

## Clinical Practice

*This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

## EVALUATION AND MANAGEMENT OF CHRONIC MITRAL REGURGITATION

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A 56-year-old man with no history of cardiac disease and no cardiac symptoms has a holosystolic murmur at the apex that radiates to the axilla. Echocardiography shows moderate mitral regurgitation with mild left ventricular dilatation. How should this patient's care be managed?

**T**HERE are about 500,000 discharge diagnoses of mitral-valve disease annually in the United States.<sup>1</sup> However, estimates of the prevalence of mitral regurgitation are confounded by the presence of benign flow murmurs in many adults and by the small amount of physiologic regurgitation detected on echocardiography in 80 percent of adults. Only about 18,000 patients undergo mitral-valve surgery annually, suggesting that most patients with a diagnosis of mitral regurgitation never need surgical intervention. Thus, the challenge for the clinician is first to determine which patients have pathologic mitral regurgitation and then to provide them with appropriate care.

### THE CLINICAL PROBLEM

#### Causation

Normal mitral-valve function depends on the complex interactions of all the components of the valve apparatus (Fig. 1). In surgical series, the most common causes of severe mitral regurgitation are mitral-valve prolapse (20 to 70 percent of cases), ischemia (13 to 30 percent), rheumatic heart disease (3 to 40 percent), and endocarditis (10 to 12 percent).<sup>2</sup> Although mitral-valve prolapse is common in surgical series, most patients with mitral-valve prolapse have only mild disease and never need surgery. Mitral-valve prolapse and ischemic disease are also common in patients with milder regurgitation, but the most common causes are ventricular dilatation and systolic dysfunction. In the elderly, mitral regurgitation may be

due to annular calcification; typically, regurgitation in older persons is mild to moderate and intervention is rarely necessary. Accurate identification of the mechanism of mitral regurgitation is essential because the clinical outcome, the medical therapy prescribed, and the potential need for surgical intervention depend as much on the cause as on the severity of disease.

#### Pathophysiological Process

Chronic left ventricular volume overload as a result of mitral regurgitation leads to compensatory dilatation of the left ventricle. Although this response initially maintains cardiac output, myocardial decompensation eventually results in symptoms of heart failure and an increased risk of sudden death.<sup>3</sup> In some patients, left ventricular contractility is irreversibly impaired in the absence of symptoms.<sup>4</sup> In addition, back-flow into the left atrium results in enlargement of the left atrium, atrial fibrillation, and elevated pulmonary pressures.

