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Valvular Heart Disease (J Dal-Bianco, Section Editor)

Workup and Management of Primary Mitral Regurgitation

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Abstract

Purpose of review We summarize the current concepts and methods for diagnosis and management of primary mitral regurgitation due to leaflet prolapse or flail.
Recent findings Current practice guidelines emphasize accurate diagnosis of chronic primary severe MR, differentiating between symptomatic and asymptomatic states, and assessing both hemodynamic and functional impact, thereby ensuring timely surgical or transcatheter intervention for those who stand to benefit from it. No effective medical therapy for chronic severe mitral regurgitation has been found to date. Surgical repair has significant advantages over valve replacement in primary MR patients with favorable anatomy. Transcatheter interventions may be an option in selected patients who are at prohibitive surgical risk.
Summary Successful management of chronic severe primary MR relies on accurate diagnosis and careful timing of intervention. Care should be individualized and rely on input from a heart valve team that includes expert imagers, surgeons, and interventional cardiologists.

Introduction

Defining primary mitral regurgitation

Mitral regurgitation (MR) is the most common valve disease in US adults with significant MR (moderate to severe) affecting nearly 10% of those 75 years or older [1, 2]. Mechanistically, MR can be broadly divided into primary MR, an intrinsic disease of the valve apparatus,

and secondary MR produced by extrinsic processes, typically ventricular and annular remodeling and dysfunction, that affect valve function. In primary MR, valve components—leaflets, chords, annulus, and less commonly papillary muscles—are involved with underlying disease processes including myxomatous degeneration, rheumatic heart disease, endocarditis, and radiation- and drug-induced valvulopathies.

The most common form of primary mitral regurgitation in the developed world is degenerative mitral regurgitation (DMR), also known as myxomatous mitral regurgitation—a spectrum ranging from focal disease involving a single scallop (termed fibro-elastic deficiency) to diffuse Barlow's disease affecting leaflet tissue from commissure to commissure (Fig. 1). Intermediate involvement (forme fruste) involves multiple scallops but less extensively than Barlow's disease. Milder forms of myxomatous disease, with involvement of a single chord or scallop, tend to present later in life while Barlow's is often detected in younger patients. This review will discuss the evaluation and management of patients with primary degenerative mitral regurgitation (DMR), emphasizing the importance of imaging, expanding options for intervention and areas of controversy in clinical decision-making. Recommendations made are consistent with current professional guidelines [2–6].

Natural history, morbidity, and predictors of adverse outcomes

In DMR, MR results from malcoaptation of the prolapsing or flail leaflets. About half DMR patients are expected to live their lives without significantly increased mortality or morbidity while approximately 18% will develop significant MR and/or LV systolic dysfunction (EF < 50%). Patients in the remaining medium-risk group (30%) have been reported as not subject to excess mortality but to be at higher risk for adverse cardiac events [7]. The development of MR is often a chronic process characterized by worsening severity and ultimately symptoms leading to overt heart failure if untreated and it is this group of patients with chronic DMR that is the focus of this review. The less common scenario in which there is sudden severe MR (usually ruptured chord) is discussed briefly.

Workup of chronic degenerative MR

Chronic DMR often presents as a murmur or incidental finding on an echocardiogram performed for another indication. Occasionally, long-standing but previously undiagnosed DMR presents with left heart failure syndrome.

History

Common symptoms of DMR include dyspnea, initially on exertion, fatigue, palpitations (most commonly due to atrial fibrillation), orthopnea, and decline in exercise tolerance. Symptoms may be absent even in the presence of severe MR from a flail leaflet, due to compensatory left ventricular (LV) dilation and a compliant left atrium (LA) that can accommodate the regurgitant volume without retrograde transmission of pressure to the lungs. Note that small flail segments may not be associated with severe MR [8]. Many patients subconsciously scale back their physical activity to avoid symptoms making it important to try to elicit not only symptoms but also changes in physical activity [6].

Physical examination

Physical findings of chronic DMR are dependent on MR severity, chronicity, and upstream effects. A systolic murmur often preceded by a click generated by tensing of redundant leaflets and chords is the norm. Mitral valve prolapse can produce non-holosystolic murmurs—usually in mid to late systole while flail is

