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Myocardial Dysfunction in Primary Mitral Regurgitation

A Review

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IMPORTANCE Primary mitral regurgitation (MR) is a prevalent valvular lesion. Current American College of Cardiology/American Heart Association guidelines include class I recommendations for intervention for severe primary MR at the onset of symptoms, significant left ventricular (LV) enlargement (end-systolic dimension ≥ 40 mm), or dysfunction (ejection fraction $\leq 60\%$), with a class IIA recommendation for mitral valve repair when performed at an experienced surgical center. Recent data suggest a survival penalty when waiting for class I surgical guideline indications, and novel markers of decompensation are under investigation.

OBSERVATIONS Comprehensive assessment of MR severity using echocardiography is critical, and when warranted, cardiac magnetic resonance (CMR) is complementary. Assessment of LV size and function, as well as serial changes in both, is crucial for determining timing of surgery. New-onset atrial fibrillation, left atrial enlargement, pulmonary hypertension, and exercise-induced changes in LV function should also be considered in borderline scenarios. The roles of LV volumes, global longitudinal strain, CMR-derived measures of myocardial dysfunction, and cardiac biomarkers are worthy of further investigation regarding consideration for early surgical intervention.

CONCLUSIONS AND RELEVANCE A more refined approach incorporating assessment of extravalvular cardiac injury, novel imaging markers, and biomarkers is needed to optimize surgical timing in primary MR. Further research is warranted to validate these emerging parameters and refine guidelines to improve patient outcomes.

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Mitral regurgitation (MR) is the most common valvular disorder in the United States.^{1,2} MR is classified as primary when caused by intrinsic pathology involving the valve leaflets and as secondary when caused by abnormalities affecting the left atrium (atrial functional MR) or left ventricle (ventricular functional MR). Severe primary MR has an adverse prognosis if left untreated, with more than 90% of patients developing heart failure or death at 10 years, but appropriately timed surgical intervention can result in a normal longevity.³

The optimal timing of surgery in primary MR is dependent on multiple factors, including symptoms, MR severity, valve morphology, and the status of the left ventricle (LV). The initial LV response to MR is eccentric hypertrophy that compensates for the volume overload. If uncorrected, progressive myocardial dysfunction will eventually occur, resulting in heart failure and death. Ideally, surgery should be performed before this transition occurs. The current American College of Cardiology/American Heart Association (ACC/AHA) and European guidelines-based indications for operation include symptoms or a decrease in LV ejection fraction (EF) and/or increase in LV end-systolic dimension (LVESD). However, waiting for these indications may be too late, as irreversible myocardial injury may have already occurred. In addition, mitral valve (MV) repair can now be performed in experienced centers at a low operative risk and with excellent

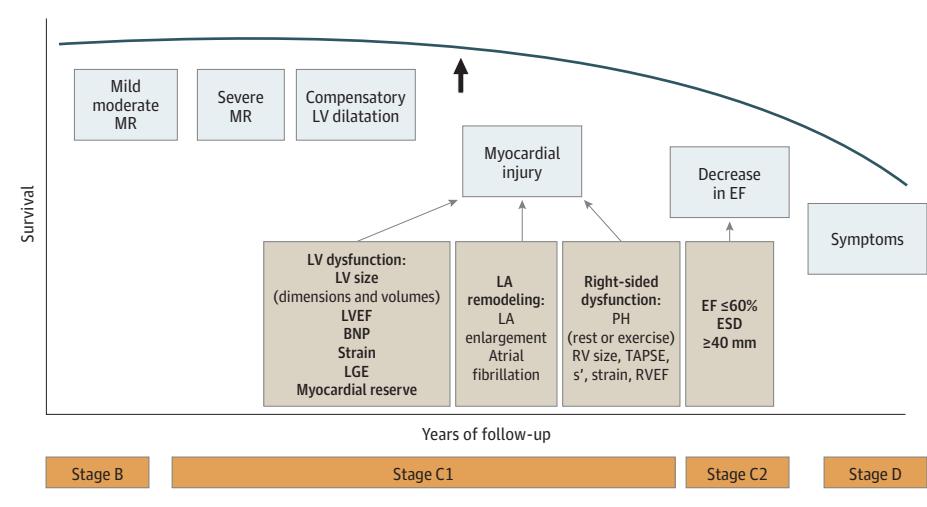
long-term outcome.^{4,5} Thus, early operation should be considered in asymptomatic patients before the onset of myocardial dysfunction or other adverse consequences. Thus, ACC/AHA and European guidelines emphasize that the presence of severe primary MR is itself an indication for surgical repair in asymptomatic patients in whom repair has a high likelihood of success and durability.⁶⁻⁸ Successful mitral valve repair is generally defined as perioperative mortality less than 1%, mild or less residual MR, preserved LV function without significant lateral wall hypokinesis, and a transmural gradient less than 4 to 5 mm Hg.⁹

Much of the information discussed in this article is based on retrospective data or our opinion because prospective studies on this topic are lacking. Transcatheter therapies are an emerging treatment for patients with primary MR. At present, such therapies are indicated for patients who are symptomatic and not candidates for surgery and therefore beyond the scope of this review.

