholesterol level of at least 240 mg per deciliter [6.21 mmol per liter]).[33,34] The two groups were also compared with respect to history of heart failure, atrial fibrillation, cerebrovascular disease (defined as stroke or transient ischemic attack), and syncope.[33,34]

The physical examination included measurements of body-mass index (the weight in kilograms divided by the square of the height in meters), waist-to-hip ratio, and systolic and diastolic blood pressures and assessments for mitral systolic murmur and mid-systolic click. Electrocardiographic variables assessed included the presence of atrial and ventricular ectopy, left atrial enlargement (defined as a terminal P-wave force of 1 mm by 1 mm in lead V_1), and left ventricular hypertrophy (defined by the presence of increased voltage with a pattern indicating strain).[35]

Statistical Analysis

For the dichotomous clinical variables, the differences between subjects with mitral-valve prolapse and those without prolapse were tested with use of the Wald chi-square test for logistic-regression analysis, after adjustment for age, sex, and body-mass index. Continuous variables were evaluated by means of analysis of covariance. The evaluation of the difference in age was adjusted for sex. Body-mass index and waist-to-hip ratio were adjusted for sex and age. All other comparisons were adjusted for age, sex, and body-mass index. Systolic and diastolic blood pressures were also adjusted for treatment with antihypertensive medications. Values are given as least-squares means and standard errors. All comparisons were made by comparing all the subjects with prolapse with those without prolapse. This was an a priori decision made because of the relatively small number of subjects with prolapse. All P values were two-sided. Correlation coefficients were used to express intraobserver and interobserver variability. SAS statistical software (version 6.11, SAS Institute, Cary, N.C.) was used for all calculations.

TABLE 1. PREVALENCE OF MITRAL-VALVE PROLAPSE.

TYPE OF MITRAL-VALVE PROLAPSE	ALL SUBJECTS (N=3491)	WOMEN (N=1845)	MEN (N=1646)
	number (percent)		
Classic	47 (1.3)	26 (1.4)	21 (1.3)
Nonclassic	37 (1.1)	24 (1.3)	13 (0.8)
Total	84 (2.4)	50 (2.7)	34 (2.1)

RESULTS

Prevalence of Mitral-Valve Prolapse

Quantitative evaluation revealed that 47 subjects (1.3 percent) had classic mitral-valve prolapse and 37 (1.1 percent) had nonclassic mitral-valve prolapse (Table 1). The remainder of the subjects did not meet quantitative criteria for prolapse, including all 151 subjects whose initial qualitative evaluation had not suggested prolapse. Among subjects with classic prolapse, the mean (±SD) maximal leaflet displacement was 3.8±1.0 mm, the mean thickness of the anterior leaflet was 5.0±0.6 mm, and the mean thickness of the posterior leaflet was 5.6±0.5 mm. The corresponding values in the subjects with nonclassic prolapse were 3.1±0.6 mm, 3.9±0.5 mm, and 4.1±0.6 mm. Among subjects without prolapse, the maximal leaflet displacement was −0.5±2.0 mm, the mean thickness of the anterior leaflet was 3.3±0.7 mm, and the mean thickness of the posterior leaflet was 3.4±0.8 mm.

Age and Sex

The age and sex distributions of the subjects with prolapse were similar to those of the subjects without prolapse. The sex-adjusted mean (±SE) age of the patients with classic prolapse was 56.7±1.5 years, as compared with a mean age of 55.4±1.6 years for those with nonclassic prolapse and of 54.7±0.2 years for those without prolapse (P=0.19). The range of ages for the group as a whole was 26 to 84 years; mitral-valve prolapse had no predilection for young subjects and a fairly even distribution (2 to 3 percent) among subjects in each decade of age from 30 to 80 years. With respect to sex, 59.5 percent of the subjects with mitral-valve prolapse were women, as compared with 52.7 percent of those without prolapse (P=0.21) (Table 1).

Clinical Findings and Symptoms

None of the 84 subjects with mitral-valve prolapse had a history of heart failure, 1 (1.2 percent) had atrial fibrillation, 1 (1.2 percent) had cerebrovascular

TABLE 2. PREVALENCE OF VARIOUS CLINICAL FINDINGS ACCORDING TO THE PRESENCE OR ABSENCE OF MITRAL-VALVE PROLAPSE.