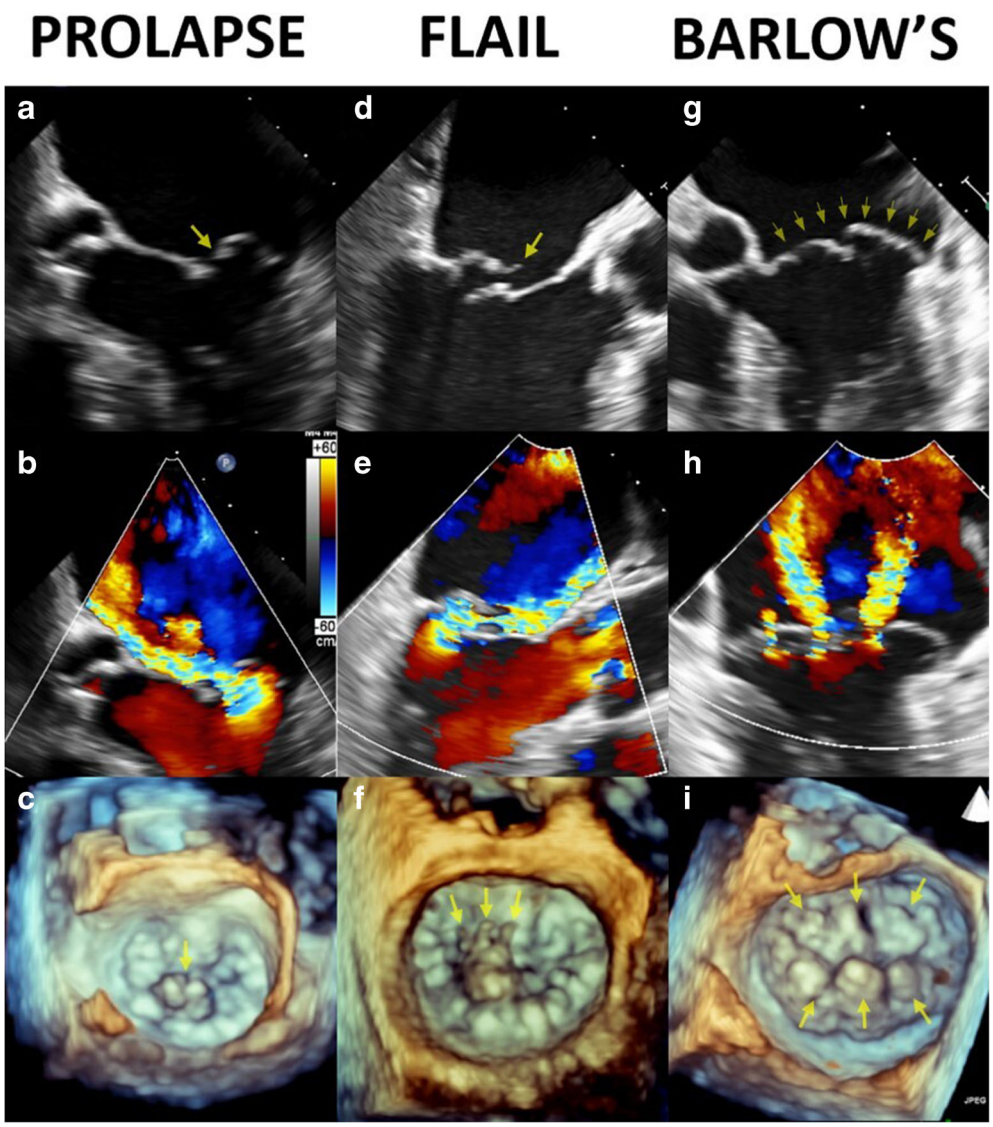

Fig. 1. Spectrum of DMR. DMR types as seen on transesophageal echo. Top row: 2D long axis views of the mitral valve; middle row: same views with color flow Doppler; bottom row: 3D volume-rendered images of the mitral valve in the surgeon's view (aortic valve on top). Focal leaflet prolapse (a–c, arrows), the milder form of DMR, is characterized by systolic billowing of the leaflet(s) above the plane of the mitral annulus. A flail leaflet (d–f, arrows) is caused by ruptured chordae tendineae. Remnants of the torn chordae can be seen on 3D echo (f, arrows). Barlow's disease is the diffuse form of DMR affecting all scallops of both mitral leaflets (g–i, arrows) and frequently associated with multiple jets of MR (h).

typically associated with holosystolic MR. Anterior leaflet flail typically results in posteriorly directed MR and a murmur best heard in the axilla, L-infrascapular area, or back. In contrast, posterior leaflet flail directs regurgitation anteriorly resulting in a murmur at the base that can be confused with aortic stenosis. Acute severe MR can produce a short early systolic murmur that can be easily missed. Valsalva or standing after squatting will transiently reduce LV filling and increase the degree and duration of prolapse resulting in a murmur that is louder and longer. The impact of these maneuvers is mitigated when

there is flail and holosystolic MR. On palpation, the apex is hyperdynamic. With decompensated MR, findings of left and subsequently right heart failure are observed.

Imaging evaluation

Chest X-ray

Radiographic findings are non-specific depending on MR severity and the degree of compensation but include cardiomegaly and evidence of left atrial (LA) enlargement.

Echocardiography

Echocardiography is the default modality for defining mitral anatomy and MR mechanism as well as assessing MR severity and its impact on cardiac chambers and hemodynamics. However, as described below, magnetic resonance imaging (MRI) plays an important complementary role in some patients.

The anterior and posterior mitral leaflets are each divided into 3 scallops, numbered according to the Carpentier classification of leaflet anatomy as P1, P2, and P3 and A1, A2, and A3 (from lateral to medial) [9]. Mitral valve prolapse is defined echocardiographically as systolic extension of one or both leaflets at least 2 mm above the plane of the mitral annulus as seen in the parasternal long axis view [10]. Because the annulus is saddle shaped, the apical views which show the most apical points of the annulus should not be used to diagnose prolapse. In prolapse, chordae are intact although frequently elongated and redundant. Leaflet flail, typically caused by chordal rupture, is defined as untethered motion of the free edge of one or more scallops. Using the Carpentier classification of MR mechanism based on leaflet motion, both prolapse and flail fall into type II [11]. The relation of leaflet insertion to the LA-LV junction is also important, as there is growing recognition of a group of patients with mitral annular disjunction who may be at increased risk for malignant arrhythmias even in the absence of significant MR [12].

In DMR, it is important to define the affected scallop(s), a process greatly facilitated by 3D imaging particularly with transesophageal echocardiography (TEE) as transthoracic echocardiography (TTE) may lack the resolution for these determinations. This information is critical to clinical decision-making and procedural planning as both surgical and catheter-based repairs are most successful with P2 and A2 pathology. The most common site of flail is P2, followed by A2 and then lateral and medial scallops. As with prolapse which may involve multiple scallops, chordal rupture may involve more than one chord and affect more than a single scallop. The direction and source of MR jets demonstrated with echocardiography should be reconciled with the presumed mechanism (i.e., anterior leaflet prolapse/flail associated with posteriorly directed MR and vice versa). With Barlow's valves, multiple jets are not uncommon.

Establishing MR severity

Key to patient management is the ability to differentiate between severe and non-severe MR as defined by echocardiography and/or angiography. The American Society of Echocardiography (ASE) guidelines recommend an integrated

approach to quantitating MR that includes qualitative, semi-quantitative, and quantitative elements based on color and spectral Doppler as well as imaging [3]. As shown in Fig. 2, the ASE has proposed an algorithm to provide some guidance in weighing the various criteria and the final echocardiographic grading of MR represents the synthesis of multiple parameters both from TTE and TEE. There are 2 groups of specific signs for either mild or severe MR, and per the algorithm, if at least 4 are present, mild or severe MR is likely present. Intermediate cases require additional quantitative assessment.