Primary MR

Degenerative mitral regurgitation (DMR) is the most common type of primary MR in the Western world. This review focuses on DMR given its prevalence in developed countries and its potential for successful surgical repair.

Figure 1. Natural History of Mitral Regurgitation (MR)



Natural history of MR, including progressive changes in the left ventricular (LV) and extravalvular involvement and parameters associated with onset of decompensation (arrow). BNP indicates brain natriuretic peptide; EF, ejection fraction; ESD, end-systolic dimension; LA, left atrial; LGE, late gadolinium enhancement; LV, left ventricular; PH, pulmonary hypertension; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion.

Natural History of MR

MR leads to increased LV preload and reduced afterload, which causes compensatory LV hypertrophy and dilation, resulting in a large compliant LV with increased LV end-diastolic volume and increased stroke volume. The mitral regurgitant volume also results in progressive left atrial (LA) enlargement. The compensated phase is characterized by LV enlargement, eccentric hypertrophy, and preserved LV function (LVEF $\geq 60\%$). It is followed by a transitional phase associated with an increase in wall stress and early myocardial dysfunction. Ultimately, if untreated, decompensated MR develops and is associated with progressive and irreversible LV systolic dysfunction and symptoms of heart failure (Figure 1).¹⁰ Identifying and managing MR before it reaches the transitional stage is crucial, as irreversible myocardial dysfunction may occur before onset of symptoms. Among asymptomatic patients with severe primary MR, those with LVEF of 60% or less have increased mortality if untreated, while surgery is associated with improved survival.^{11,12} Despite the lack of randomized studies, retrospective data suggest surgery is likely within 6 to 10 years of diagnosis of severe MR, emphasizing the need for continued monitoring.¹²⁻¹⁵ Factors associated with clinical outcomes, particularly mortality, have been older age, heart failure, reduced LVEF, increased LVESD, LA enlargement, pulmonary hypertension (PH), right ventricle (RV) dysfunction, and atrial arrhythmias (Figure 1).^{10,16-19} Biomarkers such as brain natriuretic peptide, LV strain, LV volumes, and presence of myocardial fibrosis with cardiac magnetic resonance (CMR) have emerged as novel markers of LV dysfunction.²⁰⁻²² Recent data suggest that waiting for the onset of current Class 1 guideline recommendations before operating in patients with severe DMR is associated with reduced postoperative survival.²³ Because medical therapy cannot alter the course of the disease, and surgery appears inevitable within 6 to 10 years, it is reasonable to consider surgical repair in asymptomatic severe MR, particularly when repair can be performed with a high success rate (>95%) and low complication rate at expert valve centers.

Assessment of MR Severity

The decision to pursue surgical repair in asymptomatic patients rests on certainty that the degree of MR is indeed severe. Severity of primary MR, particularly associated with MV prolapse, can be difficult to assess,

and a comprehensive approach is recommended (eTable in the *Supplement*).²⁴ A thorough assessment of primary MR also includes correlating physical examination findings (eTable in the *Supplement* and Table 1). LA/LV size and pulmonary pressures should also be assessed. These extravalvular changes can be helpful in confirming chronic severe MR, even when Doppler parameters are equivocal. In cases where discordance persists, additional imaging with transesophageal echocardiography and/or CMR should be considered. Discrepant findings are most often encountered in cases of nonholosystolic jets and eccentric or multiple jets.²⁵ CMR allows assessment of regurgitant volume by determining the difference between LV stroke volume and forward aortic stroke volume (Table 1). However, access to CMR and expertise in its interpretation is not widely available, and CMR may not be practical when serial assessment is needed. Hemodynamic catheterization and contrast ventriculography also have a role when discordance between imaging findings persists. Finally, artificial intelligence (AI) holds promise as a future tool for determining the severity of MR through image interpretation and analysis.²⁶⁻²⁸

Evaluation of LV Response and Remodeling

Established Markers: LV Dimensions and EF

Adverse outcomes in LV function and survival have been observed after surgery in patients with preoperative LVEF 60% or less.⁸ This evidence forms the foundation for the ACC/AHA and European practice guidelines, which recommend surgical repair in patients with an LVEF 60% or less.^{6,7} Additionally, LVESD, which is a measure that incorporates both LV remodeling and systolic function, has also been shown to have prognostic value, and a threshold of 40 mm was associated with poor outcomes.^{6,7} However, LVEF 60% or less and LVESD of at least 40 mm, currently included in the guidelines to guide timing of intervention, may represent irreversible LV dysfunction.¹⁰ Therefore, there is a need to identify other measures of LV remodeling that can better capture patients before the onset of the transitional phase.

