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Mitral Valve Regurgitation in the Contemporary Era

Insights Into Diagnosis, Management, and Future Directions

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CME/MOC Objective for This Article: After reading this article the reader should be able to: 1) diagnose and manage patients with mitral valve regurgitation in the contemporary era; 2) interpret the echocardiographic 2D and Doppler features of mitral valve regurgitation to identify its mechanism and severity, as well as the potential pitfalls of quantification; and 3) predict the likelihood of successful surgical and transcatheter mitral valve repair in mitral regurgitation.

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ABSTRACT

Mitral valve regurgitation (MR) is the most common valvular heart disease. Primary MR is a disease of the mitral valve apparatus, whereas secondary MR is a disease of the left ventricle. Diagnosing and managing MR is often challenging and requires a structured approach, integrating findings on history, physical examination, and imaging. Decisions regarding treatment depend on knowledge of the etiology, natural history, and outcome of interventions for these patients with mitral valve disease. The optimal timing of intervention requires a comprehensive 2-dimensional and Doppler echocardiogram in each patient to determine the cause of the mitral valve disease, the severity of the regurgitation, and the effect of the volume overload on the left ventricle, as well as determining if a durable valve repair can be performed. Advances in both surgical and catheter-based therapies have resulted in recommendations for lower thresholds for operation and extension of interventional treatments to the older, sicker population of patients with MR. The current review discusses the pathophysiological rationale for current diagnostic and management strategies in MR.
(J Am Coll Cardiol Img 2018;11:628–43)

The mitral valve (MV) apparatus is a dynamic structure that has complex interactions with surrounding anatomy. Disruption of any component of the apparatus or surrounding anatomy can lead to mitral valve regurgitation (MR) (1). MR is the most common valvular heart disorder (2). The incidence of MR increases with age, and thus the number of patients with MR requiring hospitalization or intervention will rise sharply in the next decades (3). Untreated severe MR is associated with poor outcomes due to the adverse consequences of long-standing volume overload on the left ventricle. However, early intervention may result in excellent long-term outcomes in primary MR, making early recognition, classification of etiology, and appropriate timing of intervention critical in patients presenting with suspected severe MR. The purpose of the current review was to outline an integrative clinical and echocardiographic approach to chronic MR, with a focus on the contrasts between degenerative and secondary MR.

PRIMARY MR

ETIOLOGY. Primary MR is defined as a primary abnormality of the MV apparatus. The most common cause of primary MR is myxomatous degeneration of the MV leaflets leading to MV prolapse (4). The spectrum of severity of myxomatous degeneration ranges from fibroelastic deficiency, with thin leaflets and focal prolapse, to Barlow's disease, with diffusely thickened and redundant leaflets (5). Fibroelastic deficiency usually presents with chordal rupture and flail leaflet. Barlow's disease usually causes long-standing MR but is associated with poor outcomes, including arrhythmias and sudden cardiac death (6).

Primary MR can also occur from leaflet perforation and cleft leaflets, which are deep indentations that extend to the annulus. Rheumatic disease, drugs, radiation, and connective tissue disease can cause restricted leaflet motion from thickening of the leaflet edges and subvalvular apparatus. An increasing cause of mitral regurgitation in the elderly population is mitral annular calcification, which is a degenerative process that starts in the posterior annulus and extends into the base of the leaflets and subvalvular apparatus, affecting annular and leaflet function (7).

PATHOPHYSIOLOGY. In the early stages of MR, left ventricular (LV) wall stress due to volume overload is countered by increased LV fractional shortening due to a low resistance run-off into the low-pressure left atrium. If forward cardiac output is maintained by these compensatory mechanisms, an evolution from the acute to the chronic compensated stage of MR will then occur. In the compensated stage, LV dilatation maintains normal wall stress and diastolic pressures. Patients remain asymptomatic during this phase for years to decades.

However, with long-standing MR, there will eventually be progressive LV enlargement beyond that of a compensated stage. This scenario is due to increasing severity of MR, continued compensatory chamber enlargement, or a combination of both. Progressive

ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass graft

EF = ejection fraction

ERO = effective regurgitant orifice

LV = left ventricular

LVESD = left ventricular end-systolic dimension

MR = mitral valve regurgitation

MRI = magnetic resonance imaging

MV = mitral valve

PISA = proximal isovelocity surface area

RVol = regurgitant volume

TTE = transthoracic echocardiography

LV enlargement itself can cause increasing degrees of MR from altered ventricular geometry and annular dilatation, thus the term "MR begets MR." As the disease progresses, systolic LV wall stress is increased due to a larger ventricular minor axis as the ventricle assumes a more spherical shape. This outcome leads to an increase in end-diastolic pressure and eventually a decreased contractile state, with reduced myofiber content and interstitial fibrosis (8). As this process continues, irreversible LV dysfunction occurs, which leads to the decompensated stage of MR with symptoms of heart failure and a poor prognosis. Importantly, the irreversible ventricular dysfunction may occur before onset of symptoms (**Figure 1**).

NATURAL HISTORY. Natural history studies of primary MR have shown a poor outcome of untreated severe primary MR. Overall, 90% of patients who presented with severe MR due to a flail leaflet were dead or required surgery at 10 years' follow-up (9). There was a 30% incidence of atrial fibrillation and 63% incidence of heart failure, both of which were shown to be independently associated with reduced survival. With the advent of MR Doppler quantification, a prospective study of 456 patients with asymptomatic severe MR reported increased mortality and cardiac events as the degree of regurgitation increased, with the poorest outcome when the effective regurgitant orifice (ERO) area was ≥40 mm^2 (10).

The outcome of patients with severe MR depends on the initial symptoms and presence or absence of ventricular dysfunction. Patients with severe MR and New York Heart Association functional class I and II who did not undergo operation had a mortality rate of 4.1% per year compared with 34.0% in those with class III and IV symptoms. Moreover, when stratified according to ejection fraction (EF), patients with EF <60% had markedly lower 10-year survival compared with those with EF ≥60%. Sudden death is a frequent catastrophic event responsible for approximately one-fourth of deaths in patients receiving medical treatment (11). Although the outcome is poorest in those patients who have already developed symptoms or LV systolic dysfunction, in a subset of patients from a multicenter study who were completely asymptomatic with normal ventricular function, the 5-year combined incidence of atrial fibrillation, heart failure, or cardiovascular death was 42 ± 8% (12).

RESULT OF OPERATIVE INTERVENTION. Once a patient develops symptoms, MV operation with repair or replacement in the patient with severe primary MR will uniformly result in improvement or resolution of symptoms. However, the older strategy of surgical intervention only for symptoms is accompanied by excess morbidity and mortality, primarily due to heart failure from residual LV dysfunction. Once LV dysfunction occurs, MR has already transitioned into the decompensated stage, and prognosis is worse (13). Studies found that low preoperative EF (<60%) as well as high left ventricular end-systolic dimension (LVESD) (>40 mm) predicted postoperative LV dysfunction and were independently associated with increased postoperative mortality (14–16).