The 3 principle quantitative parameters in MR assessment are the effective regurgitant orifice area (EROA), the regurgitant volume (RVol), and the regurgitant fraction (RF). Exceeding one or more of the "60-50-40" cutoff values (RVol ≥ 60 mL, RF ≥ 50%, and EROA ≥ 40 mm^2) suggests severe MR [3] (Fig. 2).

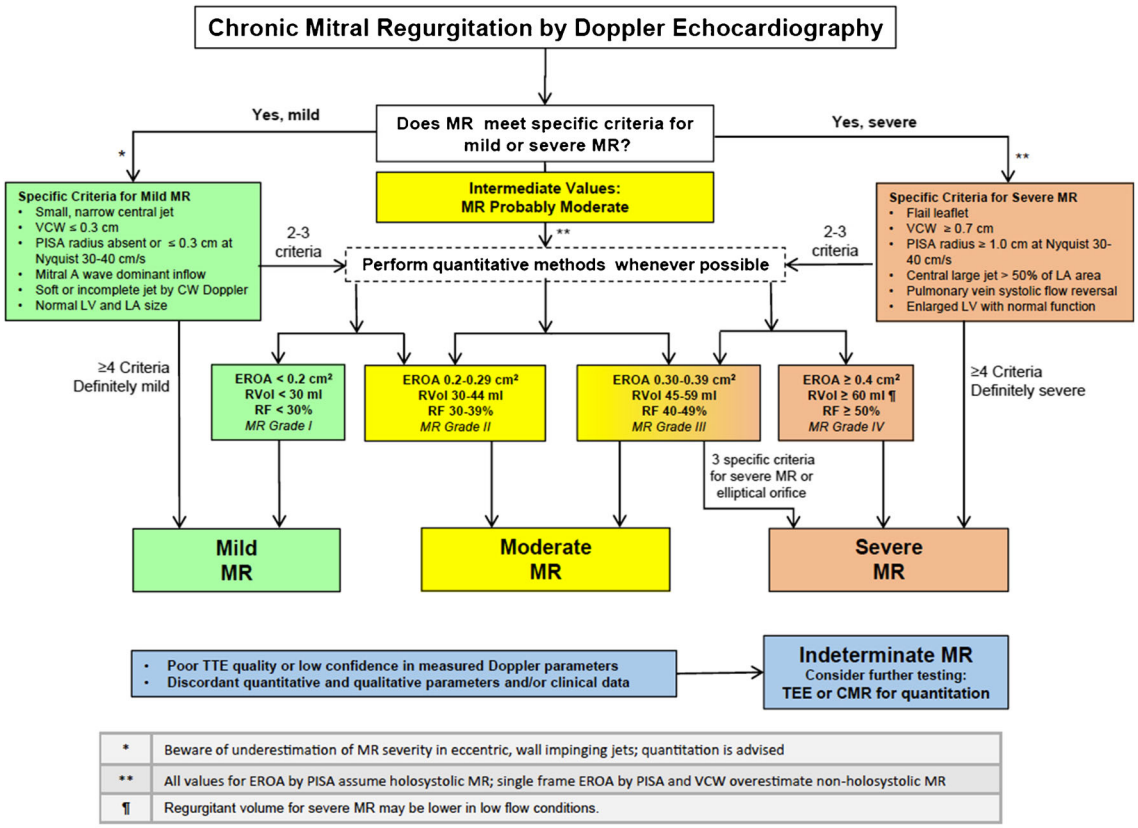

Fig. 2. Grading of mitral regurgitation severity. VCW, vena contracta width; PISA, proximal isovelocity surface area; LA, left atrium; LV, left ventricle; EROA, effective regurgitant orifice area; RVol, regurgitant volume; RF, regurgitant fraction; TEE, transesophageal echocardiogram; CMR, cardiac magnetic resonance. Reproduced with permission from Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA et al. Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A Report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr*. 2017;30 (4):303–71. doi:https://doi.org/10.1016/j.echo.2017.01.007.

Common echo pitfalls in assessment of MR severity (Fig. 3)

A detailed critique of the strengths and limitations of echocardiographic methods is beyond the scope of this review but several important pitfalls of color Doppler deserve attention. These include failure to account for hemodynamic effects, technical settings, and duration of MR in systole (Fig. 3(A, B)). These can result in both under- and over-estimation of severity. MR may be significantly overestimated in some patients with mitral valve prolapse where MR is restricted to late systole (Fig. 3(C–G)). In such cases, the regurgitant orifice develops only in late systole when leaflet prolapse is at its peak. As a result, there is only a brief burst of regurgitation, overall RVol is low, and MR is typically mild. These cases expose another shortcoming of all color Doppler methods for assessing regurgitation (vena contracta, PISA-derived EROA/RVol, and color jet dimensions) in that they are taken at a single systolic time point