Recent data indicate that an indexed LVESD 20 mm/m² or greater is an independent predictor of mortality, providing incre-

Table 1. Cardiac Magnetic Resonance Assessment of MR Severity

Parameter	Advantages	Limitations and technical details
Volumetric assessment: Regurgitant volume = LV SV - RV SV ^a	<ul style="list-style-type: none"> • Easy to assess • Can be performed without contrast 	<ul style="list-style-type: none"> • Requires several breath-holds and stable cardiac rhythm. • Artifacts due to arrhythmias, breathing motion or cardiac implantable electronic devices. • Cannot be used in the presence of another valve regurgitation >mild in severity. • Variability in tracing of the basal LV slices can result in significant changes in LV and mitral regurgitant volumes.
Indirect method: Regurgitant volume = LV SV - forward aortic stroke volume measured by phase contrast ^{b,c}	<ul style="list-style-type: none"> • Can perform assessment of MR severity and of concomitant AR or TR if/when present • Allows volumetric quantification of MR even in cases of eccentric and multiple jets • Quick acquisition (1-2 min) and complementary to the delta stroke volume method above • Concomitant assessment of TR/PR severity requires phase-contrast acquisition of the pulmonary artery flow 	<ul style="list-style-type: none"> • Attention to several details are important for accurate quantification: (1) patient needs to be at the magnet isocenter and field of view without wrapping; (2) verify profile of the flow curve to determine if background offset error correction is necessary or not; (3) plane of interrogation needs to be orthogonal to the ST junction and to main pulmonary artery (3 cm above the pulmonic valve); (4) in case of concomitant mixed aortic valve stenosis/regurgitation, adjust accordingly the VENC limit to avoid aliasing. • In case of significant arrhythmias such as frequent PVCs or bigeminy, quantification by all methods will be compromised. • For atrial fibrillation with R-R interval variability <20%, free breathing acquisition with increased number of averages (3) allows for accurate quantification.
4D flow assessment (indirect and direct methods are possible within the same - but longer -acquisition) Regurgitant volume = LV SV - Aortic flow estimated by 4D flow analysis ^{b,c}	<ul style="list-style-type: none"> • 3D VENC phase-contrast acquisition captures dynamic blood flow over time across all 4 valves within 1 free-breathing acquisition • It is complementary to the 2 other methods above 	<ul style="list-style-type: none"> • While IV contrast administration is not needed, quality of 4D flow signal to noise and volume to noise ratio are improved after gadolinium agent administration. • Needs further validation and comparison with echocardiography and outcomes. • Longer acquisition time (8-10 min) and postprocessing (10 min) for analysis. • Training and learning curve for data acquisition, dedicated postprocessing workflow, and interpretation expertise is necessary.
4D flow MR jet method	<ul style="list-style-type: none"> • Retrospective valve tracking accounts for the mitral annulus motion during cardiac cycle, enabling measurement of MR jet volume 	<ul style="list-style-type: none"> • Can be technically challenging especially in cases of eccentric and multiple jets where indirect method is recommended. • Needs validation in larger studies, and comparison with echocardiography or 2D phase-contrast derived regurgitant volume and clinical outcomes

Abbreviations: 2D, 3D, 4D, 2-, 3-, and 4-dimensional; AR, aortic regurgitation; IV, intravenous; LV, left ventricular; MR, mitral regurgitation; PVCs, premature ventricular contractions; PR, pulmonary regurgitation; RV, right ventricle; SV, systolic volume; TR, tricuspid regurgitation; VENC, velocity-encoded.

^a Cannot be used in cases of other regurgitant valve lesions that are more than mild in severity.

^b In case of AR, subtract aortic regurgitant volume from the LV SV to calculate mitral regurgitant volume.

^c Instead of LV SV, mitral valve inflow volume can also be estimated and used for calculating the stroke volume. The imaging plane for mitral inflow volume estimation is placed at the annulus level.

mental predictive value over LVESD, in patients with primary MR due to flail leaflets.²⁹ Limited data suggest that for the same degree of regurgitation, females have smaller LV sizes even after normalization to body surface area.^{30,31} An analysis of 4589 patients revealed that the risk for mortality for females increased at LVESD of 36 mm, lower than the guideline threshold of 40 mm.⁶⁻⁸ After indexing to body surface area, the risk for mortality increased at 18 mm/m² for females compared with 21 mm/m² in males.³¹