#### Diagnosis

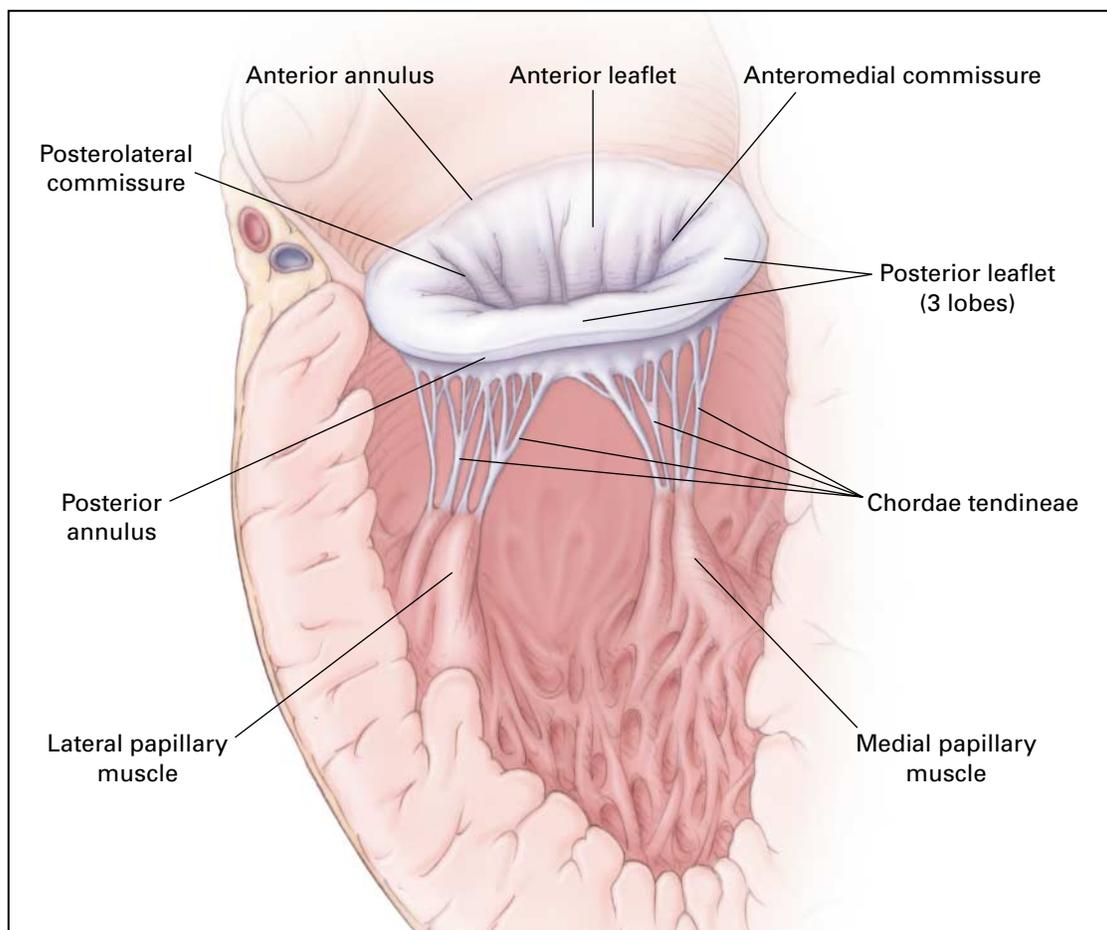
Mitral regurgitation may be diagnosed on the basis of the presence of a systolic murmur in asymptomatic adults or incidentally when echocardiography is performed for other indications. Some patients with primary disease of the valve leaflets present with symptoms of heart failure, atrial fibrillation, or endocarditis. The symptoms may be precipitated by a superimposed hemodynamic stress, such as that induced by pregnancy, anemia, or an infection. In patients with secondary regurgitation, valve dysfunction is most often identified during an evaluation of the underlying disease process.

On physical examination, the murmur of mitral regurgitation is classically an apical holosystolic murmur that radiates to the axilla. However, physical examination is not always reliable in distinguishing mitral regurgitation from other types of systolic murmurs and does not provide an accurate measure of the severity of regurgitation.<sup>5</sup> On electrocardiography and chest radiography, evidence of enlargement of the left atrium, left ventricle, or both is seen only late in the course of disease and is not sensitive or specific for the diagnosis of mitral regurgitation.

#### Echocardiography

Echocardiography allows accurate evaluation of the presence or absence, severity, and cause of mitral regurgitation. Echocardiography is indicated in patients who have a systolic murmur and any cardiac symptoms, a loud murmur ( $\geq$  grade 3/6) alone, or other cardiac findings on physical examination. In most cas-

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**Figure 1.** Mitral Valve.

The mitral valve consists of the mitral annulus, anterior and posterior leaflets, chordae tendineae, and the papillary muscles. Mitral regurgitation may be due to a disease that primarily affects the valve leaflets, such as mitral-valve prolapse or rheumatic mitral-valve disease, or may result from alterations in the function or structure of the left ventricle, such as those induced by ischemic disease or dilated cardiomyopathy.