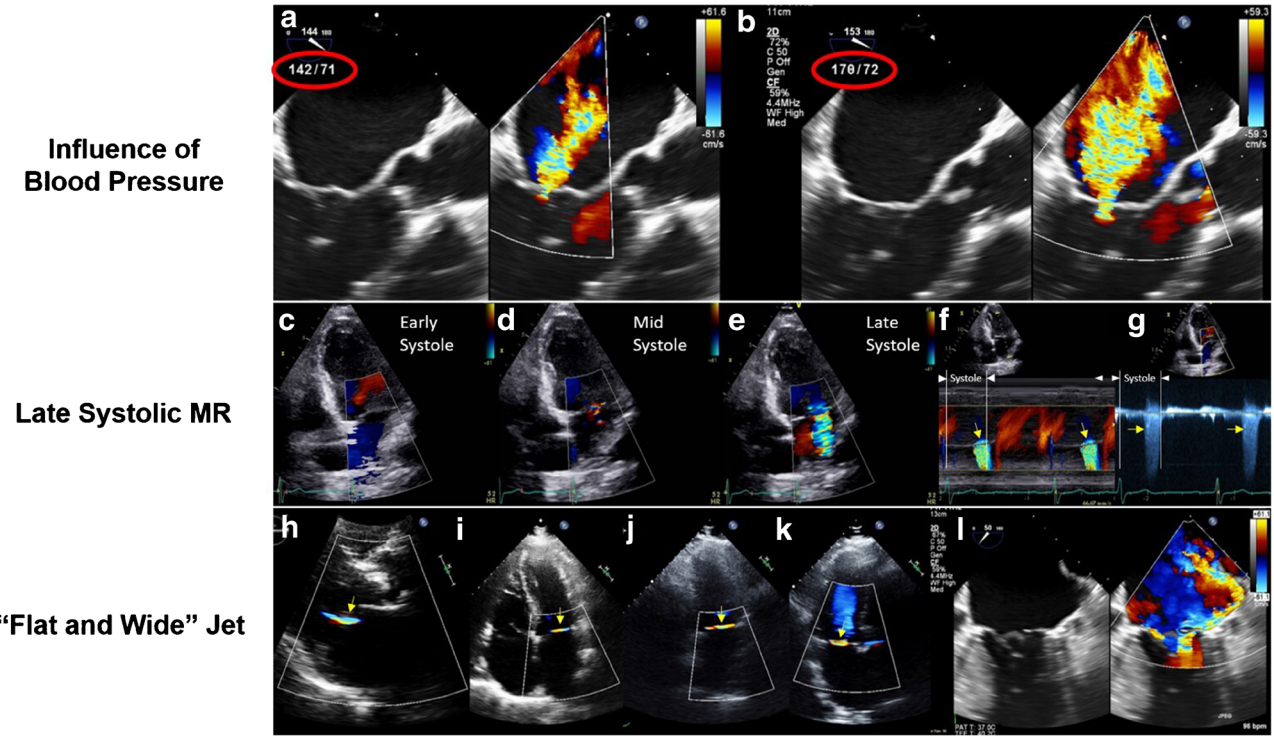

Fig. 3. Common color Doppler pitfalls in assessment of MR severity. Color Doppler is helpful to detect MR presence but is not reliable as a sole method to determine MR severity. The size of the regurgitant jet on color Doppler can be influenced by systemic blood pressure at the time of image acquisition—higher blood pressure increases the momentum of the regurgitant jet leading to entrainment of non-regurgitant blood in the LA thereby increasing the color Doppler jet area (a, b). Inappropriate settings (low Nyquist limit, increased color gain, decreased transducer frequency, etc.) can artificially increase color jet area by emphasizing low velocity flow. Mitral valve prolapse is frequently associated with non-holosystolic MR—predominantly in late systole (c–g, arrows) when prolapse is at its peak. Note that no significant MR is seen on color flow Doppler in early and mid-systole (c, d) until a prominent MR jet suddenly appears for a short time during late systole (f, g, arrows). Overall regurgitant volume is low because the flow is short lived. A "flat and wide" jet restricted to peri-annular region is usually caused by extremely eccentric jets (usually flail leaflet) and the misleadingly small (truncated) color flow jet area may lead to underestimation of MR severity on transthoracic echo (h-k). In such cases, a TEE can unmask leaflet pathology and reveal the full extent of the regurgitant jet (l).

which is assumed to be representative of all systole [3].

Another common pitfall of color Doppler is the "flat and wide" turbulent jet (Fig. 3(H–K)). These are frequently restricted to a narrow area in the LA just above the mitral annulus and reflect a highly eccentric, wall-hugging jet eluding most standard echo planes with only the jet origin at the coaptation line exposed. These jets always represent asymmetric leaflet pathology, often near the commissures. TEE usually reveals significantly larger and highly eccentric jets and MR is frequently severe. A "flat and wide" jet in the setting of acute hemodynamic instability usually represents a flail leaflet.

Quantitative Doppler approaches are limited by imaging and Doppler methods available to determine total LV stroke volume from which forward stroke volume is subtracted to yield the RVol. Continuity equation-based methods for assessing forward flow across the aortic valve (AV) are reasonably robust in the setting of a normal AV.

Acute MR may be unimpressive on color flow Doppler due to rapid equalization of LV and LA pressures with pressure gradient and regurgitant flow disappearing rapidly in early systole. The result is a short Doppler signal that may be monochromatic without aliasing.

Indirect assessment of MR includes LV and LA size, pulmonary vein flow (systolic blunting or reversal with severe MR), pulmonary pressures (increased with severe MR), and right heart function.

Uncertain MR severity

In many instances, grading MR is difficult, time-consuming, and technically demanding. Intermediate cases, particularly those on the cusp of severe MR, frequently require additional testing and more careful analysis of multimodality and serial data. Adjudicating MR as severe may direct the patient to intervention and it is critical that there be no doubt as to severity in the asymptomatic patient with no evidence-based trigger if intervention is contemplated (see below).

Rapid expansion of transcatheter interventions has led to increased demand for dedicated structural imagers or interventional echocardiographers [13]. They and other imaging expert members of a multidisciplinary valve team may help adjudicate borderline cases—a role emphasized in the most recent update to the ACC valve guidelines [6].

TEE

In many cases, including all in which an intervention is contemplated, TEE is indicated due to its improved spatial resolution and avoidance of annular artifact. Peripheral (non A2-P2) pathology, underappreciated on TTE, is often obvious on TEE. While MR severity may be better assessed with TEE, sedation used during TEE is associated with hemodynamic changes that may lessen MR, analogous to the impact of general anesthesia in the OR [14, 15].