Emerging Markers

LV Volumes | Considering the varying changes in LV shape that accompany the volume overload in MR, assessment of LV volumes rather than linear dimensions is preferable. However, there are limited data on LV volumes in chronic primary MR, and LV volume assessment by echocardiography is limited by reproducibility.³² However, this variability improves with the use of image-enhancing agents, 3-dimensional (3D) echocardiography when feasible, and automated measurements using AI.³²⁻³⁵

CMR is considered the reference standard for assessment of LV size and function since it requires no geometric assumptions and has better reproducibility compared with 2D echocardiography (Figure 2A).³² Volumetric assessment by CMR captures the LV remodeling in MR better than linear dimensions. In a prospective study including 258 patients, CMR-derived LVESV, and not linear dimension, was associated with mortality (hazard ratio, 1.40; 95% CI, 1.05-1.81) and indication for MV surgery (hazard ratio, 1.30; 95% CI, 1.10-1.56).²⁵

In 109 asymptomatic patients with more than moderate MR on echocardiography, an LV end-diastolic volume greater than 100 mL/m² by CMR was associated with reduced survival without surgery at 5 years. Indexed LVESV greater than 36 mL/m² was also studied to identify asymptomatic patients who would develop indications for surgery, but the sensitivity and specificity of CMR-derived LVESV in identifying those patients was lower.³⁶

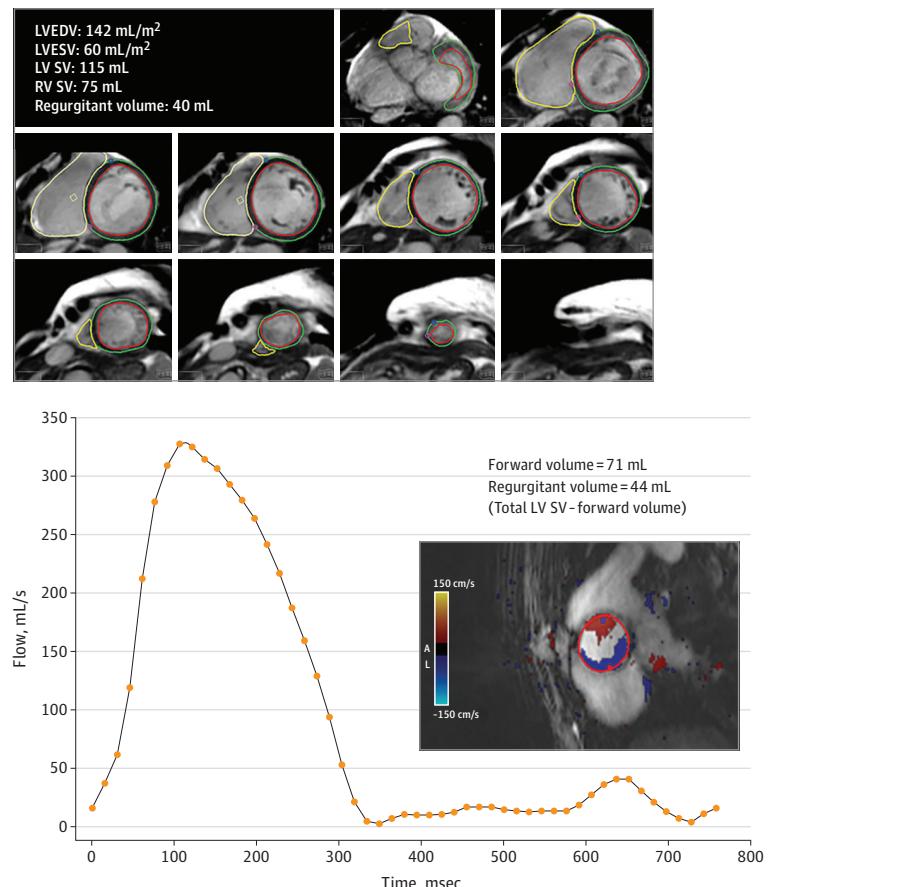
As with echocardiography, sex differences have emerged using CMR assessment. For the same degree of MR severity, females had smaller indexed LV and RV volumes.³⁷ However, to date, there are no available studies evaluating sex-specific thresholds at which LV volumes have prognostic value. This is particularly important because females tend to be referred for surgery less frequently and later compared with males.^{30,38,39}

Cardiac computed tomography (CT) with retrospective electrocardiogram-gated acquisition provides accurate and reproducible LV volumes and can be considered as a reliable alternative for patients who cannot undergo CMR.⁴⁰ In a recent analysis of 243 patients undergoing MV repair, preoperative LVEF by CT was a significantly better predictor of postoperative LV systolic dysfunction than echocardiographic LVEF, and indexed LVESV by CT was a significantly better predictor than LVESD by echocardiography.²²