CLINICAL FINDING	MITRAL-VALVE PROLAPSE (N=84)	NO MITRAL-VALVE PROLAPSE (N=3407)
	no. (%)	
Congestive heart failure	0	25 (0.7)
Atrial fibrillation	1 (1.2)	58 (1.7)
Cerebrovascular disease*	1 (1.2)	52 (1.5)
Syncope	3 (3.6)	103 (3.0)

*Cerebrovascular disease refers to stroke or transient ischemic attack.

TABLE 3. PREVALENCE OF VARIOUS CLINICAL CHARACTERISTICS.*

CHARACTERISTIC	CLASSIC MITRAL-VALVE PROLAPSE (N=46)	NONCLASSIC MITRAL-VALVE PROLAPSE (N=37)	NO MITRAL-VALVE PROLAPSE (N=3403)	P VALUE†
	number (percent)‡			
Chest pain	5 (10.7)	4 (10.9)	604 (17.5)	0.12
Dyspnea	5 (11.6)	5 (14.8)	734 (20.1)	0.13
Coronary heart disease	0	1 (1.9)	237 (4.4)	0.06
Risk factors for coronary heart disease				
Cigarette smoking	7 (13.9)	2 (4.9)	650 (18.5)	0.04
Hypertension	15 (31.8)	8 (22.9)	1135 (29.6)	0.74
Diabetes	1 (1.7)	2 (5.3)	218 (4.5)	0.52
Hypercholesterolemia§	10 (21.6)	4 (10.5)	526 (14.8)	0.65

*The five subjects who had undergone mitral-valve surgery were excluded (four in the group without mitral-valve prolapse and one in the group with classic prolapse).

†The P values are for the comparison of all subjects with mitral-valve prolapse and those without prolapse.

‡All percentages were adjusted for age, sex, and body-mass index.

§The mean (±SE) cholesterol levels, adjusted for age, sex, and body-mass index, were 203±5 mg per deciliter (5.25±0.13 mmol per liter) among subjects with classic mitral-valve prolapse, 199±6 mg per deciliter (5.15±0.16 mmol per liter) among subjects with nonclassic prolapse, and 204±1 mg per deciliter (5.28±0.03 mmol per liter) among subjects without prolapse.

disease (stroke or transient ischemic attack), and 3 (3.6 percent) had syncope, as compared with unadjusted prevalences of these findings in the group without prolapse of 0.7, 1.7, 1.5, and 3.0 percent, respectively (Table 2). One subject with classic prolapse had undergone mitral-valve repair before the examination; he was also the one subject with prolapse who had atrial fibrillation. Subjects with prolapse had a greater degree of mitral regurgitation than those without prolapse. The mean (±SE) ratio of the jet area to the left atrial area was 15.1±1.3 percent among subjects with classic mitral-valve prolapse, 8.9±1.5 percent among subjects with nonclassic prolapse, and 2.4±0.6 percent among 218 control subjects without prolapse ($P<0.001$). However, on average, subjects with classic prolapse had mild regurgitation and those with nonclassic or no prolapse had trace regurgitation. Severe regurgitation, with the area of the regurgitant jet being greater than 40 percent of the area of the left atrium, occurred in 7 percent of the subjects with classic prolapse, as compared with none of the subjects who had nonclassic prolapse and 0.5 percent of those without prolapse. One subject with classic prolapse had a remote history of infective endocarditis.

The prevalences of chest pain and dyspnea were similar in the patients with prolapse and those without it (Table 3). The prevalence of coronary heart disease was marginally lower among the subjects with prolapse ($P=0.06$). The prevalences of risk factors for coronary heart disease, including smoking, hypertension, diabetes, and hypercholesterolemia, are summarized in Table 3.

Physical and Electrocardiographic Findings

Physical and electrocardiographic findings are shown in Table 4. Subjects with prolapse were significantly leaner on the basis of body-mass index and waist-to-hip ratio and were more likely to have systolic murmurs and mid-systolic clicks than those without prolapse. There were no significant differences between the two groups in systolic or diastolic blood pressure or in the prevalence of electrocardiographic abnormalities.