3D echocardiography

3D echo, particularly TEE, is an increasingly important tool in the workup of the patient with DMR. It may clarify MR mechanism and severity, precise location of pathology, and the feasibility of repair. Native 3D data allow reconstruction

of any echocardiographic plane captured within the acquired 3D volume and 3D reconstruction of the narrowest portion of the color jet—the vena contracta—allows direct planimetry of the regurgitant orifice area [3], avoiding the pitfalls of geometric assumptions.

Stress echocardiography

Some patients with MR may experience exertional symptoms that cannot be explained by the degree of MR seen on a resting echocardiogram. This is an indication for stress echocardiography which will reveal whether MR worsens with exercise and provide information on functional capacity, exercise-associated symptoms, and LV and pulmonary pressure response to exercise [2]. An important alternative scenario is the asymptomatic patient with clearly severe MR on echo in which the test will determine whether the patient is truly asymptomatic with adequate ventricular compensation.

Treadmill and bicycle stress protocols are similar to those used for coronary disease. Dobutamine stress is not an alternative because its direct vasodilatory effects reduce MR [2]. Poor prognostic signs include increase in MR by at least one grade, exertional PASP ≥ 60 mmHg, lack of contractile reserve (increase in EF by < 5% or < 2% improvement in global longitudinal strain), and insufficient RV augmentation (TAPSE < 18) [4].

Assessment of the LV size, and systolic function

Accurate measurements of LV size and left ventricular ejection fraction (LVEF) are critically important in the management of primary MR as alterations in either may trigger referral for intervention. Linear measurements of the basal LV diameter in systole should be performed in a consistent manner on serial studies for reliable comparison. The LV volume and LVEF are best assessed by volumetric measurements such as Simpson's biplane method of disks [16]. This method involves tracing the LV cavity in 2 orthogonal planes (apical 4- and 2-chamber views), automated apex to base segmentation, and addition of each of the created volume slices. The accuracy of this method depends on good image quality, maximal exposure of the LV cavity (absence of apical foreshortening), and absence of regional wall motion abnormalities in the LV segments located outside of the traced planes. 3D echo with a true volumetric approach overcomes the need for geometric assumptions but requires good image quality and substantial expertise [17]. Due to its relatively low spatial resolution in defining the myocardial/blood pool interface, 3D echocardiography systematically underestimates LV volumes compared to cardiac MRI—the current gold standard for LV volume and LVEF assessment because of its superior accuracy and reproducibility. Cardiac MRI can be used to assess LV size and function if echocardiography data are inadequate or uncertain [2, 3]. Strain imaging, an automated tracking of myocardial regions throughout systole, has been shown to detect early changes in LV contractility—before a detectable decline in LVEF—and may help identify patients for early surgery [3].

Assessment of left atrial size

Left atrial enlargement is another negative prognostic factor in severe DMR, although less specific due to its occurrence in many other disease states (HTN,

diastolic dysfunction, etc.). Nevertheless, LA volume index ≥ 60 mL/m^2 is associated with higher mortality in primary MR if surgery is not performed [18]. Since the LA expands predominantly in the medio-lateral direction, its size can be significantly underestimated with conventional antero-posterior linear measurements. Therefore, LA size is best measured by volume and indexed to body surface area [16].

MRI

If echocardiography data are inadequate to confidently assess LV size, function, or MR severity, cardiac MRI may help [2, 3]. MRI allows precise and reproducible measurements of LV and RV volumes and mitral regurgitant RVol and RF. By providing an independent reference standard for grading MR, MRI has helped refine echocardiographic methods. It is notable that, in a prospective study of patients with DMR evaluated by both MRI and echocardiography, echocardiography tended to overestimate the severity of MR and it has been argued that MRI confirmation of severe regurgitation should be considered prior to sending an asymptomatic patient with DMR for surgery [19].

Catheterization

In some DMR cases, invasive hemodynamics may be helpful. Right heart catheterization allows assessment of LV filling pressures, pulmonary artery pressures, and right-sided pressures. A large v wave on a wedge tracing confirms hemodynamically significant MR. Additionally, stress hemodynamics using supine bicycle or handgrip can be useful. Left ventriculography may provide angiographic grading of MR [20] and concomitant coronary angiography may determine whether coronary revascularization is required.

BNP

Elevated or increasing plasma brain natriuretic peptide (BNP) level in asymptomatic patients with severe chronic primary MR has been associated with higher risk for cardiac events and represents another factor that may affect the decision to operate early [2, 21]. A combination of strain imaging with BNP may be a better predictor of adverse outcomes in asymptomatic patients than BNP alone [22].

Management (Fig. 4)

If, with confidence, MR is deemed mild and the patient is asymptomatic, no further diagnostic work up is required and the patient should be followed clinically every 1–2 years with TTE every 3–5 years or earlier if there is a change in clinical status (Fig. 4). If there is still uncertainty about MR severity, then a consultation with imaging expert may be helpful to make the final adjudication of MR severity [6].

There are several agreed upon triggers for intervention for severe DMR. Symptoms for which MR is the putative cause carry a class I indication for intervention for patients with an LVEF > 30%, although it is noted that, in some cases, it may be difficult to determine the contribution of comorbidities such as