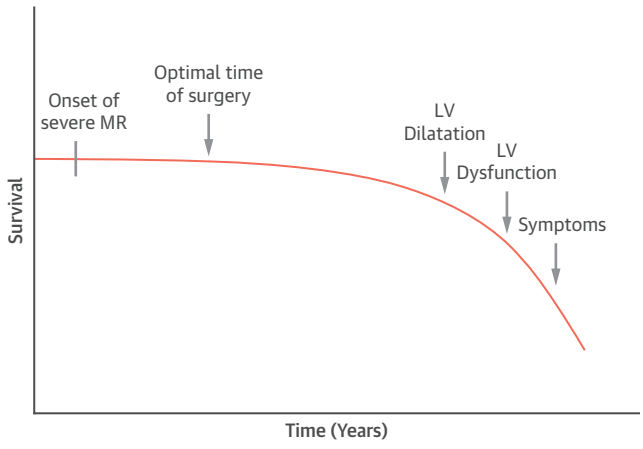
These criteria of an EF <60% and LVESD >40 mm indicate when the patient has reached the stage of irreversible LV dysfunction and do not determine when the actual transition to LV dysfunction occurs. Although a transient, but often irreversible, postoperative drop in EF is expected in patients who meet these parameters, "unexpected LV dysfunction" (defined as a depressed EF after the correction of MR) may occur even before these parameters are reached (17). It is therefore important to recognize that the "cutoff criteria" are measurements of when the decompensated stage of LV dysfunction has already occurred. Ideally, operation should be performed before this end-stage occurs.

Advances in MV repair have presented a paradigm shift in the surgical management of severe primary MR. MV repair is associated with a lower operative mortality, greater long-term survival and quality of life, and less endocarditis and bleeding from anticoagulation compared with MV replacement (18). The outcome of successful repair in patients with preserved LV function is excellent, comparable to an age-matched control population without heart disease. This finding has resulted in an approach to consider early MV surgery in asymptomatic patients with severe MR even with an EF >60% or LVESD <40 mm if there is a high probability of repair with low operative risk. Studies in which patients were stratified according to timing of surgery have shown that patients undergoing early surgery had an improved survival rate and better outcome compared with the conservatively managed group (19). The beneficial effect of early surgery was observed in both asymptomatic and minimally symptomatic patients, as well as those with heart failure symptoms.

INTEGRATIVE APPROACH TO DIAGNOSIS AND MANAGEMENT IN PRIMARY MR. As with any diagnosis in clinical medicine, the approach to the diagnosis and treatment of primary MR relies on Bayesian probability and integrative use of all diagnostic

information. The initial indication that severe primary MR is present should be based on a careful history and physical examination. Eliciting reports of fatigue or exercise intolerance, either from history or through stress testing, is important, as many patients will adapt their lifestyle to accommodate limitations from chronic valve disease. Physical examination can often detect very specific signs of severe MR, including a loud holosystolic murmur, diastolic rapid filling sound or flow rumble, and a hyperdynamic enlarged apical impulse. A late systolic murmur associated with mitral prolapse is rarely severe. Alternatively, a holosystolic MR in a patient with previous click and/or late systolic murmur should raise concern for a flail leaflet, which nearly always indicates severe MR. The direction of radiation of murmur can identify the leaflet involved with a posterior directed murmur in anterior leaflet prolapse, and radiation to the left sternal border with posterior prolapse. The history and physical examination set a high pre-test probability that severe MR is present, and transthoracic echocardiography (TTE) should then be performed (**Figure 2**).

FIGURE 1 Pathophysiology and Natural History of Primary MR

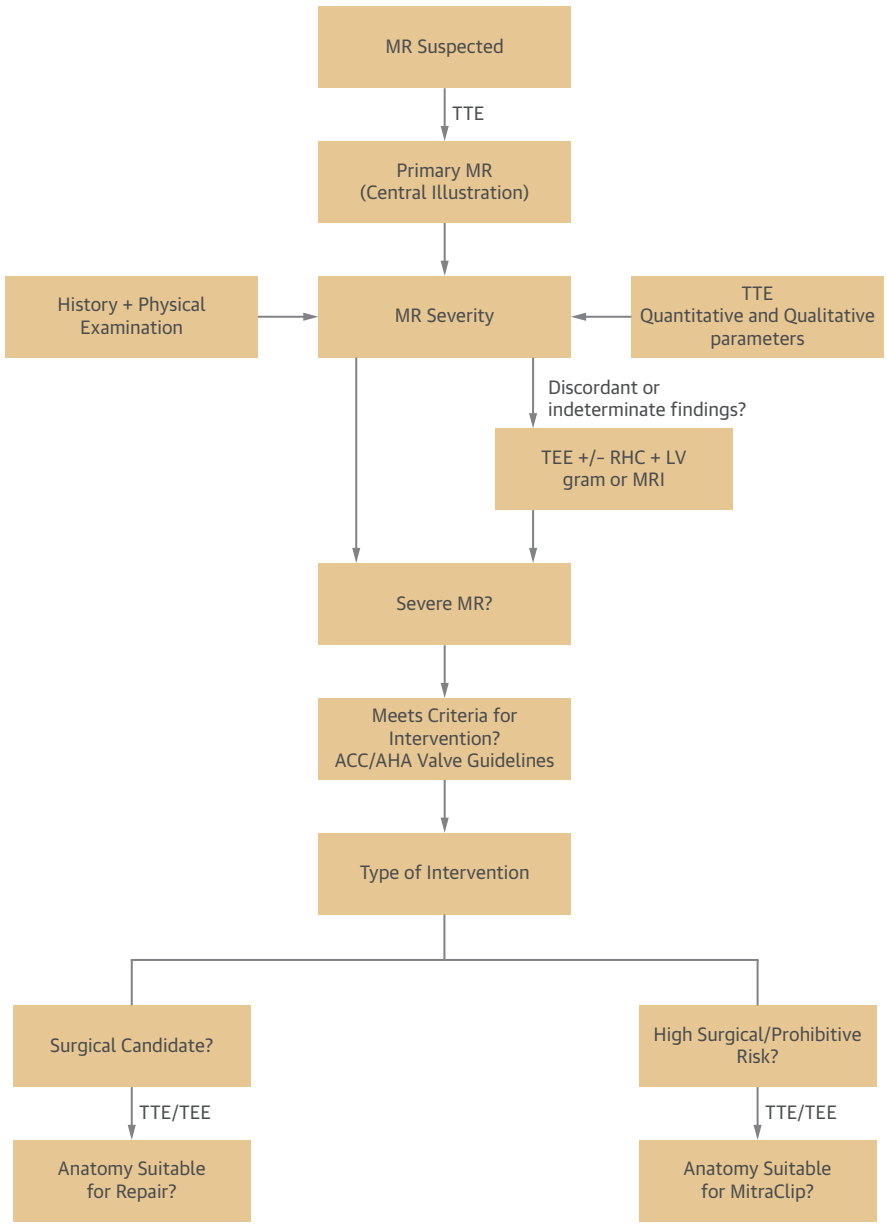


Untreated severe mitral valve regurgitation (MR) will eventually lead to left ventricular (LV) dilatation followed by LV dysfunction and onset of symptoms. The optimal time of surgery would be before the decompensated stage where irreversible damage to the left ventricle can occur.

The role of TTE is as follows: 1) to identify the etiology of the MR; 2) to quantify the severity of the regurgitation; 3) to assess the response of the left ventricle to the volume overload; and 4) to determine the feasibility of durable repair. If at any step the TTE is nondiagnostic, a transesophageal echocardiogram is indicated (20). Newer imaging modalities with high-resolution images such as 3-dimensional echocardiography, magnetic resonance imaging (MRI) scanning, and intracardiac ultrasound are being evaluated to determine if they provide further incremental benefit.