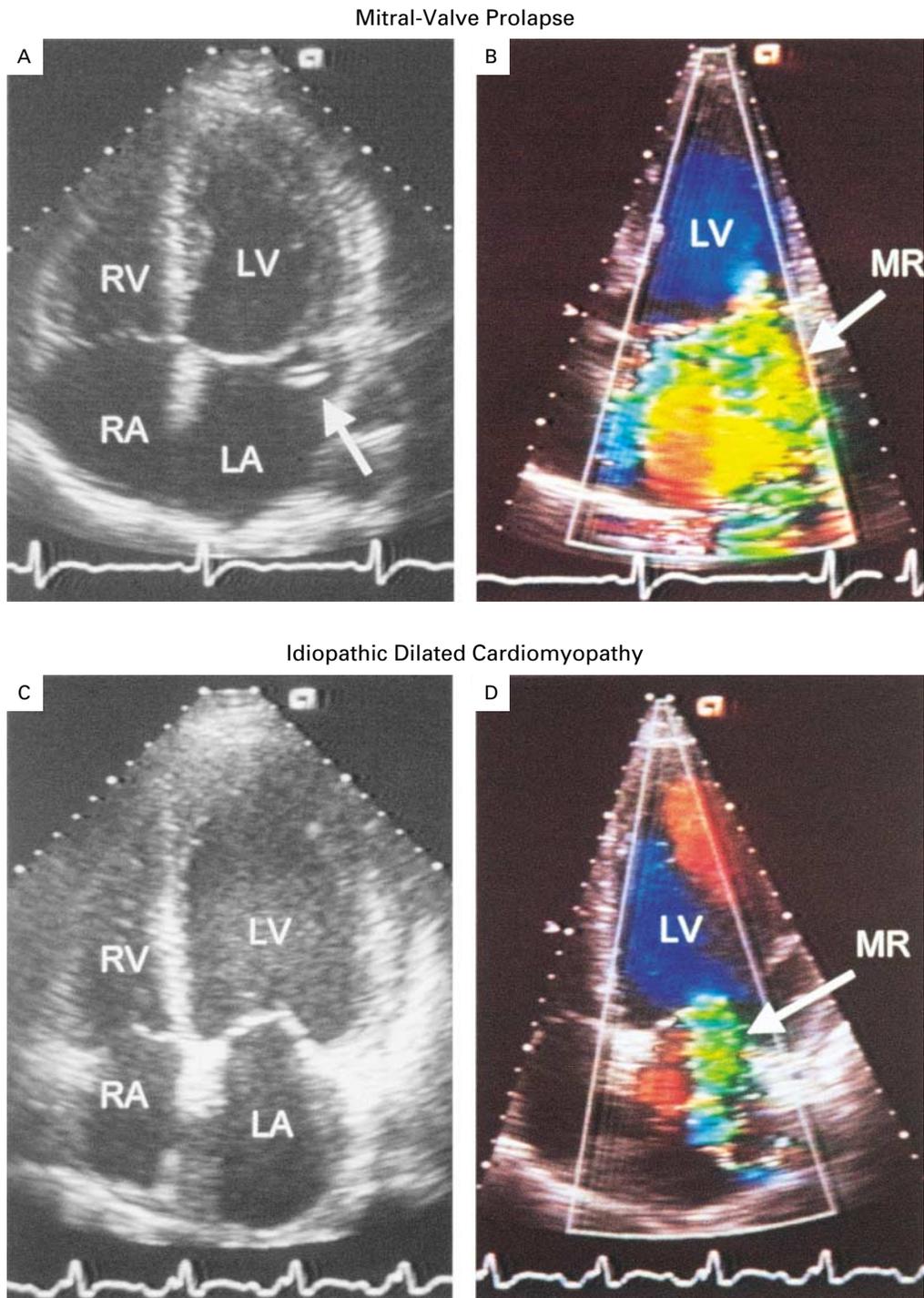
es, the cause of mitral regurgitation can be deduced from the two-dimensional images (Fig. 2). Although Doppler echocardiography provides several methods of quantifying the severity of regurgitation, none have been shown to predict the clinical outcome. Most centers grade regurgitation as mild, moderate, or severe using a combination of color flow, continuous, and pulsed-wave Doppler imaging.<sup>6</sup>

The most important aspect of the echocardiographic examination is the quantitation of left ventricular systolic performance. Although calculation of the ejection fraction is an imperfect means of assessing contractility, from a practical point of view, the ejection fraction in conjunction with the end-systolic dimension provides a clinically useful measure of ventricular performance. Transesophageal echocardiography

allows accurate assessment of the feasibility of valve repair and should be performed before surgical intervention.<sup>7</sup>

#### Outcome

Patients with mitral regurgitation may remain asymptomatic for many years; the average interval from diagnosis to the onset of symptoms is 16 years.<sup>8</sup> There are few data on the rate of hemodynamic progression of disease in patients with mild-to-moderate regurgitation, since most series are restricted to patients with severe regurgitation. In addition, the available data are difficult to interpret, since the criteria for evaluating the severity of regurgitation vary and are not always clearly defined. Furthermore, even though the clinical outcome is strongly dependent on



**Figure 2.** Echocardiographic Images (Panels A and C) and Color Doppler (Panels B and D) in a 42-Year-Old Man with Mitral-Valve Prolapse and a 65-Year-Old Man with Idiopathic Dilated Cardiomyopathy.