Reproducibility of Echocardiographic Findings

The intraobserver and interobserver correlations for mitral-leaflet displacement, leaflet thickness, and the degree of mitral regurgitation in 20 subjects exceeded 0.97.

DISCUSSION

The prevalence of mitral-valve prolapse in this unselected group of ambulatory subjects was substantially lower than that previously reported (classic prolapse, 1.3 percent; nonclassic prolapse, 1.1 percent).[1-7] In contrast to previous reports, we found that the rates of heart failure, atrial fibrillation, cerebrovascular disease, and syncope were no higher among subjects with mitral-valve prolapse than among those without prolapse. Chest pain and dyspnea were present in 11 to 15 percent of those with prolapse, a range that was lower than the value in subjects without prolapse and that is consistent with previous reports.[36] In addition, as reported previously,[1,4,5,37,38] we found that subjects with prolapse were leaner (lower body-mass index and waist-to-hip ratio) than those without prolapse. Subjects with prolapse were more like-

TABLE 4. PHYSICAL AND ELECTROCARDIOGRAPHIC FINDINGS.*

VARIABLE	CLASSIC MITRAL-VALVE PROLAPSE (N=46)	NONCLASSIC MITRAL-VALVE PROLAPSE (N=37)	NO MITRAL-VALVE PROLAPSE (N=3403)	P VALUE†
Body-mass index‡	24.4±0.7	24.9±0.7	27.2±0.1	<0.001
Waist-to-hip ratio‡	0.89±0.01	0.87±0.01	0.90±0.001	0.007
Blood pressure — mm Hg§				
Systolic	125±2.4	125±2.6	126±0.3	0.62
Diastolic	75±1.4	75±1.5	74±0.2	0.66
Systolic murmur — no. (%)¶	11 (22.6)	4 (9.6)	138 (4.0)	<0.001
Systolic click — no. (%)¶	10 (11.1)	6 (7.9)	82 (1.5)	<0.001
Left atrial enlargement — no. (%)¶	2 (2.6)	1 (1.9)	51 (1.1)	0.25
Left ventricular hypertrophy — no. (%)¶	3 (3.7)	1 (1.9)	63 (1.3)	0.11
Atrial ectopy — no. (%)¶	2 (3.2)	0	64 (1.6)	0.84
Ventricular ectopy — no. (%)¶	0	1 (2.6)	53 (1.4)	0.81

*The five subjects who had undergone mitral-valve surgery were excluded (four in the group without mitral-valve prolapse and one in the group with classic prolapse).

†The P values are for the comparison of all subjects with mitral-valve prolapse and those without prolapse.

‡Values were adjusted only for age and sex.

§Values were adjusted for age, sex, body-mass index, and antihypertensive treatment.

¶All percentages were adjusted for age, sex, and body-mass index.

ly to have mitral regurgitation ($P<0.001$), but the degree of regurgitation in those with prolapse was, on average, mild.

The numerous referral-based studies have increased our understanding of the pathophysiology and management of prolapse in its most severe forms. Our findings, however, imply that a small proportion of persons in an outpatient setting have mitral-valve prolapse and that the clinical profile of these subjects is more benign than previously indicated by the available literature.

Mitral-valve prolapse has been described as the most common cardiac valvular abnormality in industrialized countries.[39] In previous studies with higher prevalences, the subjects have largely been volunteers,[2,3,6] some self-referred and some "self-selected." In two studies,[3,6] subjects were selected from large clinic or hospital practices. Such studies are subject to selection bias: volunteers who respond to advertisements and randomly selected volunteers who agree to participate in a study may, in fact, be concerned about their cardiac status because they have affected relatives or a remote history of a heart murmur. As a result, the reported prevalences may not reflect those in the general community.