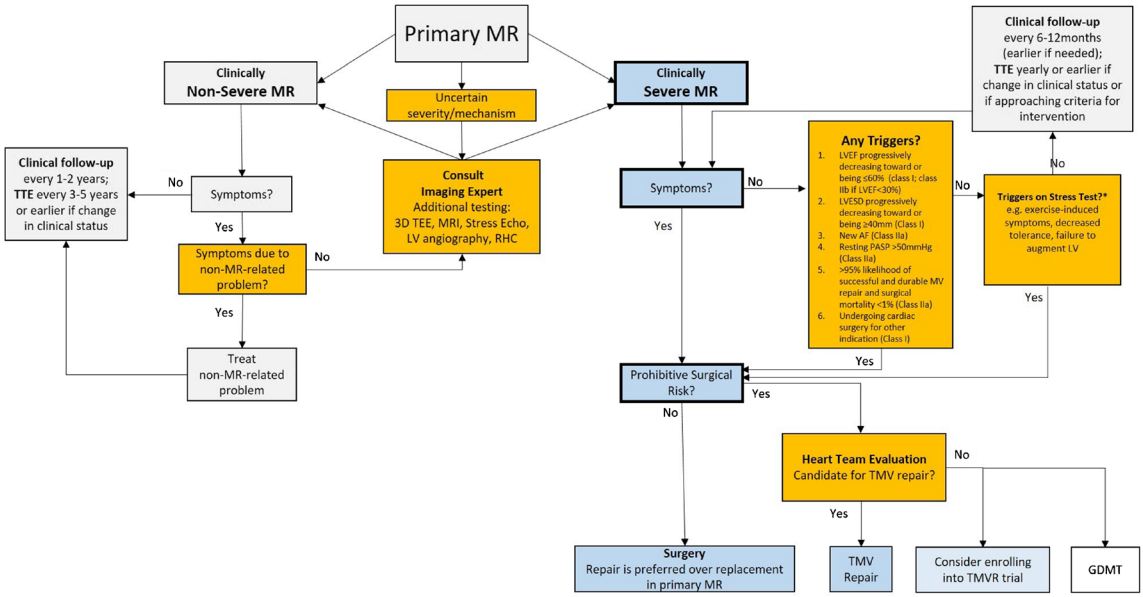

Fig. 4. Management of chronic primary (degenerative) mitral regurgitation. *Additional factors to consider in deciding on early surgery for asymptomatic patients include global longitudinal strain imaging, BNP, LAVI > 60 mL/m^2, presence of a flail, and mitral annular disjunction. MR, mitral regurgitation; TTE, transthoracic echocardiogram; TEE, transesophageal echocardiogram; MRI, magnetic resonance imaging; LV, left ventricle; RHC, right heart catheterization; LVEF, left ventricular ejection fraction; PASP, pulmonary artery systolic pressure; TMV, transcatheter mitral valve; TMVR, transcatheter mitral valve replacement; GDMT, guideline-directed medical therapy. Based on Bonow, R. O., et al. (2020). "2020 Focused Update of the 2017 ACC Expert Consensus Decision Pathway on the Management of Mitral Regurgitation: A Report of the American College of Cardiology Solution Set Oversight Committee." *J Am Coll Cardiol* 75 (17): 2236–2270.

lung disease. Even with medical symptom control, intervention should be considered unless contra-indicated by prohibitive surgical risk or reduced life expectancy due to other illnesses. In the absence of symptoms, there are additional triggers for intervention. These include LV systolic dysfunction defined as either LVEF 30–60% (class I) or progressively decreasing to this level on serial studies (class II) or left ventricular end-systolic diameter (LVESD) ≥ 40 mm (class I) or progressively increasing (class II). LVESD reflects both impaired systolic performance and left ventricular enlargement. "Normal LVEF" in primary MR is approximately 70% [2] and is increased as a reflection of the Starling curve, due to expansion of end-diastolic volume. Other deleterious effects of chronic severe MR considered reasonable (class II) indications for surgery include new-onset atrial fibrillation and significant pulmonary hypertension (PASP > 50 mmHg). If the patient has another indication for cardiac surgery, mitral repair should be performed in the same setting (class I). Surgery can also be considered for patients with primary MR and severe LV systolic dysfunction defined by LVEF≤ 30%, although the benefits are not as clear for this population (class II) [6].

There is ongoing debate about the best approach to asymptomatic patients with severe DMR and none of these triggers [23, 24] with an important consideration being the likelihood of successful repair vs. replacement. The likelihood of successful repair is a function of both valve anatomy and the experience of

the surgeon/surgical center. In general, isolated P2 flail has the highest likelihood of repair followed by A2 disease and then involvement of medial or lateral scallops or Barlow's disease. Guidelines indicate that there must be a high probability of successful repair—defined as 95% with < 1% predicted mortality, setting a high bar [2]. Leaflet anatomy must be meticulously defined with 3D TEE and the patient risk-stratified for surgery (see below). Additionally, since there can be no doubt that the patient has severe MR, an argument can be made for an important role for MRI to complement echocardiography. If the required expertise is not available locally, patients should be referred to a valve center of excellence. Unexpected valve replacement should be considered a procedural complication of valve repair given that attendant increased risks of infection and need for anticoagulation. An alternative approach to intervention is close medical follow-up, for which the term watchful waiting was originally coined [25] but now termed active surveillance [26]. Data in support of this approach suggest that up to half asymptomatic patients with severe MR and no surgical triggers may remain asymptomatic and without triggers for up to 8 years [25], during which time an initially successful mitral repair may fail. It is noted that mitral surgery may have significant complications including death in even low-risk patients and that iatrogenic mitral stenosis may render symptomatic highly active patients who were previously symptom free. While there have been studies arguing better outcomes with early surgical intervention, these studies suffer from lack of a standardized approach to follow-up in non-surgical patients. Unfortunately, there has been no randomized prospective trial comparing the two approaches. For the time being, the typical patient for whom prophylactic surgery might be considered would be a low-risk patient with isolated P2 flail. Of note, catheter-based intervention is not currently an option for these patients. It is possible that, as experience is gained with more sensitive indices of LV systolic function such as strain, these may complement LVEF as triggers for intervention, but these are not included in current guidelines.

Medical management

Medical options for compensated asymptomatic DMR are limited to the treatment of concomitant hypertension which reduces afterload and increases forward flow. Although beta blockers had shown potential to prevent deterioration of LVEF in a small randomized trial using MRI-derived LV volumes [27], to date, no intervention has been definitively shown to mitigate LV remodeling or improve hemodynamics. Specifically, no benefit from vasodilators has been shown in normotensive patients with chronic DMR [2].

When present, LV systolic dysfunction (LVEF < 60%) can be treated with beta blockers, ACEi/ARB, and +/− aldosterone blockers [2] but this should be viewed as temporizing or palliative as surgical or transcatheter intervention is indicated where possible.