The man with prolapse (Panels A and B) has severe mitral regurgitation (MR), a partial flail posterior leaflet (arrow in Panel A), a normal-sized left ventricle (LV), normal systolic function (ejection fraction, 0.66), moderate enlargement of the left atrium (LA), and mild pulmonary hypertension. The man with idiopathic dilated cardiomyopathy (Panels C and D) has enlargement of all four chambers, with severely reduced left ventricular systolic function (ejection fraction, 0.22), anatomically normal mitral-valve leaflets, and moderate mitral regurgitation. RV denotes right ventricle, and RA right atrium.

the cause of the disease, patients with diverse mechanisms of regurgitation are often included in the same study.

In patients with severe symptomatic mitral regurgitation, the clinical outcome is poor: survival rates are as low as 33 percent at eight years in the absence of surgical intervention. The average mortality rate is approximately 5 percent per year; most deaths are related to heart failure, but there is a substantial incidence of sudden death, suggesting that ventricular arrhythmias may be an important feature of the disease process.<sup>8,9</sup> Other complications include atrial fibrillation, cerebral ischemic events, and endocarditis.

In patients with mitral-valve prolapse, the clinical outcome depends on the extent of leaflet disease and the severity of mitral regurgitation. The progression of disease may be slow and insidious or may be abrupt, as a result of a chordal rupture leading to flail leaflet. In one study of patients with initially asymptomatic severe mitral regurgitation caused by mitral-valve prolapse, only 28 percent required surgery within five years because of the onset of symptoms.<sup>10</sup> In contrast, 90 percent of patients with a flail mitral-valve leaflet died or underwent surgery within 10 years, whether or not they initially had symptoms.<sup>11</sup>

Mitral regurgitation as a sequela of rheumatic fever is uncommon in the United States and is typically associated with some degree of mitral stenosis.<sup>12</sup> Ischemic mitral regurgitation encompasses several mechanisms, including papillary-muscle dysfunction, regional ventricular dysfunction, and left ventricular dilatation. The outcome is related to the severity of symptoms at presentation and the extent of underlying coronary disease.<sup>13</sup> In patients with dilated cardiomyopathy, mitral regurgitation has diverse causes, including annular dilatation, changes in the shape and size of the left ventricle, and systolic dysfunction.<sup>14</sup>

### STRATEGIES AND EVIDENCE

Most patients in whom chronic mitral regurgitation is diagnosed have mild-to-moderate disease and are unlikely ever to need surgical intervention. Management is directed toward identifying the cause and severity of the regurgitation, treating underlying disease processes, preventing complications, educating the patient, and evaluating risk factors for coronary disease. In patients with primary mitral-valve disease, periodic echocardiography allows early detection of impaired left ventricular systolic function on the basis of the measurement of the end-systolic dimension and ejection fraction (Table 1). Other echocardiographic measures that are useful in clinical decision making include assessment of the size of the left atrium and pulmonary systolic pressure.

#### Medical Therapy

No known medical therapies directly affect the disease process in the valve leaflets in patients with mi-

**TABLE 1. RECOMMENDED FREQUENCY OF ECHOCARDIOGRAPHY IN PATIENTS WITH CHRONIC MITRAL REGURGITATION AND PRIMARY MITRAL-VALVE DISEASE.**

SEVERITY OF MITRAL REGURGITATION	LEFT VENTRICULAR FUNCTION*	FREQUENCY OF ECHOCARDIOGRAPHY†
Mild	Normal ESD and EF	Every 5 yr
Moderate	Normal ESD and EF	Every 1–2 yr
Moderate	ESD >40 mm or EF <0.65	Annually
Severe	Normal ESD and EF	Annually
Severe	ESD >40 mm or EF <0.65	Every 6 mo

\*ESD denotes end-systolic dimension, and EF ejection fraction.