Prolapse is an abnormal displacement of the mitral leaflets relative to their surrounding structures. Previous studies used M-mode echocardiography or less specific two-dimensional criteria (including displacement of the anterior leaflet in the apical four-chamber view) to diagnose mitral-valve prolapse. M-mode echocardiography fails to display the leaflets in relation to their surrounding annular attachments,[16] and the results vary widely depending on the orientation of the transducer.[17] Two-dimensional views display the leaflets and annulus, but the results must be interpreted in the context of the three-dimensional saddle-like shape of the valve.[20,21] A side-to-side (four-chamber) view through such a structure can normally show leaflets apparently bulging upward relative to the low points of the annular saddle in the absence of any leaflet disease or distortion.[20-22] Eliminating the use of such views reduces the frequency of diagnosis without excluding persons with thickening of the leaflets, regurgitation, or valve-related complications characteristic of the myxomatous process.[22,24] Prior reports have in fact shown that estimates of the prevalence of prolapse are lower when more specific criteria are used.[7]

In addition to ensuring a low false positive rate through the use of newer diagnostic criteria, our study design minimized false negative rates as well. All subjects suspected of having prolapse at any prior examination with the use of older, less specific criteria were screened with use of the newer, highly specific criteria, and the results were then assessed in a blinded fashion. The low false negative rate was confirmed by the finding of no cases of mitral-valve prolapse among our control subjects.

Mitral-valve prolapse has been reported to be the leading cause of isolated mitral regurgitation[39] and regurgitation requiring surgery.[40] Duren et al., for example, found complications such as the need for mitral-valve surgery, stroke, infectious endocarditis, and sudden death in one third of patients with mitral-valve prolapse (100 of 300) who were followed for an average of 6.1 years, with an average complication rate of 5.4 percent per year.[10] Marks et al. reported complications in 27 percent of patients with classic mitral-valve prolapse (86 of 319).[12] A strong association with complications is generally reported in hospital-based samples, in which patients are commonly referred for the complications under investigation. Some authors have documented this referral bias by showing that the rate of complications was lower among affected family members of referred study patients.[13]

The design of the Framingham Heart Study effectively minimizes selection bias. Consequently, we found a low prevalence of conditions reported by others as complications attributable to prolapse. This low prevalence is also consistent with the relatively low risks of serious complications reported in some

previous studies.[11,13] The low prevalence of serious complications among subjects with prolapse in the community is similar to the findings in studies of hypertrophic cardiomyopathy. Studies at major referral institutions suggested that this disease was frequently symptomatic and had a high rate of severe complications, including sudden death. Eliminating such patient-referral and selection biases through the use of outpatient samples has dramatically changed the perception of hypertrophic cardiomyopathy and its natural history.[14,15]

Referral bias or patterns of seeking medical attention for symptoms may also help explain the previous perception of prolapse as a disease heavily affecting young women, which is not what we found. The relatively low sensitivity of clicks and murmurs for prolapse in our study may also reflect the relatively mild nature of prolapse in the general population as compared with referral-based series, as does the absence of a significant difference in the prevalence of ventricular ectopy between those with prolapse and those without prolapse. This finding is consistent with previous findings that serious ventricular arrhythmias and sudden death are more likely in patients with prolapse who have severe mitral regurgitation and left ventricular dysfunction.[39] Long-term follow-up will be necessary for the fullest determination of complication rates and natural history in this sample.

Although the number of subjects in the study was large — 3491 — the number of subjects with prolapse was moderate (84), and there was a low prevalence of potential complications. The low prevalence of prolapse and potential complications resulted in wide 95 percent confidence intervals. In addition, as with any cross-sectional study, the prevalence of prolapse and the severity of complications were affected by survival bias. In fact, those who had the most serious complications of prolapse, such as sudden death, may not have been included in our study because they were not among the members of the cohort who participated in the fifth study examination. Finally, the subjects were predominantly white, and it is possible that the results may not be generalizable to other ethnic and racial groups.

Quantification of the prevalence of mitral-valve prolapse in the general population is important for several reasons. It defines the magnitude of the condition and provides a basis for determining the validity of proposed associations. It also allows researchers to address whether prolapse occurs more frequently among patients with presumed complications, such as stroke, than in the general population. In addition, both prevalence and complication rates are important factors in balancing the potential risks and benefits of antibiotic prophylaxis against endocarditis.[19] The low frequency of complications in our study may alter the perception of the severity of the disease and allay anxiety for those in whom mitral-valve prolapse is diagnosed in a general outpatient setting.