Intervention for degenerative MR

While catheter-based approaches for DMR are evolving, surgery remains the primary intervention. Repair is preferred over replacement in DMR because of lower perioperative morbidity and mortality and potential risks of prosthetic

valves (see below). In fact, in a patient with primary MR due to pathology involving less than a half of the posterior leaflet, MV replacement without first attempting repair is considered harmful [2]. Successful repair has been reported to return the patient to the normal life expectancy curve of an age-matched population [2, 28].

Surgical repair

Posterior leaflet repairs are generally easier and associated with best outcomes. But even if the anterior leaflet is involved, repair outcomes are better than MV replacement with respect to freedom from recurrence and reoperation [2]. Additionally, by preserving the native valve apparatus, repair helps maintain LV shape and contractile function.

The feasibility of repair is determined by multiple anatomic factors and surgical expertise. Complicating issues include leaflet and annular calcification, thickened subvalvular apparatus, and septal hypertrophy, which increases the risk of post-op mitral systolic anterior motion and dynamic left ventricular outflow obstruction. Repair techniques include leaflet resection or remodeling, reconstruction of chords (reimplantation of native chords or implantation of artificial chords), and ring annuloplasty. Intraoperative TEE is required to guide repair [2]. If MV repair is successful, significant (≥ 3+) MR requiring reoperation does not recur for at least 15–20 years after the operation in > 80% of cases [2]. It is essential to check and test the repair before leaving the operating room as even mild MR increases the risk of reoperation. As previously noted, MR severity may be underestimated with general anesthesia which can decrease preload, afterload, and LV contractility. The repair result should be tested by completely filling the LV and ensuring the blood pressure is in the normal range. While mitral systolic anterior motion and LV outflow tract obstruction may occur post repair, this can generally be avoided with an optimized repair based on pre-procedure imaging [2].

Replacement

If repair is impractical and/or unsuccessful, valve replacement may be required. The patient should be matched to the optimal prosthesis, both in type and in size. Mechanical prostheses have the potential for greater durability but require lifelong anticoagulation. Biologic prostheses may not require chronic anticoagulation but are prone to degeneration resulting in reoperation. The choice of prosthesis should account for patient's age (and the likelihood of reoperation), preference, and ability to tolerate and comply with anticoagulation. Younger patients (< 50 years old) are often good candidates for mechanical prostheses and these valves may also be preferred in patients for whom reoperation will pose a serious risk such as those with prior radiation therapy or porcelain aorta [29]. However, assuming average bioprosthetic durability of 15 years, elderly patients may reach their natural life expectancy before the bioprosthesis reaches its own. In addition, a degenerated bioprosthesis can be treated percutaneously with a new valve delivered endovascularly and expanded inside the degenerated bioprosthesis providing an instant complete internal remodeling with a brand-new set of leaflets—a procedure known as "valve-in-valve."

The surgeon's experience with mitral repair becomes a key consideration in referral. A surgeon performing > 100 mitral operations per year is three times more likely to perform a successful repair than one with only 5–10 mitral cases a year [30]. Better outcomes are expected with experience of > 25 mitral cases (repair or replacement) per year per operator and > 50 cases per year per institution [6].

Transcatheter interventions (Fig. 5)

Presently, access to approved and investigational devices is limited to patients deemed at high or prohibitive surgical risk per STS and EuroScore scores with additional consideration of difficult anatomy (porcelain aorta, post-radiation scarring, severe mitral annular calcification), major organ system compromise, and frailty [2].

While there have been several catheter-based approaches to repair DMR, only one, the MitraClip™, is FDA approved for symptomatic patients at high surgical risk. The procedure, termed edge to edge (E2E) repair, mimics the surgical Alfieri stitch, creating dual orifices by clipping opposing anterior and posterior leaflet scallops. Although optimally used for selected patients based on multiple anatomic criteria (Table 1), as experience has grown and second-

