Mitral Valve Prolapse Prevalence and Complications
An Ongoing Dialogue

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Mitral valve prolapse (MVP) is generally understood to be the systolic displacement of an abnormally thickened, redundant mitral leaflet into the left atrium during systole.¹ This valvular abnormality has been associated with mid-systolic clicks, late systolic murmurs, and serious complications such as bacterial endocarditis, severe mitral regurgitation, and sudden death.² Unfortunately, our understanding of the prevalence, complication rate, and associations of mitral valve prolapse has been clouded by the use of varying techniques, changing diagnostic criteria, and conclusions drawn from highly selected referral populations. Despite this confusion, an understanding of the prevalence of mitral valve prolapse and the identification of subgroups most susceptible to complications remain important because MVP is the most common cause of valve repair/replacement for isolated mitral regurgitation in the United States,³ and the thickened leaflets form a recognized substrate for bacterial endocarditis.⁴

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Since the early 1970s, echocardiography has been suggested to be the ideal method for noninvasively recording the movement of the prolapsing mitral leaflets.¹ Unfortunately, the continually changing echocardiographic methods and criteria for diagnosis for MVP over the last 30 years have often obscured rather than enhanced our understanding of the disorder.⁵ During the past decade, new echocardiographic criteria for MVP have been established on the basis of an understanding of the 3-dimensional structure of the mitral valve.⁶ Recent studies that used these criteria have shed new light on the prevalence and complications of MVP in the general population,⁷ although less is known about the natural history of MVP as diagnosed by these new criteria. The report in this issue of Circulation by Avierinos et al⁸ expands our understanding by describing the clinical outcomes in a group of 833 asymptomatic patients with echocardiographic MVP monitored for a mean of 5.4 years. The study assesses the rates of mortality and morbidity associated with MVP and contrasts these findings with the earlier report from the Framingham study that described MVP as a “benign” condition in the general population.

Before discussing the results of the study of Avierinos et al,⁸ it is important to examine the study design because doing so may help place the results in appropriate perspective. Although presented as a “community study,” the patient cohort does not include the whole population of Olmsted county, nor is this a randomly selected cohort from that population, but rather, it describes patients with MVP identified either clinically or echocardiographically. Thus, the subjects in this retrospective study represent a hospital or referral population that is, by nature, subject to selection or referral bias and as such should have higher complication rates than found in a truly random population. If one considers the denominator or total population of Olmsted County (124 272),⁹ the prevalence of disease on the basis of these data would be only 0.67%, which is approximately 28% of that in the Framingham study,¹° suggesting that only more severely affected subjects are being identified. The higher prevalence of atrial fibrillation (AF), reported at 8% (likely an underestimation because only new-onset AF is reported and no entry values are given) versus 1.2% in the Framingham population again suggests a selected population. In the Strong Heart Study,¹¹ which used the same criteria for MVP, a prevalence of 1.7% was reported in a population of similar age, but the authors noted that the studies were limited and the appropriate prevalence should be ≥2%, which approximates the Framingham data. If the Framingham data are correct, there should be approximately 2983 individuals in Olmsted County with MVP, and the data should be viewed from that perspective. In addition, although patients are reported as asymptomatic, only dyspnea and angina were criteria for exclusion, so it is possible that other symptoms might have suggested MVP to the clinician.

Avierinos et al⁸ report 96 total deaths during a total of 4581 patient years of follow-up (41 cardiovascular [CV], of which 31 are listed as MVP related). The good news for patients with MVP is that the overall mortality of the total group was not different from that expected for this population (risk ratio 1.08). The overall CV mortality was 9±2% and is not indicated to be different than expected. Although 31 patients died of an MVP-related event, the actual cause of death was not stated. MVP-related events in this study included heart failure, mitral valve surgery, and endocarditis. Only 4 patients had endocarditis and it is unlikely that they all died. The mortality of mitral valve repair is extremely low (0.3% thirty-day mortality in one large series), which leaves MVP-related heart failure as a cause of death. It is difficult to imagine that in a well-monitored population with excellent, readily available surgical support, patients with MVP would

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.
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(Circulation. 2002;106:1305-1307.)
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Circulation is available at http://www.circulationaha.org
DOI: 10.1161/01.CIR.0000031759.92250.F3
die of heart failure. Thus, we are left wondering what happened to these patients, and whether these deaths are truly related to MVP.

The major predictors of mortality (independent of age, sex, and comorbidity) were moderate or greater mitral regurgitation (MR) (relative risk = 3.0) and an ejection fraction (EF) < 50% (relative risk = 3.8). MR is the most common complication of MVP.7,11 Prior studies of referral populations have reported that MR diagnosed on the basis of the presence of a systolic murmur is associated with an increased risk for serious adverse events, including progressive valve dysfunction necessitating replacement,12–15 infective endocarditis,4,15 and sudden death.16,17 In clinical and necropsy series, most patients with MVP in whom the condition contributed to death had clinical and pathological evidence of important MR. Thus, this study confirms prior observations on the prognostic implication of important MR and provides additional support for the concept that moderate or severe MR should be an indication for valve repair/replacement. Although MR was an independent predictor of mortality, patients with moderate or greater MR more frequently had an EF < 50%, which suggested that the relationship of MR to outcome was related in part to the LV dysfunction it induces. The finding that death was related to ejection fraction is also consistent with prior observations. The American Heart Association/American College of Cardiology guidelines for the management of patients with MVP and chronic MR suggest that mitral valve surgery is appropriate once echo-cardiographic indicators of LV dysfunction (an EF ≤ 0.60 or an end-systolic dimension of ≥ 45 mm) are present.18 The guidelines note that the data on postoperative survival are more strongly correlated with LVEF than with LV diameters, which, although widely used, were not found to be predictive of mortality in the current study (an area worthy of further investigation). Avierinos et al8 also reported no association between flail leaflet and mortality, which is in contrast to an earlier study by the same group that showed an increase in sudden death in such patients.17 Unfortunately, no attempt was made to reconcile these discrepancies.