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REFERENCES

1. Levy D, Savage D. Prevalence and clinical features of mitral valve prolapse. Am Heart J 1987;113:1281-90.
2. Markiewicz W, Stoner J, London E, Hunt SA, Popp RL. Mitral valve prolapse in one hundred presumably healthy young females. Circulation 1976;53:464-73.
3. Procacci PM, Savran SV, Schreiter SL, Bryson AL. Prevalence of clinical mitral-valve prolapse in 1169 young women. N Engl J Med 1976;294:1086-8.
4. Savage DD, Garrison RJ, Devereux RB, et al. Mitral valve prolapse in the general population. 1. Epidemiologic features: the Framingham Study. Am Heart J 1983;106:571-6.
5. Savage DD, Devereux RB, Garrison RJ, et al. Mitral valve prolapse in the general population. 2. Clinical features: the Framingham Study. Am Heart J 1983;106:577-81.
6. Bryhn M, Persson S. The prevalence of mitral valve prolapse in healthy men and women in Sweden. Acta Med Scand 1984;215:157-60.
7. Warth DC, King ME, Cohen JM, Tesoriero VL, Marcus E, Weyman AE. Prevalence of mitral valve prolapse in normal children. J Am Coll Cardiol 1985;5:1173-7.
8. Nishimura RA, McGoon MD, Shub C, Miller FA Jr, Ilstrup DM, Tajik AJ. Echocardiographically documented mitral-valve prolapse: long-term follow-up of 237 patients. N Engl J Med 1985;313:1305-9.
9. Devereux RB, Hawkins I, Kramer-Fox R, et al. Complications of mitral valve prolapse: disproportionate occurrence in men and older patients. Am J Med 1986;81:751-8.
10. Duren DR, Becker AE, Dunning AJ. Long-term follow-up of idiopathic mitral valve prolapse in 300 patients: a prospective study. J Am Coll Cardiol 1988;11:42-7.
11. Wilcken DEL, Hickey AJ. Lifetime risk for patients with mitral valve prolapse of developing severe valve regurgitation requiring surgery. Circulation 1988;78:10-4.
12. Marks AR, Choong CY, Sanfilippo AJ, Ferré M, Weyman AE. Identification of high-risk and low-risk subgroups of patients with mitral-valve prolapse. N Engl J Med 1989;320:1031-6.
13. Zuppiroli A, Rinaldi M, Kramer-Fox R, Favilli S, Roman MJ, Devereux RB. Natural history of mitral valve prolapse. Am J Cardiol 1995;75:1028-32.
14. Spirito P, Chiarella F, Carratino L, Berisso MZ, Bellotti P, Vecchio C. Clinical course and prognosis of hypertrophic cardiomyopathy in an outpatient population. N Engl J Med 1989;320:749-55.
15. Maron BJ, Casey SA, Poliac LC, Gohman TE, Almquist AK, Aeppli DM. Clinical course of hypertrophic cardiomyopathy in a regional United States cohort. JAMA 1999;281:650-5.
16. Sahn DJ, Wood J, Allen HD, Peoples W, Goldberg SJ. Echocardiographic spectrum of mitral valve motion in children with and without prolapse: the nature of the false positive diagnosis. Am J Cardiol 1977;39:422-31.
17. Markiewicz W, London E, Popp RL. Effect of transducer placement on echocardiographic mitral valve motion. Am Heart J 1978;96:555-6.
18. Leatham A, Brigden W. Mild mitral regurgitation and the mitral prolapse fiasco. Am Heart J 1980;99:659-64.
19. Devereux RB, Frary CJ, Kramer-Fox R, Roberts RB, Ruchlin HS. Cost-effectiveness of infective endocarditis prophylaxis for mitral valve prolapse with or without a mitral regurgitant murmur. Am J Cardiol 1994;74:1024-9.
20. Levine RA, Triulzi MO, Harrigan P, Weyman AE. The relationship of mitral annular shape to the diagnosis of mitral valve prolapse. Circulation 1987;75:756-67.
21. Levine RA, Handschumacher MD, Sanfilippo AJ, et al. Three-dimensional echocardiographic reconstruction of the mitral valve, with implications for the diagnosis of mitral valve prolapse. Circulation 1989;80:589-98.
22. Levine RA, Stathogiannis E, Newell JB, Harrigan P, Weyman AE. Reconsideration of echocardiographic standards for mitral valve prolapse: lack