†An increased frequency of echocardiography is recommended if there is an interim change in symptoms or findings on physical examination, new-onset atrial fibrillation, evidence of progressive left ventricular dilatation or systolic dysfunction, or a progressive increase in pulmonary-artery systolic pressure. A decreased frequency of echocardiography is appropriate if findings are stable for two to three examinations. Echocardiography is also warranted in some cases as part of the preoperative evaluation for noncardiac surgery, monitoring during pregnancy, or intraoperative monitoring.

tral-valve prolapse or rheumatic valve disease. There has been sustained interest in the concept of using vasodilator therapy to decrease the severity of mitral regurgitation and the rate of left ventricular dilatation. The rationale for vasodilator therapy is that a reduction in the afterload may increase aortic flow and decrease mitral backflow. To some extent, this rationale has been validated in small, short-term studies that demonstrated a decrease in systemic vascular resistance and regurgitant fraction and an increase in cardiac output with vasodilator therapy, often with a decrease in ventricular volumes and end-diastolic pressure.<sup>15,16</sup> However, these studies show that vasodilators are most effective in improving symptoms in patients with mitral regurgitation associated with ventricular dilatation and impaired systolic function.<sup>17</sup> There are no data that support the use of vasodilator therapy in patients with asymptomatic mitral regurgitation and normal ventricular function.<sup>18</sup> Most important, the use of medical therapy should not delay consideration of surgical intervention in patients with symptoms or evidence of left ventricular systolic dysfunction.

Medical therapy is primarily directed toward the treatment of the complications of mitral regurgitation and the prevention of endocarditis with antibiotic prophylaxis. If atrial fibrillation occurs, standard approaches to rate control, cardioversion, and anticoagulation are indicated.<sup>18</sup> In patients with mitral regurgitation as a result of ischemic disease, prevention of ischemia with medical therapy, percutaneous transluminal coronary intervention, or bypass grafting is appropriate. In patients with mitral regurgitation due to dilated

cardiomyopathy, medical therapy for heart failure, including afterload reduction, often results in improvement in left ventricular shape, size, and systolic function in association with a reduction in the severity of regurgitation.

#### Mitral-Valve Surgery

The optimal surgical intervention for mitral regurgitation is valve repair. As compared with valve replacement, successful valve repair results in superior hemodynamics and ventricular function, avoidance of a prosthetic valve and the need for long-term anticoagulation, and less distortion of ventricular shape. The feasibility of valve repair is highest in patients with mitral-valve prolapse, especially in those whose disease is confined to the posterior leaflet. As surgical techniques improve, an increasing number of patients are becoming candidates for this procedure. When valve repair is not technically possible, every effort is made to maintain the integrity of the mitral chordal apparatus. With chordal preservation, there is little change in the ejection fraction after surgery, as compared with an average decline of 10 ejection-fraction units in patients with transected chords. The operative mortality rate is lower for mitral-valve repair than for valve replacement (2 to 4 percent vs. 5 to 10 percent). In patients with mitral-valve prolapse, long-term clinical outcome is excellent, with survival rates of 80 to 94 percent at 5 to 10 years with valve repair as compared with 40 to 60 percent with valve replacement.<sup>19,20</sup>

In patients with symptoms due to mitral regurgitation, surgical intervention is indicated, unless they have severe left ventricular dysfunction. In asymptomatic patients with severe mitral regurgitation, the outcome is improved if surgery is performed before the onset of irreversible ventricular dysfunction. No randomized trials have assessed the optimal timing of intervention for asymptomatic severe mitral regurgitation, and the ideal measure of ventricular contractility remains elusive. However, a consensus has been reached that left ventricular end-systolic dimension and ejection fraction can be used to identify early systolic dysfunction. The evidence supporting this approach is derived from studies in patients who were undergoing valve surgery for severe mitral regurgitation that assessed the value of preoperative variables as predictors of postoperative ventricular performance.<sup>4,21-23</sup> Indicators of early systolic dysfunction are an end-systolic dimension of 45 mm or more or an ejection fraction of 0.60 or less. Systolic dysfunction is most likely when both values are abnormal and sequential studies show a progressive deterioration. Other factors that may affect the timing of surgical intervention include the feasibility of valve repair, the onset of atrial fibrillation, and the development of progressive pulmonary hypertension (Fig. 3). There are two noteworthy features of these criteria: the degree

of ventricular dilatation seen with isolated volume overload due to mitral regurgitation is much less than that seen in aortic regurgitation, a condition characterized by combined pressure and volume overload, and these criteria only apply to patients with severe mitral regurgitation.