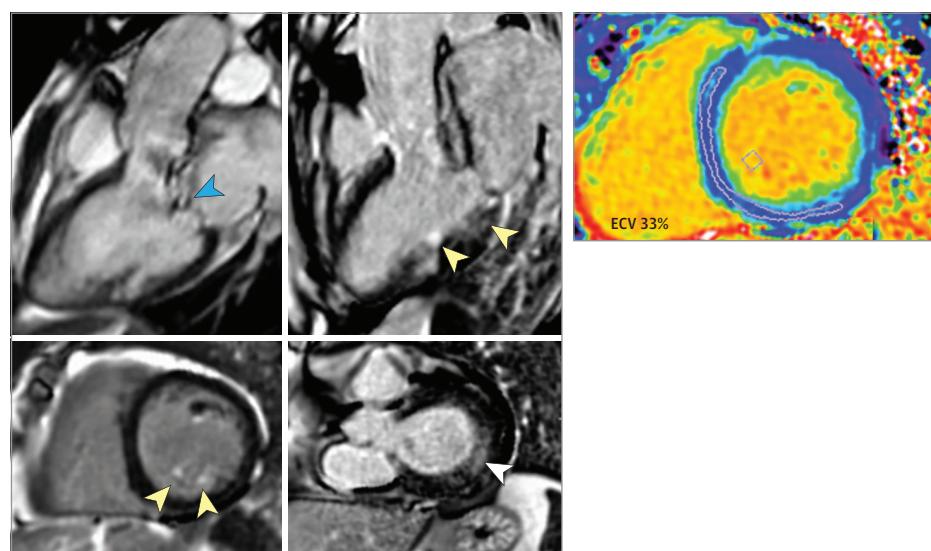
Global Longitudinal Strain | LV global longitudinal strain (LVGLS), which is less load dependent than LV volumes or EF, may be abnormal in patients with preserved EF greater than 60%, and conceptually, could identify the onset of the transitional phase of early

Figure 2. Cardiac Magnetic Resonance (CMR) Imaging Showing Assessment of Left Ventricular (LV) Size and Mitral Regurgitation (MR) Severity

A CMR showing LV size and MR severity



B CMR showing MVP, replacement fibrosis, and diffuse interstitial fibrosis



A, LV volumes were calculated using cine short-axis and MR severity evaluated by LV and right ventricular (RV) stroke volume difference (40 mL) and indirect method subtracting aortic forward stroke volume by 2-dimensional phase contrast imaging at the ST junction from total LV stroke volume (44 mL). B, CMR imaging showing mitral valve prolapse (MVP) and flail (blue arrowhead), and late gadolinium enhancement (replacement fibrosis) along basal inferolateral wall and posteromedial papillary muscles (yellow arrowheads). In the same patient, there was also increased myocardial extracellular volume (diffuse interstitial fibrosis) (normal extracellular volume [ECV]: 23%-27%). LVEDV indicates left ventricular end-systolic dimension; LVESV, left ventricular end-systolic volume; SV, systolic volume.

myocardial dysfunction. In 593 patients with severe primary MR, LVGLS at least 20.6% was associated with better outcomes after surgical MV repair than LVGLS less than 20.6%.²¹ The higher thresh-

old of "normal" to differentiate from myocardial dysfunction is likely due to reduced afterload in MR and is analogous to having "normal" LVEF being 60%. In addition, abnormal GLS and more pro-

Table 2. ACC/AHA and ESC/EACTS Practice Guidelines for the Management of Patients With Chronic Primary MR

ESC/EACTS	ACC/AHA
Class I	
Ia: Surgery is recommended in symptomatic patients regardless of LV function. (LOE: B)	
Ib: Surgery is recommended in asymptomatic patients with severe primary MR and LV systolic dysfunction (LVEF ≤60%, LVESD ≥40 mm or ≥20 mm/m ²). (LOE: B)	
Ic: Surgical MV repair is recommended in low-risk asymptomatic patients without LV dysfunction (LVESD 60%) when a durable result is likely, if at least 3 of the following criteria are present: AF, PASP >50 mm Hg, LA dilatation (LAVi ≥60 mL/m ² or LA diameter ≥55 mm), Concomitant secondary TR ≥moderate. (LOE: B)	NA
Class II	
IIa: Surgery should be considered in asymptomatic patients with preserved LV function (LVEF >60% and LVESD <40 mm) who have AF due to MR or pulmonary hypertension (PASP at rest >50 mm Hg) (LOE: B)	IIa: In asymptomatic patients with severe primary MR and normal LV systolic function (LVEF ≥60% and LVESD ≤40 mm), it is reasonable to consider MV repair if the probability of a successful and durable repair with minimal residual MR is >95% and the expected mortality rate is <1%, especially when the procedure is performed at a primary or comprehensive valve center. (LOE: B)
IIa: MV repair should be considered in low-risk asymptomatic patients with preserved LV function (LVEF >60%, LVESD <40 mm), and significant LA dilation (volume index ≥60 mL/m ² or diameter ≥55 mm), especially when performed at a heart valve center where a durable repair is likely. (LOE: B)	IIb: In asymptomatic patients with severe primary MR and normal LV systolic function (LVEF >60% and LVESD <40 mm), MV surgery may be considered if there is a progressive increase in LV size or a decrease in EF observed across ≥3 serial imaging studies, regardless of the likelihood of a successful and durable repair. (LOE: C)
Abbreviations: ACC, American College of Cardiology; AF, atrial fibrillation; AHA, American Heart Association; EACTS, European Association for Cardio-Thoracic Surgery; EF, ejection fraction; ESC, European Society of Cardiology; ES, end-systolic dimension; LA, left atrial; LAVi, left atrial volume index; LOE, level	
of evidence; LV, left ventricular; MR, mitral regurgitation; MV, mitral valve; NA, not applicable; PASP, pulmonary artery systolic pressure; TR, tricuspid regurgitation.	