of association between leaflet displacement isolated to the apical four chamber view and independent echocardiographic evidence of abnormality. J Am Coll Cardiol 1988;11:1010-9.
23. Perloff JK, Child JS. Mitral valve prolapse: evolution and refinement of diagnostic techniques. Circulation 1989;80:710-1.
24. Nidorf SM, Weyman AE, Hennessey R, Newell JB, Levine RA. The relationship between mitral valve morphology and prognosis in patients with mitral valve prolapse: a prospective echocardiographic study of 568 patients. J Am Soc Echocardiogr 1993;6:S8. abstract.
25. Dawber TR, Meadors GF, Moore FE Jr. Epidemiological approaches to heart disease: the Framingham Study. Am J Public Health 1951;41:279-86.
26. Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families: the Framingham Offspring Study. Am J Epidemiol 1979;110:281-90.
27. Shah PM. Echocardiographic diagnosis of mitral valve prolapse. J Am Soc Echocardiogr 1994;7:286-93.
28. Chandraratna PAN, Nimalasuriya A, Kawanishi D, Duncan P, Rosin B, Rahimtoola SH. Identification of the increased frequency of cardiovascular abnormalities associated with mitral valve prolapse by two-dimensional echocardiography. Am J Cardiol 1984;54:1283-5.
29. Weissman NJ, Pini R, Roman MJ, Kramer-Fox R, Andersen HS, Devereux RB. In vivo mitral valve morphology and motion in mitral valve prolapse. Am J Cardiol 1994;73:1080-8.
30. Louie EK, Langholz D, Mackin WJ, Wallis DE, Jacobs WR, Scanlon PJ. Transesophageal echocardiographic assessment of the contribution of intrinsic tissue thickness to the appearance of a thick mitral valve in patients with mitral valve prolapse. J Am Coll Cardiol 1996;28:465-71.
31. Vivaldi MT, Sagie A, Adams MS, et al. 10-Year echocardiographic and clinical follow-up of patients with nonclassic mitral valve prolapse: does it progress? Circulation 1994;90:Suppl I:I-222. abstract.
32. Helmcke F, Nanda NC, Hsiung MC, et al. Color Doppler assessment of mitral regurgitation with orthogonal planes. Circulation 1987;75:175-83.
33. Kannel WB, Wolf PA, Garrison RJ, eds. The Framingham Study: an epidemiological investigation of cardiovascular disease. Section 35. Survival following initial cardiovascular events: 30 year follow-up. Bethesda, Md.: National Heart, Lung, and Blood Institute, 1988. (NIH publication no. 88-2969.)
34. Kannel WB, Gordon T, eds. The Framingham Study: an epidemiological investigation of cardiovascular disease. Section 30. Some characteristics related to the incidence of cardiovascular disease and death: Framingham Heart Study, 18-year follow-up. Washington, D.C.: Government Printing Office, 1974. (DHEW publication no. NIH-74-599.)
35. Levy D, Labib SB, Anderson KM, Christiansen JC, Kannel WB, Castelli WP. Determinants of sensitivity and specificity of electrocardiographic criteria for left ventricular hypertrophy. Circulation 1990;81:815-20.
36. Devereux RB, Kramer-Fox R, Brown WT, et al. Relation between clinical features of the mitral prolapse syndrome and echocardiographically documented mitral valve prolapse. J Am Coll Cardiol 1986;8:763-72.
37. Devereux RB, Brown WT, Lutas EM, Kramer-Fox R, Laragh JH. Association of mitral-valve prolapse with low body-weight and low blood pressure. Lancet 1982;2:792-5.
38. Cohen JL, Austin SM, Segal KR, Millman AE, Kim CS. Echocardiographic mitral valve prolapse in ballet dancers: a function of leanness. Am Heart J 1987;113:341-4.
39. Devereux RB, Kramer-Fox R, Kligfield P. Mitral valve prolapse: causes, clinical manifestations, and management. Ann Intern Med 1989;11:305-17.
40. Waller BF, Morrow AG, Maron BJ, et al. Etiology of clinically isolated, severe, chronic, pure mitral regurgitation: analysis of 97 patients over 30 years of age having mitral valve replacement. Am Heart J 1982;104:276-88.

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