Etiology of MR. Patients with primary MR should be grouped according to the Carpentier classification, which is useful for understanding etiology as well as therapeutic approaches (**Central Illustration**). Carpentier type I primary MR has normal leaflet size and motion, with the MR due to leaflet perforation or congenital clefts; Carpentier type II MR has excessive leaflet motion with prolapse or flail leaflets; and Carpentier type IIIa MR describes leaflet restriction in diastole, most commonly seen in rheumatic disease. The classification will aid in determining the feasibility of valve repair, which in itself will help with timing of operation. MV prolapse is seen on echocardiography by systolic displacement of the leaflet at least 2 to 3 mm above the annular plane (7), but even less significant systolic displacement is often pathologic and associated with subsequent clinical MR over prolonged follow-up (21). This diagnosis is best made in the parasternal long-axis view or apical long-axis view (7). Use of the apical 4-chamber view cuts the saddle-shaped annulus at its low points, giving the false impression of prolapse (22). Identifying which leaflet is involved is crucial for determining adequacy for repair (23). The color Doppler jet direction is typically opposite to the prolapsing leaflet. Flail leaflets are diagnosed by seeing the free edge of the leaflet prolapsing into the left atrium and an eccentric holosystolic Doppler regurgitant jet, and are almost always associated with severe regurgitation. In patients with bileaflet prolapse and intact chordal structures, there is frequently mid-late systolic MR with a central jet, and these rarely cause severe regurgitation. Evaluation of the severity of myxomatous degeneration, redundancy, and leaflet thickness are important factors to determine feasibility of repair. The presence, degree, and localization of calcium in the annulus or valve should be assessed. Rheumatic MV disease (Carpentier type IIIa) is diagnosed by noting leaflet thickening, especially at the leaflet edges and commissures, usually with some degree of coexisting mitral stenosis. There is thickening and shortening of the chordal apparatus, resulting in retraction of the leaflets in both systole and diastole. The anterior leaflet assumes hockey-stick morphology, and the posterior leaflet is fixed (7). In patients who have previous infective endocarditis or those with a congenital cleft, the morphology and motion of the MV may be normal (Carpentier type I), but there is regurgitation through the clefts or areas of direct damage to the leaflets.

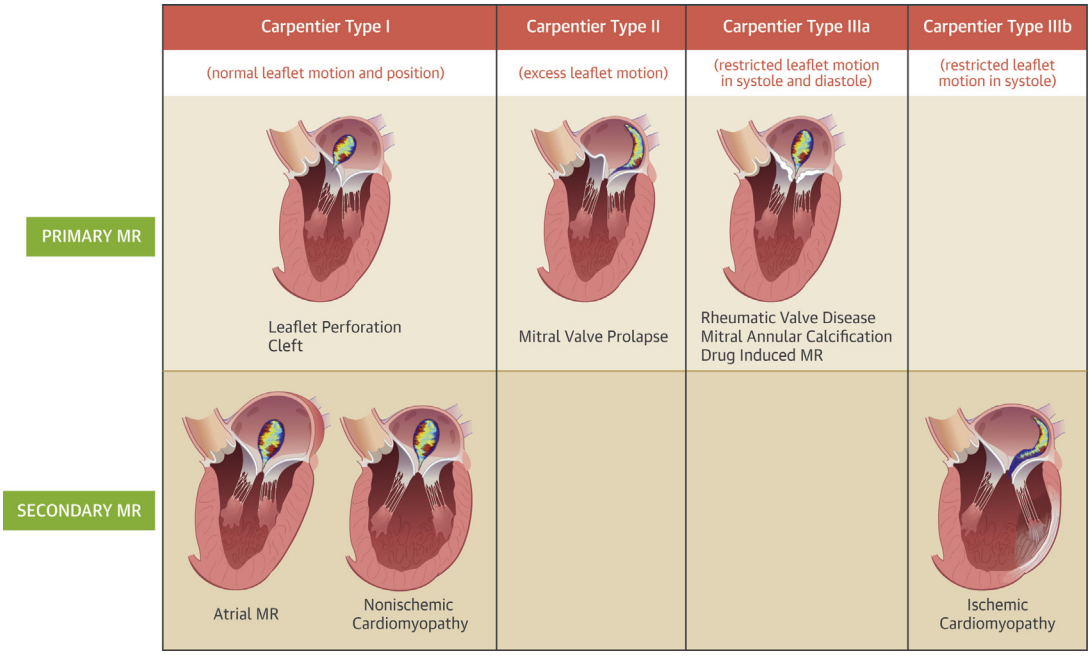
FIGURE 2 Pathway for Diagnosis and Management of Primary MR



When primary mitral valve regurgitation (MR) is suspected based on history and physical examination, transthoracic echocardiography (TTE) is required to identify the etiology by using the Carpentier classification and to quantify severity. If there are discordant or indeterminate findings regarding severity, further quantification with transesophageal echocardiography (TEE), right heart catheterization (RHC) and left ventriculogram (LV gram), or magnetic resonance imaging (MRI) is then warranted. If severe, the next step would be to determine if any of the criteria for intervention are met based on the American College of Cardiology/American Heart Association (ACC/AHA) valve guidelines and to then determine surgical candidacy and feasibility of repair. If the patient is not a surgical candidate, an assessment for suitability for MitraClip intervention can be considered.

Quantifying the severity of MR. There is no single best measurement to quantify MR severity; rather, an integrative approach incorporating physical examination and pre-test probability with qualitative and quantitative measures should be pursued (Table 1). For example, presence of flail leaflet with a thick eccentric jet is specific for severe MR (7); alternatively, the presence of normal LV and left atrial size

CENTRAL ILLUSTRATION **Classification of the Etiology of MR**



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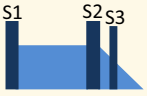
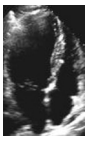
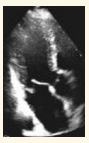
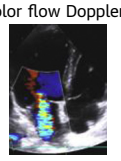
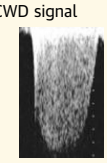
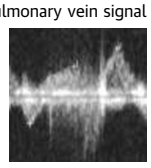
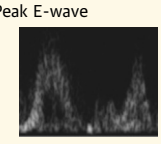
Primary and secondary mitral valve regurgitation (MR) groupings with their respective Carpentier's functional classification. Carpentier type I represents normal leaflet motion and position. Carpentier type II represents excess leaflet motion. Carpentier type IIIa represents restricted leaflet motion in systole and diastole. Carpentier type IIIb represents restricted leaflet motion in systole.

should make one question a diagnosis of severe chronic MR (20) regardless of the appearance of the size of the color flow jet. The size and direction of the color flow Doppler jet are frequently used to screen for significant MR, but it is important to remember that color Doppler only displays velocity (and not flow). Therefore, a small regurgitant volume but high velocity jet can misleadingly appear visually like severe MR (7). Moreover, visual assessment of the size of the color flow jet can underestimate MR in eccentric jets that hit the wall of the left atrium and lose velocity and energy (Coanda effect), as well as in severe mitral annular calcification in which acoustic shadowing can occur behind the rim of the calcified annulus. Indirect hemodynamic findings such as pulmonary hypertension or a high transmitral E-wave velocity (indicating a large "v" wave in the left atrial pressure) may help in further establishing the diagnosis of severe MR.