nounced mechanical dispersion have been observed in patients with mitral valve prolapse (MVP) and associated annular disjunction with increased risk of ventricular arrhythmias.^{41,42} These findings highlight the role of GLS in identifying the presence of cardiomyopathic abnormalities that affect myocardial mechanics at an earlier stage than a decrease in LVEF.^{21,41,43} LV myocardial strain can also be assessed using CMR and was reduced in patients with MVP when compared with the controls in 1 study.⁴⁴

Myocardial Fibrosis Assessment by CMR | The presence of diffuse interstitial fibrosis or replacement fibrosis has been associated with the onset of LV decompensation (Figure 2B).

Late gadolinium enhancement (LGE) is more prevalent in primary MR in the presence of myxomatous valve disease.⁴⁵ This suggests a fibrotic milieu associated with Barlow disease. Fibrosis, when present predominantly in the posteromedial papillary muscle and basal inferolateral segment, appears to result from the mechanical tug associated with mitral annular disjunction in setting of MVP (Figure 2B).^{46,47} This phenotype can be associated with malignant ventricular arrhythmias.^{47,48} The degree of LGE increased with greater MR severity, suggesting a contributing factor of volume overload to myocardial injury in addition to the mechanical stress. In 1 series of patients with MVP, LGE was associated with greater risk of arrhythmic events, including sudden cardiac death, aborted cardiac arrest, and sustained or inducible ventricular arrhythmia, than absence of LGE (7.7% vs 2.7%) at a median follow-up of 1354 days.⁴⁵ Another series reported a 2.6-fold risk of cardiac death, heart failure, atrial arrhythmias, embolic events, and ventricular arrhythmias in individuals with LGE.^{49,50} Data from a prospective analysis demonstrated a decrease in extracellular volume after MV surgery with no change in LGE, suggesting interstitial fibrosis may be reversible but replacement fibrosis likely not.⁵¹ Observational data suggest that the presence of either LGE or extracellular volume can be used to assist in the detection of myocardial dysfunction and optimal timing for surgery.⁵² The role of these imaging markers to assess reverse cardiac remodeling after MV surgery, and whether

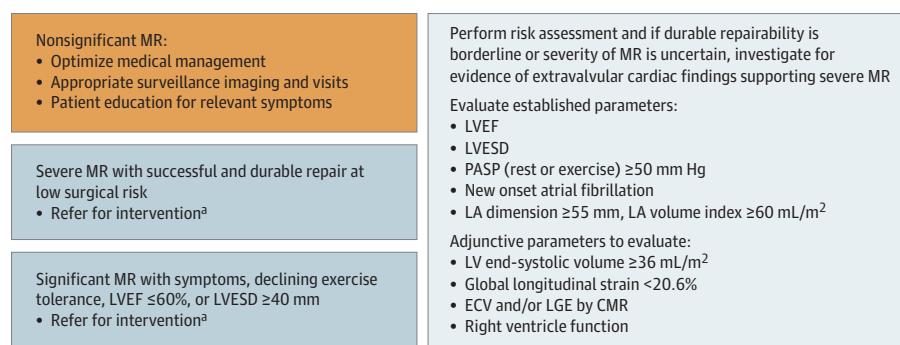
they would be adjunctive to current measures in the timing of intervention will need further validation and testing.

Evaluation of LA Remodeling | Patients with MR develop LA remodeling and enlargement because of volume overload. The myocardial stretch and increased wall tension lead to the upregulation of neurohumoral pathways, which eventually leads to atrial fibrosis and dysfunction.⁵³ These structural and functional changes in the LA are associated with AF, increased LA and pulmonary pressures, symptoms, and mortality independent of LV size and function. It is also important to note LA enlargement can also develop in patients with AF without significant MR.