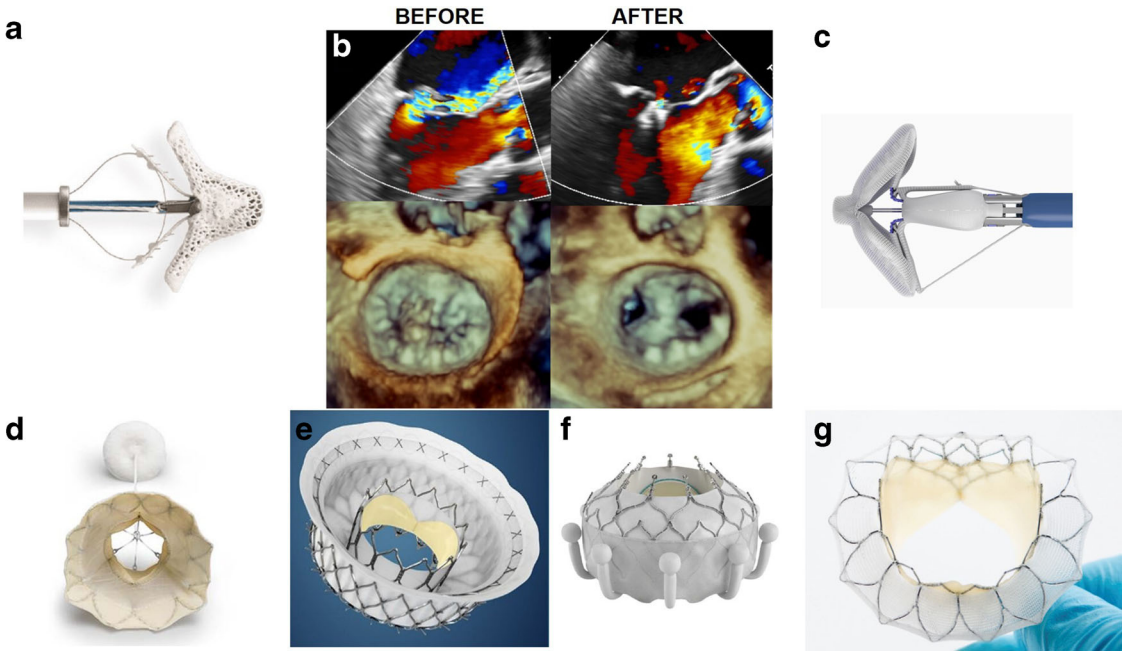

Fig. 5. Transcatheter devices for treatment of mitral regurgitation. The MitraClip™ (Abbott) is currently the sole transcatheter device approved by FDA for treatment of severe symptomatic primary mitral regurgitation for patients who are at prohibitive surgical risk (a). The procedure, termed edge to edge (E2E) repair, mimics the surgical Alfieri stitch, creating dual orifices by clipping opposing anterior and posterior leaflet scallops (b). Another E2E device (c), Pascal (Edwards Lifesciences, Irvine, CA), has been approved for use in Europe and is currently undergoing pivotal trial in the USA. Several transcatheter mitral valve replacement (TMVR) platforms are currently in clinical trials. Abbott's Tendyne™ device is implanted via transapical access and secured by the long apical tether (d). Other TMVR platforms that have advanced to clinical trials include Medtronic's Intrepid™ (e), Edwards Lifesciences' Evoque valve (f), and Neovasc's Tiara valve (g). None of the TMVR platforms has yet been approved for clinical use in the USA, outside of clinical trial setting.

Table 1. Anatomic features in primary MR predicting success of transcatheter mitral edge to edge repair

Optimal	Rarely feasible
MVA > 4.0 cm^2	MVA < 3.5 cm^2
Leaflet length > 10 mm	Leaflet length < 7 mm
No leaflet calcification in the grasping area	Severe calcification in the grasping area
Single target jet at A2P2	Barlow's disease with multiple significant jets
Flail gap < 10 mm; flail width < 15 mm	Rheumatic MV disease, leaflet perforation, endocarditis
	Cleft in the grasping area

MVA, mitral valve area by planimetry

generation iterations have emerged, a broader range of patients has been successfully treated (Fig. 5(A, B)).

The procedure uses venous access and transseptal puncture to approach the mitral valve under 2D and 3D TEE guidance. A full description of this procedure and its complications has been reported elsewhere [31].

While E2E repair may not provide complete elimination of MR in most cases compared to more definitive surgical repair or replacement, achieved MR reduction results in reverse remodeling and the procedure was reported to be significantly safer than surgery in a randomized trial setting, attributable mostly to fewer bleeding complications [32].

For patients who are poor E2E repair candidates, transcatheter mitral replacement, currently all investigational procedures, may be an option (Fig. 5). Current challenges for these devices include device-associated LVOT obstruction and severe mitral annular calcification which limits anchoring and creates a substrate for significant paravalvular regurgitation. As a result, there are multiple anatomic exclusion criteria specific for each device, many best evaluated by cardiac computed tomography. Performance standards with specific recommendations for experience and procedural volume to participate in transcatheter mitral valve therapy have been recently published [33].

Post-intervention follow-up

Patients are followed closely in the post-operative period with clinical visits around 30 days, 3–6 months, and yearly thereafter and should receive antibiotic prophylaxis prior to procedures posing risk of significant bacteremia [29]. All patients having undergone mitral intervention should have an early echocardiographic profile of their new or modified mitral valve including transmitral gradients, integrated assessment of MR, assessment of LV size, pulmonary pressures, and function of the right side of the heart. This early study (within the first 3 months after surgery) serves as a useful clinical reference for future assessments of valve function. For example, persistently high transvalvular gradients tracing back to the baseline post-op study are more likely to be due to patient-prosthesis mismatch rather than valve degeneration. Unless prompted by a change in patient's

symptoms, echocardiographic re-assessment of prosthetic valves implanted less than 3 years earlier is generally not necessary [34]. As the valve ages, particularly beyond 10 years, occasional echocardiographic surveillance is appropriate, although it is not clear how often this should be done in the absence of clinical and/or echocardiographic evidence of valve dysfunction. Changes in clinical status, including pregnancy, should prompt unscheduled echocardiographic examinations [34].

Acute primary MR

Acute MR is a relatively rare syndrome which classically occurs due to chordal rupture (spontaneous or as a result of infection) with a flail leaflet segment, or as a mechanical complication of myocardial infarction with papillary muscle rupture. A rare cause is leaflet perforation complicating endocarditis. More recently, transient acute MR and its often dramatic effects may be seen at intermediate stages of various transcatheter structural interventions if a misguided catheter is allowed to pin down a papillary muscle or otherwise compromise leaflet coaptation. This acute MR usually resolves immediately after repositioning the catheter as the integrity of mitral valve apparatus is restored.

The presentation of acute MR depends on the regurgitant volume load but when severe is typically that of pulmonary edema and cardiogenic shock. The murmur is often short and quiet, or even absent due to rapid equalization of pressure between LV and LA in cases with very severe acute MR. The Doppler equivalent of this phenomenon is the triangular-shaped envelope with rapidly rising peak pressure in early systole and little flow later on due to lack of driving pressure gradient.

Open heart surgery is the definitive therapy, although MitraClip has been used successfully in an emergent setting in inoperable patients [35]. In the interim, mechanical (Impella or intra-aortic balloon pump) or pharmacologic (vasodilators) support may help.

Conclusions

The workup and management of primary MR require basic and sophisticated tools from history and physical examination to advanced 3D imaging. The field is evolving with new options for treatment and the potential for new measures that would support early intervention. There is ongoing controversy as to the best approach to the treatment of asymptomatic severe disease with the hope that a randomized control trial might resolve this uncertainty.

Compliance with Ethical Standards

Conflict of Interest

Leo Marcoff declares that he has no conflict of interest. Linda D. Gillam declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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