If patients are being considered for early mitral intervention, it is important to obtain quantitative measurements of the severity of MR (**Table 1**). Regurgitant volume (RVol) and ERO can be calculated through either the proximal isovelocity surface area (PISA) or the continuity method (7). In experienced centers, these measurements are reproducible and have been correlated with long-term outcomes (10). The PISA method estimates the ERO at peak MR velocity and extrapolates flow through this ERO for the duration of systolic flow (as determined by the MR tissue velocity integral) to calculate RVol. The PISA method does have limitations: 1) the ERO is not static throughout systole and varies as prolapse worsens dynamically throughout systole (24); and 2) the assumption of a hemispherical shape for PISA calculation may not be accurate with complex ERO shapes, such as with prolapse or flail, or with eccentric jets. If there is only a late systolic jet of MR, ERO will overestimate MR severity, and the RVol is better reflective of MR severity (25). All these quantitative measurements must always be cross-checked with clinical and other echocardiographic data.

The continuity equation is an alternative method for quantifying MR and can be used in early and late systolic MR and eccentric and multiple jets. Limitations of this method include errors of mitral annulus

TABLE 1 Quantitative and Qualitative Measures of the Severity of MR

	Qualitative Parameters	
Parameter	**Severe MR**	**Disadvantages**
Physical examination 	Loud, holosystolic, with diastolic murmur; outward displaced apical impulse	Findings can be nonspecific for severe MR
LA and LV size 	Normal excludes severe MR	Nonspecific; can be secondary to other conditions.
MV apparatus anatomy 	Flail leaflet	Not sensitive
Color flow Doppler 	Large jet area	Affected by transducer settings and hemodynamic loading conditions; underestimates eccentric jets
CWD signal 	Dense and triangular signal; decreased slope of positive dp/dt suggests LV dysfunction	Underestimates in eccentric jets or if poor gain
Pulmonary vein signal 	Systolic flow reversal	Affected by LA pressure, direction of jet, and atrial fibrillation
Peak E-wave 	E-wave >1.2 m/s	Affected by LA compliance, LV diastolic function and atrial fibrillation

Continued on the next page

diameter measurement given its noncircular dimension and inapplicability in the presence of concomitant aortic regurgitation (7). Given the complexity of MR assessment, there is sometimes discordance in MR severity between physical examination findings and TTE. If that occurs, additional testing, including TEE, MRI, or cardiac catheterization with a left ventriculogram, is warranted (Online Figure 1, Online Videos 1 and 2) (20).

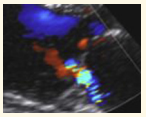
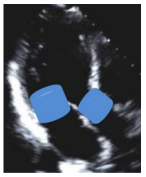
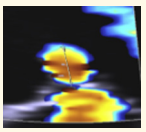
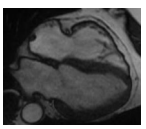
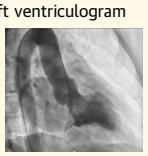
Measurement of LV response to MR. Although it would be ideal to have true LV volume measurements to determine the LV response to volume overload, LV dimensions are currently used as a surrogate. There are problems with the reproducibility of LV volume measurements by 2-dimensional echocardiography. Although 3-dimensional echocardiography, MRI (26), or computed tomography scanning now provides a more reliable method of measuring LV volumes, no outcome studies are yet available that can be used to incorporate these measurements into clinical decision-making. Thus, current recommendations for timing of intervention are based on LV dimensions derived from a parasternal long-axis view taken at the level of the papillary muscle and cannot be used in the presence of regional wall motion abnormalities. In cases in which there has been a change in the reported dimensions or EF, it is important to obtain serial measurements to look for trends in progression of LV size and function.

Determination of repairability. It is critical to determine the feasibility of a successful durable valve repair, particularly when considering operation in the asymptomatic patient with preserved LV systolic function. The anticipated success rate must take into consideration the valve morphology (Carpentier classification), as well as the surgical expertise. There is a wide variation in the ability to perform durable MV repair among surgeons in the United States, and each surgeon's data should be available.

The valve abnormality that lends itself to a successful repair is the degenerative disease with fibroelastic deficiency or chordal rupture involving a scallop of the posterior leaflet (Carpentier type II). In patients with this condition, quadrangular or triangular resection with implantation of an annular ring will result in successful repair, achievable by the majority of cardiac surgeons. Repair becomes more difficult if there is calcification of the annulus, precluding adequate ring annuloplasty, or calcification and fibrosis of the valve leaflets. The echocardiographic findings of the likelihood of successful repair are summarized in **Figure 3** (27). It requires a higher level of surgical expertise to achieve a successful durable repair with increasing leaflet redundancy and excessive tissue involving the anterior leaflet, as this anatomy requires additional surgical procedures such as chordal transfer and implantation of artificial chords, as well as addressing commissural problems (**Figure 4**).

Surgeons with expertise in valve disease can usually repair clefts and isolated damage to the valve from previous infective endocarditis, if there has not been extensive involvement from the infection (Carpentier type I). Repair of other valves, such as those of the rheumatic etiology (Carpentier type IIIa), should be performed by highly experienced surgeons who have dedicated their surgical career to MV repair.

TABLE 1 Continued

Quantitative Parameters		
Parameter	**Severe MR**	**Disadvantages**
Vena contracta 	≥0.7 cm	Not valid in multiple jets; overestimates MR if not holosystolic
Continuity equation 	RVol ≥60 ml/beat RF ≥50% EROA ≥0.4 cm^2	Measurement of flow at MV annulus prone to error especially if calcified; not valid with concomitant AR
PISA 	RVol ≥60 ml/beat RF ≥50% EROA ≥0.4 cm^2	Not valid in multiple jets; less accurate in eccentric jets or crescent-shaped orifices
Cardiac MRI 	RVol ≥60 ml/beat RF ≥50%	Severity thresholds not well established; less accurate with atrial fibrillation
Left ventriculogram 	4+ Mitral regurgitation	Invasive; requires contrast use.

AR = aortic regurgitation; CW = continuous wave; dp/dt = the rate of early systolic left ventricular pressure rise; LA = left atrial; LV = left ventricular; MV = mitral valve; MR = mitral valve regurgitation; PISA = proximal isovelocity surface area.