The changes in LA remodeling can be captured by measurement of LA size (dimension and volumes) or LA function (LA strain) using echocardiography. LA size is better assessed using LA volumes rather than dimensions. In the Mitral Regurgitation International Database, both enlarged LA diameter 55 mm or greater and LA volumes 60 mL/m² or greater were associated with mortality with medical management.^{17,54} LA dimension 55 mm or greater and volume 60 mL/m² or greater are included in the European guidelines as a class IIa indication for surgery when durable valve repair is feasible at a heart valve center.^{7,8}

LA function can be assessed using speckle tracking strain analysis. Among 566 patients undergoing MV repair, reduced LA reservoir strain less than 22% was associated with all-cause mortality after valve repair, even after adjusting for age, comorbidities, LVEF, and LVGLS, and had an incremental value over the baseline model including these factors.⁵⁵ Even though LA strain has been shown to be associated with early decompensated MR, limited data suggest that changes in LA may not reverse after repair.⁵⁶

LA size can also be evaluated by CMR and cardiac CT, and this is particularly useful if assessment by echocardiography is not feasible. In an analysis of normal participants and patients with primary MR, CT-derived LA volume index correlated well with echocardiographic LA volumes and was superior to LA diameter in predicting incident AF and the combined end point of death or need for MV surgery.⁵⁷

Figure 3. Decision for Surgical Intervention in Mitral Regurgitation (MR)

The assessment of a patient with MR includes careful and thorough clinical examination as well as echocardiography. In patients with discordance between clinical presentation and echocardiography, between different echocardiographic measures of MR severity, or when echocardiographic data are inconclusive, cardiac magnetic resonance (CMR) imaging may be useful. Here we outline the management decisions based on MR severity along with established and emerging parameters obtained from imaging studies and

additional variables to consider when standard data are inconclusive regarding MR severity or left ventricular (LV) function. These thresholds require further validation. ECV indicates extracellular volume; EF, ejection fraction; ESD, end-systolic dimension; LA, left atrial; LGE, late gadolinium enhancement; PASP, pulmonary artery systolic pressure.

^aCurrent guideline recommendation.

AF accompanied by degenerative severe MR is associated with decreased survival^{58,59} even after surgical repair or replacement.^{59,60} New-onset AF is a class IIa recommendation in the European guidelines but not in the ACC/AHA guidelines since the latter recommends considering valve repair in severe MR, regardless of the presence of AF (Table 2).

Right Heart Function in MR

RV enlargement and dysfunction in primary MR likely represents a downstream effect of maladaptive LV chamber remodeling to volume overload from MR and subsequent PH.⁶¹ An increase in pulmonary pressures may be a manifestation of exhaustion of the LV and LA compensatory mechanisms. This might precede RV dilatation and development of significant tricuspid regurgitation and could eventually progress to RV dysfunction as an advanced manifestation of severity and chronicity of MR.⁶¹ While 2D echocardiography has limited reproducibility for the assessment of RV size and function, RV volumetric assessment with 3D echocardiography, cardiac CT, and CMR have all added incremental value in demonstrating the association of RV size and function with prognosis.⁶² Further, abnormal preoperative RV strain by echocardiography was associated with a postoperative decrease in LVEF.⁶³

In patients undergoing MV surgery, PASP 50 mm Hg or more is associated with reduced long-term postoperative survival.⁴³ Resting PASP 50 mm Hg or more is a class IIa indication for MV surgery in the European valve guidelines but is not a criterion in the ACC/AHA guidelines, since the latter recommends valve repair when MR is severe, regardless of the pulmonary pressures (Table 2).^{6,8}

Concomitant tricuspid valve repair in patients undergoing MV repair for primary MR has been linked to short- and long-term protective benefits.⁶⁴ Tricuspid annuloplasty should be considered when the annulus is dilated 40 mm or greater or more than 21 mm/m², particularly when tricuspid regurgitation is moderate or greater.^{6,65}

Exercise Stress Echocardiography

Exercise stress echocardiography can complement the evaluation of asymptomatic patients with significant MR and normal LV size and function. It helps with the objective assessment of exercise intolerance, confirmation of MR severity, detection of exercise-induced PH, and assessment of LV and RV contractile reserve, all of which aid in risk stratification and clinical decision-making. In patients with symptoms and nonsevere MR at rest, exercise stress echocardiography can unmask dynamic MR.