### AREAS OF UNCERTAINTY

#### Assessment of the Severity of Mitral Regurgitation

The current definition of severe mitral regurgitation is based on angiographic and echocardiographic descriptors of the degree of backflow across the valve. An alternative physiological definition would be mitral regurgitation severe enough to result in dilatation of the left ventricle, left atrium, or both. However, the best definition would be regurgitation leading to adverse clinical outcomes. Unfortunately, prospective data based on quantitative measures of severity are not available. Thus, it is not certain whether some patients with moderate regurgitation have severe disease that has not yet resulted in ventricular enlargement. The percentage of patients with mild regurgitation who will have a progressive increase in the severity of mitral regurgitation is also unknown.

#### Medical Therapy for Primary Valve Disease

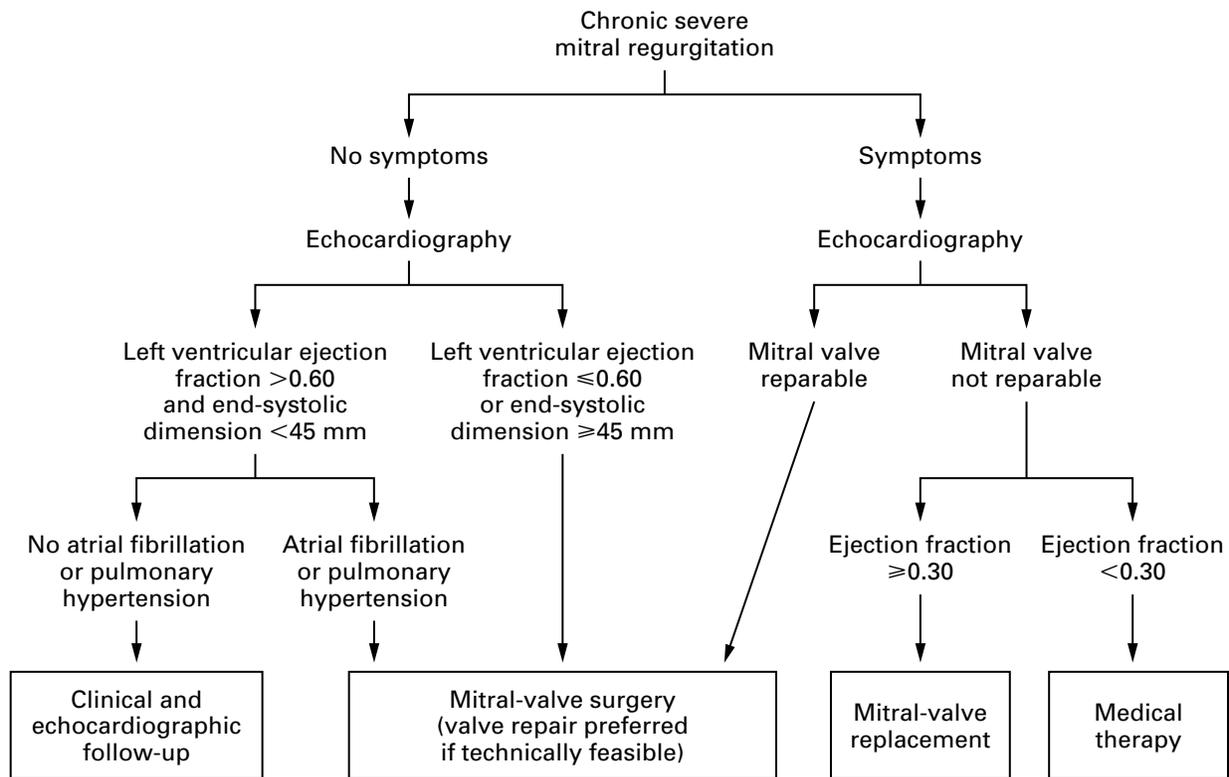
In patients with severe mitral regurgitation due to primary valve disease, there are no persuasive data that medical therapy decreases the rate of ventricular dilatation or delays valve surgery. Some clinicians argue that medical therapy may even be harmful if it increases the severity of regurgitation in patients with mitral-valve prolapse, prevents normal adaptive responses of the left ventricle, or delays the recognition of early symptoms or ventricular dysfunction.