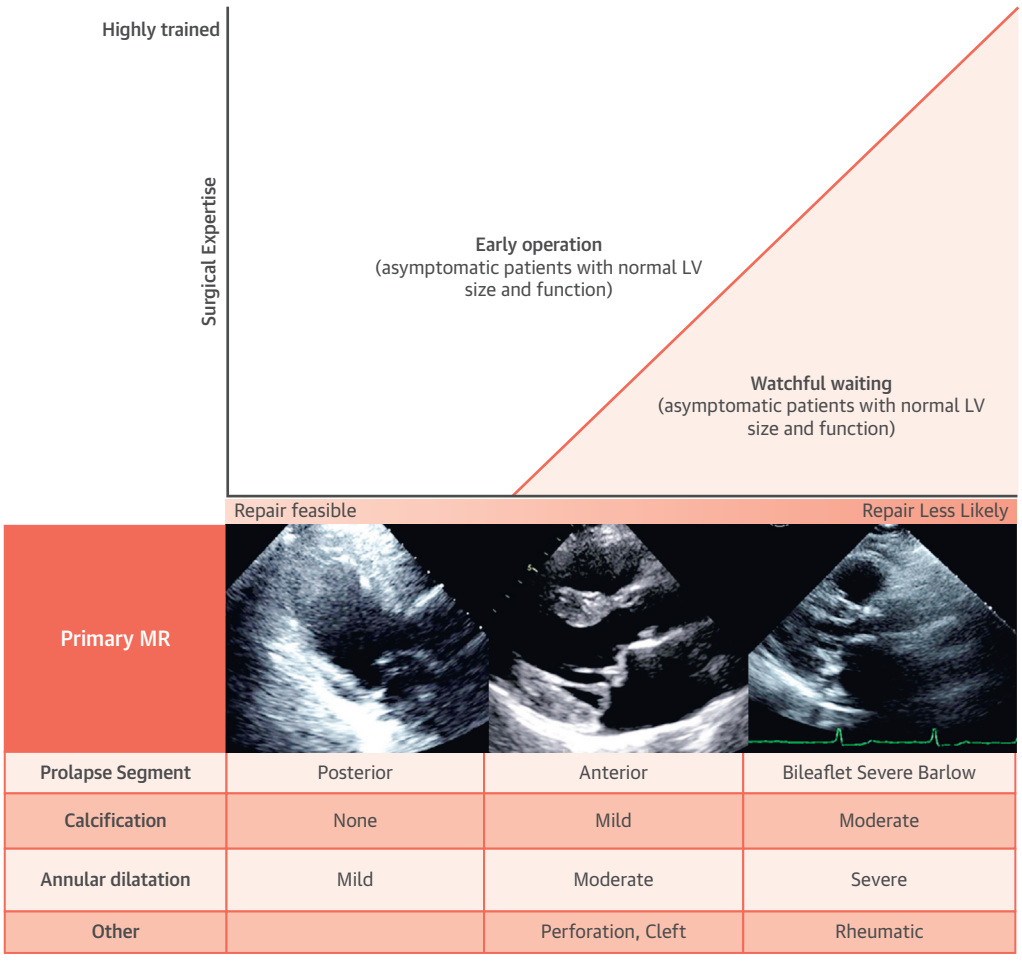
CRITERIA FOR INTERVENTION BASED ON SYMPTOMS, LEFT VENTRICLE, AND REPAIRABILITY. Surgical referral. All patients with symptoms and severe MR should be considered for operation, unless there are contraindications to surgery. Operation will universally result in improvement of symptoms, irrespective of whether the valve is repaired or replaced. However, by waiting for symptoms to develop, the long-term outcome of these patients is poor, as many patients will have already developed incipient LV dysfunction.

If the patient is not symptomatic, it is important to then determine the status of the left ventricle. The current American College of Cardiology/American Heart Association guidelines recommend operation in the asymptomatic patient if there is evidence of LV dysfunction (28). Although asymptomatic patients with LV dysfunction pre-operation and post-operation have a poorer outcome, they do better with operation versus continued medical observation. Due to the favorable loading conditions for myocardial performance (increased preload and decreased afterload), the "normal" EF in severe primary MR is higher than normal (8), such that once the EF is <60% (or in one study, 64%) (29), irreversible systolic dysfunction has already occurred and will manifest as post-repair LV dysfunction (13). Thus, repair must be performed in asymptomatic patients once the EF has declined to <60%, and it should be considered if the EF is progressively declining even above this range. LVESD >40 mm is another marker of systolic dysfunction, although, again, even progressive increases in LVESD below this range must be considered for surgery if repair is highly likely (16). For patients with advanced systolic dysfunction (EF <30%) and chronic primary MR, surgery is associated with high risk and uncertain benefit of myocardial recovery and must be considered on a case-by-case basis.

Finally, there is the asymptomatic patient with severe primary MR who maintains normal systolic function according to current parameters (EF >60% and ESD <40 mm). In the past, due to the relatively high operative mortality and adverse consequences of MV replacement, these patients were followed up until they developed symptoms or LV dysfunction. Currently, with the advances in MV repair, the recommendation is to consider early valve repair if: 1) the MR is truly severe; and 2) the valve can be repaired with a high degree of success and low operative risk. Although no randomized trials have been performed comparing early repair versus watchful waiting, the cumulative evidence supports early surgery when repair is likely (19), given its demonstrated long-term durability. For patients with a high likelihood of repair, surgery can strongly be considered above these standard cut points for asymptomatic patients if performed in a center of excellence with >95% likelihood or repair and <1% mortality to prevent adverse LV remodeling with incipient LV dysfunction, atrial fibrillation, or pulmonary hypertension (30). However, when repair is deemed less likely (due to features detected on imaging), watchful waiting is likely the preferred strategy, as premature placement of a prosthetic valve essentially replaces one disease for another, with its associated thromboembolic risks and need for re-intervention in the future.

Studies at high-volume centers have shown posterior leaflet prolapse repair success rates of >98% with low operative mortality, and 90% to 95% for anterior and bileaflet prolapse at <1% operative