Exercise stress echocardiography can unmask subclinical LV dysfunction by assessing LV contractile reserve (changes in LVEF and LVGLS) after exercise.⁶⁶ Both a less than 4% increase in LVEF post-exercise and a less than 2% increase in LVGLS during exercise were associated with adverse cardiac events.⁶⁷ Lastly, exercise LVESV greater than 25 mL/m² has also been demonstrated to be a predictive marker of poor contractile reserve and a measure of latent LV dysfunction in patients undergoing MV intervention for chronic MR.⁶⁸ However, it is unclear whether measuring GLS and LVESV during exercise will be performed extensively since measuring such small incremental changes can be challenging, especially in the setting of tachycardia requiring even higher than usual frame rates for GLS measurement.

Exercise also plays an important role in unmasking "severe MR" in patients who exhibit symptoms but nonsevere MR on a resting echocardiogram.^{69,70} Quantification of MR severity during exercise may be challenging. At the least, there should be a continuous wave Doppler of the MR, to ascertain if late systolic MR becomes holosystolic, and an attempt to replicate proximal isovelocity surface area assessment. In addition, it is important to assess pulmonary pressures at various stages of exercise while evaluating for dynamic MR.⁷⁰

Exercise-induced PH (PASP >50 mm Hg) is associated with reduced symptom-free survival and adverse events.⁷⁰⁻⁷² Furthermore, an early steep rise of PASP during exercise to 50 mm Hg or more at low workloads has been shown to have a strong association with AF, heart failure, cardiac-related hospitalization, cardiac

mortality, or need for MV surgery in the next year.^{70,73} Although exercise-induced PH is associated with increased risk of adverse events, it is not included in the current valve ACC/AHA guidelines⁶ since these guidelines recommend considering valve repair when MR is severe, regardless of exercise-induced pulmonary pressures.

AI and Machine Learning in Primary MR

There is an increasing interest in the use of AI and machine learning to aid in disease diagnosis, risk stratification, and prognosis assessment.^{26-28,74-77} AI-guided echocardiographic imaging may be a pathway to allow for more standardized and reproducible measurements and improved quantification of severity. Additionally, integration of echocardiography with AI has the potential to optimize segmentation of the cardiac cavity and functionally assess ventricular function.⁷⁷ This will be important in understanding and predicting the different phenotypes of ventricular remodeling.

Machine learning-based algorithms also have a potentially important role in risk stratification and prognostication. AI and machine learning analysis of patients identified distinct phenogroups or clusters with varying degrees of LV remodeling, extravalvular injury, and differential clinical outcomes.^{28,78} There is a need for both image-based AI analyses and machine learning algorithms to identify the onset of reversible myocardial dysfunction, enhancing clinical decision-making and a personalized approach to the optimal timing of intervention.⁷⁹ Future clinical trials incorporating machine learning and AI-based modeling are necessary to refine these models before they can be widely adopted in clinical practice.

Conclusions

Patients with severe chronic primary MR often have a long asymptomatic phase but with eventual permanent cardiac injury if not corrected. The decision on timing of surgical intervention in primary MR

depends on symptoms, physical examination, a meticulous assessment of MR severity, and the presence of extravalvular involvement (Figure 3). Accurate assessment of MR severity is often challenging. Looking for clues such as LA and LV enlargement can be helpful in suggesting severe MR when quantification is equivocal. While there are class I indications for MV surgery for severe MR based on symptoms, LVEF less than 60%, or LVESD greater than 40 mm, all low-risk patients with severe MR who have highly repairable valves should be referred to a high-volume valve center of excellence, and MV repair should be considered if MR is severe even if class I indications are not yet present. The standard echocardiographic assessment of LV dimensions and LVEF are the starting points for imaging patients with long-term MR. However, identifying the presence of extravalvular cardiac injury based on LV volumes, myocardial strain, myocardial fibrosis, LA size, pulmonary pressures, and new-onset AF is helpful in cases where quantification of MR severity is not straightforward or if repairability of the valve is uncertain. These additional parameters can aid the shared decision between the patient and the heart valve team regarding surgical intervention. If observation is chosen, close follow-up is mandatory and a progressive increase in LV size or reduction in LVEF in 3 sequential studies should raise concerns. Timely and early surgery, before the onset of significant myocardial dysfunction, may prevent irreversible postoperative dysfunction and provide the best patient outcomes. While this review focuses on earlier surgical intervention in asymptomatic patients with primary MR and low operative risk, several of the imaging features discussed may also aid in risk stratification and timing of intervention in high-risk patients who may be considered for transcatheter therapies.

Prospective, randomized studies are needed to validate the prognostic value of emerging imaging markers—such as LV volumes, myocardial strain, fibrosis, and left atrial function—and to establish optimal thresholds for their use in clinical decision-making. Additionally, sex-specific thresholds and AI-driven phenotyping warrant further investigation to enable individualized management strategies and improve patient outcomes.

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Author Contributions: Dr Anand had full access to all of the data in the study and takes responsibility

for the integrity of the data and the accuracy of the data analysis.

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