Cardiac morbidity occurred in 171 patients. Heart failure (60 patients), new atrial fibrillation (51 patients), ischemic neurological events (38 patients), peripheral arterial thromboembolism (11 patients), and endocarditis (4 patients) accounted for these events. Mitral valve repair/replacement was necessary in 65. Independent predictors of CV mortality (adjusted hazard ratios [95% confidence interval]) were age ≥ 50 (3.1 [2.0 to 5.0]), left atrium ≥ 40 mm (2.7 [1.9 to 3.8]), slight MR (3.6 [2.0 to 7.0]), moderate or greater MR (9.1 [4.9 to 18.3]), flail leaflet (2.6 [1.5 to 4.6]), and baseline atrial fibrillation (2.0 [1.3 to 3.0]). The observation that slight MR, usually considered a normal variant, had a higher risk of morbidity than flail mitral leaflet is striking but unfortunately never discussed. Also of note, moderate or greater MR is a predictor of both mortality and morbidity, but EF is not. Although low-risk patients may not have adverse outcomes during an intermediate duration study such as this one, they may still be at risk of all of the complications of MVP during the course of a lifetime.

The authors divide risk factors into primary (EF < 50% and MR moderate or greater) and secondary (slight MR, flail leaflet, left atrial diameter > 40 mm, AF, and age ≥ 50 years). Patients are then divided into high-risk (at least 1 primary risk factor), medium-risk (no primary but ≥ 2 secondary risk factors), and low-risk groups (no primary and ≤ 1 secondary risk factor), with a clear and consistent separation in terms of MVP-related events. The problem with this type of analysis is that prolapse can progress rapidly because of chordal rupture, and thus although low-risk patients may not have adverse outcomes during an intermediate duration study such as this one, they may still be at risk of all of the complications of MVP during the course of a lifetime.

The authors8 imply that their results are different from those of the Framingham study because of healthy participant bias in the latter study. The results may not be as different as suggested, however. In the Framingham study, there was only 1 patient of 84 with MVP who underwent valve replacement, but another 7 had severe MR. If we assume that these patients will ultimately have a valve replacement, the event rate as defined in this study would be 8 of 84 or 9.5%. In the present study,8 the combined mortality and morbidity (including valve repair or replacement) was 267 of 833; however, if the Framingham data are used to predict prevalence (ie, 2983 subjects with MVP), the overall event rate would be 9% (not a great difference). Even if one makes no assumptions about prevalence, the need for valve repair or replacement in the present study (65 of 833 or 7.8%) was still similar to the projected rate from the Framingham data. Although such calculations are obviously limited, they indicate that the difference between studies may be less than suggested. Looking at this question from a different perspective (ie, beginning with the number of patients in a known population [New South Wales, Australia] requiring valve replacement or repair) Wilkken et al,12 assuming a population prevalence of 4%, estimated the probability of requiring surgery for severe MR at age 60 as 1:53 for men and 1:142 for women, increasing to 1:28 and 1:83, respectively. If we assume that these cases arise predominantly from the classic MVP group (as in the Framingham study), then the population prevalence decreases to 1.3% and the cumulative risk for requiring mitral valve replacement will increase proportionately to 1:17 at age 60 for men and 1:46 for women. At age 70, this risk will be approximately 1:9 for men and 1:15 for women. Thus, by age 70, the cumulative risk for men would be roughly 11%. Given the increasing frequency of valve surgery for MVP, these data, which are more than 10 years old, probably represent an underestimation.

What, then, should we make of all this? The concept that MVP is a benign condition originated with the unfortunate overdiagnosis of the condition on the basis of M-mode and early 2D echo criteria and is consistent with the maxim that “a disease is particularly benign if you are a false-positive.”
With refinement of the diagnosis, the prevalence of MVP has decreased, whereas the number having an adverse outcome remains constant; hence, the percent of patients with complications increases. Studies of randomly selected patients like the Framingham study will have a lower percentage of complications than referral populations like that of Avierinos et al., but on an absolute basis, the number of patients with important complications (ie, death or valve replacements per 1000 people) should remain the same. When calculating mortality rates, however, it seems more appropriate to use the actual prevalence rather than the number of patients referred as a basis. In the report of the Framingham study, the choice of the term benign was unfortunate, particularly when close to 10% of the affected patients have had or can be expected to require valve repair or replacement. The report of Avierinos et al. supports these concepts, but because of the method of patient selection, the data are not directly applicable to the general population. After a review of all existing about MVP, it seems that at least 10% (likely more when the lifetime risk is considered) of patients will ultimately require valve surgery for correction of MR in addition to being at risk for all of the other complications of MVP. Patients who already have evidence of the major complications of the disease are at greater risk for mortality and morbidity, but given the propensity of the disorder to progress rapidly, all patients with clearly defined MVP may sustain important complications. The report by Avierinos et al raises many questions, including the role of ventricular dimension in the recommendations for surgery, the role of leaflet thickness in identifying high-risk patients, the role of flail leaflet as a predictor of mortality, the appropriate EF to indicate LV dysfunction, and the mortality and morbidity of MVP in unselected patients. Further study is necessary to resolve these issues.

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Circulation. 2002;106:1305-1307
doi: 10.1161/01.CIR.000031759.92250.F3

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