FIGURE 3 Predictors of Feasibility of Surgical MV Repair in Primary MR

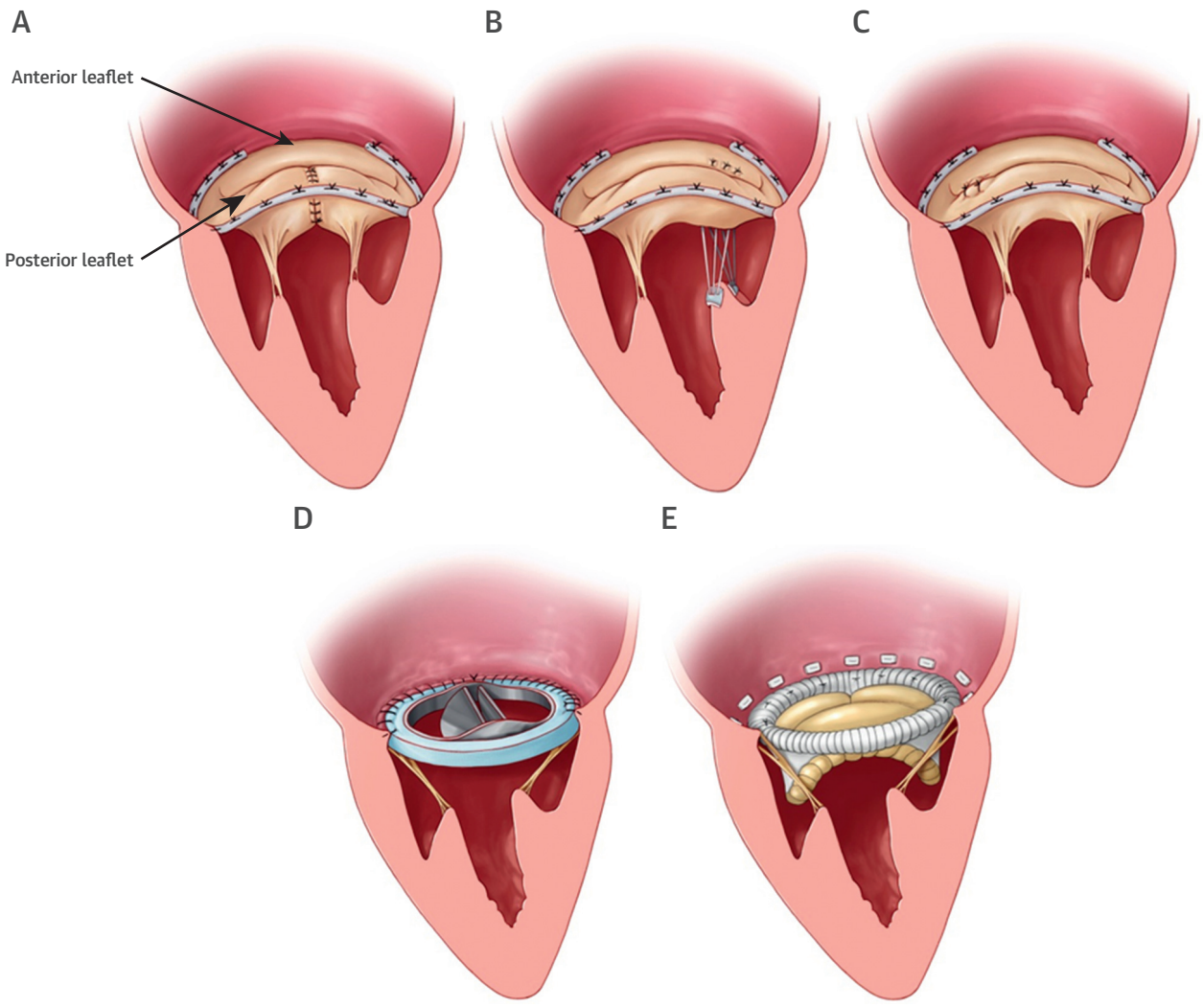


Surgical expertise is one of the major determinants in mitral valve (MV) repair feasibility. Localized posterior prolapse can be repaired by almost all surgeons. Repair of more complex anatomy (anterior or bileaflet) is feasible only by experienced surgeons. If feasibility of repair is high at a low risk by an experience surgeon, early surgery in asymptomatic severe MR is reasonable; otherwise, watchful waiting would be indicated. Abbreviations as in Figure 1.

mortality. They also report excellent 20-year durability in posterior leaflet repair with acceptable durability in anterior and bileaflet repair (31-33). Furthermore, the reoperation rate after any subset of leaflet prolapse, whether it is posterior (0.5%), anterior (1.6%), or bileaflet (0.9%), was similar to MV replacement (0.74%) (33), further supporting referral to high-volume centers for consideration of early surgery. Currently, a variety of repair techniques exist (Figure 4).

Referral for percutaneous intervention. There is emerging new technology using catheter approaches for the treatment of MR. At the present time, it is the "edge-to-edge" MitraClip device (Abbott Vascular, Santa Clara, California) that has been studied and approved for clinical use. This technique emulates the surgical Alfieri edge-to-edge leaflet repair by clipping the free edges of the anterior and posterior leaflets in the chord-free zone (34). For patients with primary symptomatic severe MR at high risk for surgery, the EVEREST (Endovascular Valve Edge-to-Edge Repair Study) trial showed that an initial strategy of MitraClip led to symptom improvement in a significant subset of patients. Although there was high crossover to surgical MV repair with higher percentage of ≥2+ residual MR (57% vs. 24%; $p < 0.001$) and need for surgery (27.9% vs. 8.9%), this strategy seemed to be safe, with no difference in

FIGURE 4 Surgical Techniques in Primary MR

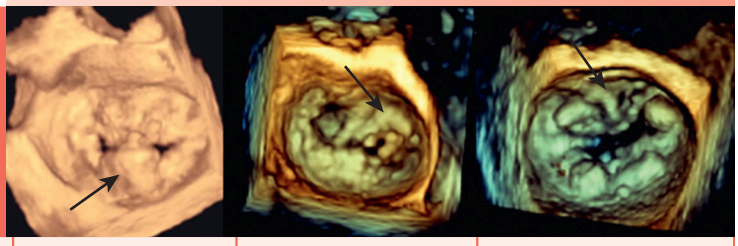


(A) Posterior prolapse repair with triangular resection. **(B)** Anterior prolapse repair with artificial chords. **(C)** Commissural prolapse repair with commissuroplasty. Almost all repairs include an annuloplasty ring. Chordal sparing mitral valve replacement using **(D)** a mechanical prosthetic valve and **(E)** a tissue prosthetic valve. MR = mitral valve regurgitation.

intermediate-term mortality or heart failure risk apart from the increased need for additional surgery (35).

There are a number of imaging characteristics to consider for MitraClip intervention, including the location of prolapse with P2-A2 prolapse best suited for MitraClip placement. Smaller flail gap and flail width, and lack of mitral inflow obstruction, are other factors favoring MitraClip success (36) (**Figure 5**). Overall, this device may be useful for treating severe symptoms due to primary MR, although the outcome is inferior to surgery. Thus, at the present time, the MitraClip device is approved for use in patients with severe symptomatic primary MR who are at high risk for conventional surgery. Other catheter-based approaches for the treatment of MR consist of different strategies, including percutaneous valve replacement, placement of annular tightening devices, and insertion of artificial chordae. Due to the complexity of the MV apparatus and the noncircular saddle-shaped annulus, much more development must occur before a percutaneous MV is widely available for clinical use.

FIGURE 5 Echocardiographic Predictors of Feasibility of Transcatheter MV Repair

Transcatheter Mitral Valve Repair	Feasible		Unlikely
			
Segment	2	1 or 3	Severe Barlow
Calcification	None	Annular- sparing grasping zone	Grasping zone involved
MVA and MV Gradient	>4 cm^2 and <4 mm Hg	3.5-4 cm^2	<3.5 cm^2 and >5 mm Hg
Flail width	<15 mm	>15 mm	
Flail gap	<10 mm	>10 mm	

The anatomy that lends itself to high likelihood of successful percutaneous repair using the MitraClip device is the presence of A2/P2 noncalcified mitral valve (MV) leaflet prolapse with a mitral valve area (MVA) >4 cm^2 and MV gradient <4 mm Hg, with a flail width (length of leaflet along the coaptation line that has flail segment on echocardiographic short-axis view) <15 mm and flail gap (the greatest distance between the edges of the flail leaflet and opposing leaflet on echocardiographic 4- or 5-chamber view) <10 mm. Percutaneous repair becomes more challenging in the presence of segment 1 or 3 involvement or severe Barlow's anatomy, calcification of the leaflet grasping zone, large flail width (can lead to inadequate reduction in MV regurgitation given the wide segment of regurgitation), and wide flail gap (can lead to inadequate grasping of both leaflets).

SECONDARY MR

ETIOLOGY. In contrast to primary MR, secondary MR is not a disease of the MV itself but rather a disease of the atrium or ventricle. MR secondary to ventricular disease can be due to either nonischemic or ischemic remodeling. There are some similarities to the underlying remodeling between these 2 broad categories of cardiomyopathy and secondary MR. Both forms of secondary MR are a result of ventricular enlargement with lateral displacement of the papillary muscles leading to abnormal tethering forces on the leaflets (37). Normally, the subvalvular apparatus exerts vertical tension to prevent prolapse during systole, which is disrupted with ventricular remodeling. In addition, ventricular and atrial enlargement lead to annular dilation, which further promotes mitral leaflet malcoaptation. The reduced closing forces from the decreased systolic tension also contribute to the MR. Furthermore, the frequent occurrence of a left bundle branch block in these forms of heart failure with reduced EF can worsen remodeling through dyssynchrony contributing to decreased closing forces and dyssynchronous papillary muscle function contributing to secondary MR (38).