#### Timing of Surgical Intervention

When severe mitral regurgitation and severely reduced ventricular function are both present, it can be difficult to determine whether ventricular dysfunction is the cause or a consequence of chronic regurgitation. In either case, the surgical outcome is poor when the ejection fraction is less than 0.30, unless chordal continuity is preserved. In some patients, a trial of medical therapy for heart failure and an evaluation for other causes of left ventricular dysfunction may clarify the situation. Because the optimal approach to these patients is controversial, clinical decision making must be individualized on the basis of the evaluation of ventricular and valvular function, the likelihood of valve repair, the presence of other underlying conditions, and the patient's preferences.

#### Valve Repair in Patients with Secondary Mitral Regurgitation

Some studies of patients with ischemic mitral regurgitation suggest that revascularization alone decreases the severity of regurgitation, whereas other



**Figure 3.** Management of Chronic Severe Mitral Regurgitation.

Modified from the American College of Cardiology–American Heart Association guidelines.<sup>18</sup>

studies suggest that concurrent valve repair or the placement of an annuloplasty ring is necessary.<sup>24</sup> Revascularization might be effective if regurgitation is due to ischemia or if revascularization improves the shape of the mitral valve. However, if there is irreversible myocardial damage or if remodeling does not occur, then mitral regurgitation may persist. In the absence of randomized clinical trials, the surgical decision is currently individualized on the basis of the mechanism of regurgitation in each patient.

In patients with dilated cardiomyopathy, mitral regurgitation is due to the change in the shape of the valvular apparatus, so that the severity of regurgitation is often decreased by medical therapy that restores the ventricular size and shape. Some centers advocate mitral-valve surgery in these patients, but this approach is not widely accepted.<sup>25</sup>

### GUIDELINES

The American College of Cardiology and the American Heart Association have developed detailed guidelines for the evaluation, follow-up, and optimal timing of surgical intervention in patients with severe mitral

regurgitation.<sup>18</sup> Appropriate candidates for mitral-valve surgery include patients with symptoms, except those with severe ventricular dysfunction, and patients with no symptoms who have mild or moderate ventricular dysfunction. Surgery is indicated in asymptomatic patients with preserved ventricular function if there is a high likelihood of valve repair or if there is evidence of pulmonary hypertension or recent atrial fibrillation. Guidelines also address the use of echocardiography, the prevention of rheumatic fever and endocarditis, and indications for anticoagulation.

### CONCLUSIONS AND RECOMMENDATIONS

In the case of patients with a cardiac murmur, the threshold for echocardiographic evaluation should be low. When the valve is anatomically abnormal, periodic clinical and echocardiographic follow-up allows early identification of symptoms, complications, and systolic dysfunction. In patients with secondary mitral regurgitation, echocardiography serves as the first step toward the evaluation and treatment of the underlying disease process. Patient education is vital, both to ensure compliance with follow-up and to al-

low the patient to participate in the decision-making process.

In the case of the patient described in the vignette, annual echocardiography and evaluation by a cardiologist are appropriate to monitor the severity of mitral regurgitation, the size of the left ventricle, and pulmonary-artery pressure. Surgical intervention in patients with severe mitral regurgitation is indicated at the onset of symptoms or in the presence of convincing evidence of left ventricular systolic dysfunction. Valve repair rather than valve replacement should be performed whenever possible. We should remain cautious in recommending valve surgery for asymptomatic patients who are considered to have severe mitral regurgitation but who have no evidence of consequences of hemodynamic abnormalities. However, the excellent anatomical and clinical outcomes of valve repair make surgical intervention appropriate earlier in the course of disease in many patients with severe mitral regurgitation as a means of preventing chronic volume overload.

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