The etiology of MR in nonischemic cardiomyopathy is multifactorial with contribution from all of the aforementioned abnormalities. However, the predominant mechanism for MR is the result of an increased ERO from annular dilation and loss of annular contraction. The MV leaflets themselves are normal with normal motion (Carpentier type I MR), but there is loss of coaptation due to the mismatch between the dilated annulus and the leaflet length (39).

Severe left atrial enlargement (most often from persistent atrial fibrillation) can also directly lead to MR, termed atrial functional MR. The annular dilation from long-standing atrial fibrillation and atrial remodeling seems to play an important role, representing a Carpentier type I form of secondary MR (40). Others have proposed that the posterior enlargement of the left atrium beyond the posterior mitral annulus tethers the posterior leaflet contributing to atrial functional MR (41).

In contrast, ischemic secondary MR is associated with regional inferior wall motion abnormalities, leading to posterior leaflet tethering and posteriorly directed MR (Carpentier type IIIb). The anterior leaflet override associated with ischemic MR should not be mistaken for prolapse because it does not cross the annular plane (7). This inferior wall motion abnormality with ischemic MR can be associated with hibernating or scarred myocardium. Ischemic MR can also cause central MR, if there are global wall motion abnormalities from multivessel coronary disease leading to equal lateral displacement of both papillary muscles similar to that seen in nonischemic cardiomyopathy (42).

PATHOPHYSIOLOGY. Any therapy that reduces LV end-diastolic volume or causes reverse remodeling chronically will improve secondary MR. The acute therapy of decompensated heart failure with vasodilator and diuretic therapy has been shown to acutely improve forward cardiac output, in part through a reduction in secondary MR via a reduction in ERO (43). The exquisite load dependence of secondary MR emphasizes the importance of reassessing MR after pre-load and afterload have been optimized through diuresis and vasodilation.

In addition to acute changes with loading conditions, chronic ventricular reverse remodeling is achieved currently in heart failure with reduced EF through numerous therapies that all independently decrease mortality. These therapies include angiotensin-converting enzyme inhibitors, beta-blockers, aldosterone antagonists, angiotensin receptor blockers combined with neprilysin inhibitors, hydralazine/isosorbide dinitrate, cardiac resynchronization therapy, and myocardial revascularization in the presence of ischemia (44). Beneficial reverse remodeling from optimal medical therapy therefore has a strong independent effect on decreasing the severity of secondary MR.

NATURAL HISTORY. Although many studies have shown that secondary MR is associated with poor outcomes, what remains unclear is if secondary MR is just a correlate of more advanced cardiomyopathic remodeling or whether secondary MR itself directly contributes to the adverse prognosis of these patients through additional LV volume loading (45). Further emphasizing the difference between primary MR, LV dysfunction in secondary MR is not the consequence but rather the cause of MR. What remains unknown is whether intervention on the MV changes the natural history in secondary MR.

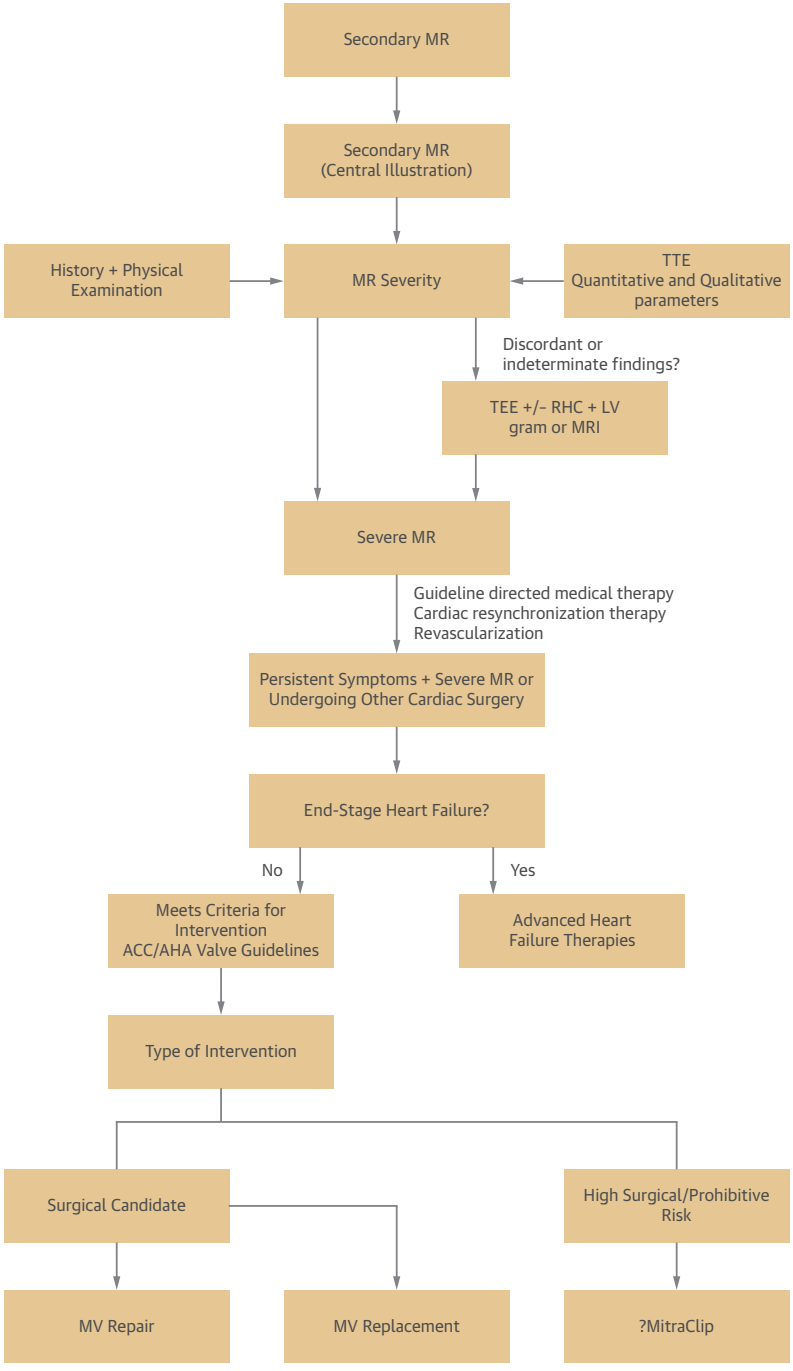
This adverse prognosis of secondary MR has been observed in both ischemic and nonischemic secondary MR. In ischemic secondary MR, a number of studies have described this adverse prognostic impact of any severity of MR (46,47). Poor outcomes in ischemic MR occur at a smaller ERO ($\geq$0.2 cm^2) compared with primary MR ($\geq$0.4 cm^2) (47).

Similarly, in nonischemic secondary MR, any degree of MR is also a poor prognostic sign, likely because it reflects worse underlying ventricular remodeling (45). Multivariable statistical modeling in all these studies attempts to correct for the various factors reflecting the severity of underlying heart failure and remodeling. However, the inability to adjust for unmeasurable confounders leads to uncertainty over whether the secondary MR is itself causative or merely correlative for an adverse outcome. Therefore, the isolated contribution of MR itself to the disease process is difficult to establish from these retrospective studies and requires prospective randomized intervention trials directed at the nonischemic secondary MR, which are currently lacking in the literature.

RESULTS OF OPERATIVE INTERVENTION. For patients with severe ischemic secondary MR and LV systolic dysfunction, revascularization with coronary artery bypass graft (CABG) or percutaneous coronary intervention should be considered if there is viable myocardium. CABG in these patients with low EF independently improves long-term prognosis and all-cause mortality (48), although the effect on ischemic MR is variable (49). The addition of MV repair for moderate ischemic MR at the time of CABG is controversial, with a recent randomized trial reporting no benefit in terms of outcomes with an increase in perioperative complications (50). At 2 years, 68% of patients who did not have mitral repair experienced a reduction in the severity of MR from revascularization alone (50).

MV intervention may be considered for symptomatic improvement in patients with severe ischemic MR unresponsive to optimal therapy for treatment of the left ventricle. A randomized trial supports the use of MV replacement over repair for these patients with severe ischemic MR (51). MV repair was associated with an unacceptably high recurrence rate of moderate or severe MR at 2 years (58.8% vs. 3.8%) and was associated with worse quality of life and heart failure-related hospitalization (51). LV reverse remodeling occurred in both groups but cannot be definitively attributed to the reduction in MR alone because nearly three-quarters of patients underwent concomitant CABG, which can independently improve ischemic cardiomyopathy. There still may be a subset of patients who would benefit from repair versus replacement in the hands of highly

FIGURE 6 Pathway for Diagnosis and Management of Secondary MR



Similar to primary MR, clinical suspicion for secondary MR is followed by TTE, which can identify the etiology of MR using the Carpentier classification (its severity as well as the status of the left ventricle). If there are discordant or indeterminate findings, further quantification with TEE, RHC and LV gram, or MRI is then warranted. If the secondary MR is severe with symptoms present, therapies targeting the underlying cause such as guideline-directed medical therapy or cardiac resynchronization therapy for LV dysfunction should be instituted. If symptoms and severe secondary MR persist, and the patient is deemed to have end-stage heart failure, assessment for advanced heart failure therapies can then be considered. If the patient is not believed to have end-stage heart failure, with persistent symptoms and severe MR, evaluation for candidacy for intervention according to the ACC/AHA valve guidelines is warranted. MitraClip intervention can be considered for high-risk patients only as a part of clinical trials because its efficacy for secondary MR is unproven. Abbreviations as in Figure 2.

experienced surgeons, including patients such as those without inferobasal aneurysms and those with a smaller sized left ventricle, particularly if additional subvalvular procedures to relieve tethering of the leaflets are performed. A subsequent analysis showed that a novel ratio of LVESD/ring size predicted recurrent MR after repair, likely due to anterior displacement of the posterior leaflet by an undersized ring, leading to worsening posterior leaflet tethering from the posteriorly displaced papillary muscle (52). However, in general, if the MV operation is being performed for treatment of intractable heart failure, MV replacement should be considered as the first line for severe ischemic MR. It is unclear as to whether percutaneous therapy for secondary MR will benefit patients with secondary MR. The COAPT (Clinical Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trial (NCT01626079) is testing this strategy of adding the MitraClip to optimal medical therapy. The results of this study will help advance our understanding of the efficacy of percutaneous therapies for secondary MR.

For severe nonischemic secondary MR, there is no randomized evidence supporting MV intervention for prolongation of life or prevention of further LV dysfunction.

INTEGRATIVE APPROACH TO DIAGNOSIS AND MANAGEMENT IN SECONDARY MR. The diagnosis of secondary MR also starts with history and physical examination, but the murmur of functional MR is often not remarkable, even with severe MR (**Figure 6**). Unlike primary MR, presence of symptoms is confounded by the underlying LV disease. Echocardiographic imaging will show the extent and type of LV dilatation and dysfunction. In secondary MR, there should be normal MV leaflet structure with abnormal tethering and tenting. Asymmetric posterior tethering occurs with ischemic cardiomyopathy and inferior wall remodeling and will result in a posteriorly directed jet of MR. Symmetric bileaflet tethering occurs due to diffuse LV remodeling, such as in nonischemic cardiomyopathy or severe ischemic cardiomyopathy, and causes a central jet of MR. Coronary angiography should be performed to evaluate the cause of systolic dysfunction or inferior wall motion abnormality.

Methods of quantifying severity in secondary MR are similar to those with primary MR, with attention to some unique pitfalls. Poor contractile function due to LV dysfunction can cause underestimation of MR severity using color flow Doppler imaging (7). The PISA formula assumes a round orifice but in secondary MR, the leaflets are pulled apart and malcoapt, forming an elliptical regurgitant orifice. Because of this state, PISA can underestimate the severity of MR depending on the 2-dimensional view used. In addition, the ERO changes dynamically throughout, systole being smallest at peak contraction due to the heightened closing forces. Because this ERO is assumed to be similar throughout systole to calculate RVol, this assumption can underestimate the severity of MR (53).

CRITERIA FOR INTERVENTION BASED ON SYMPTOMS AND LV. Management of secondary MR is primarily directed toward the underlying cardiomyopathy through guideline-directed medical therapy. Although rigorous randomized trials of medical therapy versus surgery are lacking, most evidence supports no mortality benefit to surgical intervention compared with medical therapy, with a possible improvement in symptoms in some patients (50,54,55). Thus, in the absence of rigorous evidence supporting its efficacy, surgical correction of severe secondary MR must only be considered after optimal medical therapy, cardiac resynchronization therapy, and revascularization have been completed for a reasonable period of time (at least 6 months). If patients remain symptomatic with severe secondary MR even after this treatment, and the symptoms are believed to be from the MR and not the cardiomyopathy, surgical MV replacement can then be considered. This approach should only be offered to the patient with shared decision-making, and the understanding that the only benefit, if any, would likely be from a symptom standpoint with no evidence supporting a mortality reduction with this method. The evidence for surgical treatment of secondary MR after optimal medical therapy is somewhat more established for ischemic secondary MR (51). Data are lacking for nonischemic secondary MR; for many patients who still have severe secondary MR and symptoms after optimal medical therapy, consideration of advanced heart failure therapies such as LV assist devices or transplantation must also be considered given the proven survival benefit in appropriate patients (56).

CONCLUSIONS

MR is composed of 2 completely different diseases in primary and secondary MR. Each has different natural histories, mechanisms of MR, therapeutic strategies, and response to surgical repair. Secondary MR must further be classified as ischemic or nonischemic in origin with important management differences

between the 2 types. Differentiating between these phenotypes of severe MR with echocardiography and advanced imaging modalities is critical to allow accurate diagnosis as well as guidance in choosing timing and type of intervention. However, there are limitations to our current imaging parameters, and therefore any decision in management must integrate all the diagnostic information available, including the physical examination, in a Bayesian manner to arrive at the proper diagnosis. We must continue to evaluate the outcomes of the current and newer interventions through randomized trials and large registries, not only regarding mortality but also to determine the effect on patient symptoms and quality of life measures.

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APPENDIX For a supplemental figure and videos, please see the online version of this paper.

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