

Review

Contemporary Review on Multi-Modality Imaging Evaluation and Management of Functional Mitral Regurgitation

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ABSTRACT: Functional mitral regurgitation (FMR) is a prevalent valvular disorder driven by adverse remodeling of the left ventricle and/or left atrium. This review synthesizes the contemporary evidence on multimodality imaging and its role in mechanism-specific evaluation and management of FMR, with particular emphasis on distinguishing ventricular FMR (VFMR) from atrial FMR (AFMR). FMR is mechanistically heterogeneous, requiring precise phenotyping to guide therapy. A mechanism-based framework differentiating VFMR, driven by left ventricular dilation and leaflet tethering, from AFMR, driven by left atrial and annular enlargement with preserved ventricular function, is central to contemporary management. Echocardiography remains the cornerstone for real-time assessment of MR severity, hemodynamics, and valve–ventricle interactions. Cardiac magnetic resonance (CMR) provides the gold standard for volumetric quantification and myocardial tissue characterization, enabling improved risk stratification by assessing ventricular remodeling and fibrosis. Computed tomography (CT) offers high-resolution anatomic phenotyping and is essential for procedural planning, particularly for transcatheter edge-to-edge repair (TEER) and transcatheter mitral valve replacement (TMVR). Integration of multimodality imaging supports individualized selection between guideline-directed medical therapy alone, TEER, surgical intervention, or TMVR, based on the dominant mechanism and myocardial substrate. The discordant outcomes of landmark trials such as MITRA-FR and COAPT have underscored the importance of precision in patient selection, highlighting the controversial but clinically relevant proportionate/disproportionate FMR framework and the extent of myocardial fibrosis as key modifiers of treatment response. Emerging advances in advanced imaging and artificial intelligence hold promise for automated phenotyping, improved reproducibility, and earlier identification of patients most likely to benefit from intervention, ultimately enabling a more personalized, mechanism-driven approach to improving outcomes in FMR.

Keywords: Functional mitral regurgitation; Mitral valve; Echocardiography; Cardiac magnetic resonance; Computed tomography; Transcatheter interventions; Mitral valve surgery



1. Introduction

Functional mitral regurgitation (FMR), or secondary mitral regurgitation, has traditionally been defined as valvular incompetence occurring in the setting of structurally normal mitral leaflets and chordae, where regurgitation results from adverse geometric remodeling of the left ventricle (LV) rather than from primary leaflet pathology [1]. In this classic, LV-centric paradigm, FMR is distinguished from primary (organic) mitral regurgitation by its etiology: global or regional LV remodeling displaces the papillary muscles and tethers the leaflets, thereby impairing systolic coaptation [1]. More recently, this concept has been refined, and FMR is now recognized to encompass at least two distinct pathophysiological phenotypes: ventricular FMR (VFMR) and atrial FMR (AFMR) [1]. VFMR represents the traditional LV-driven mechanism, whereas AFMR arises from left atrial (LA) enlargement with resultant annular dilatation, typically in the context of atrial fibrillation (AF) or heart failure with preserved ejection fraction (HFpEF) where left atrial pressure is chronically elevated, and this can occur despite preserved LV systolic function [1–8].

Irrespective of the underlying mechanism, FMR is a clinically important entity because of its rising prevalence, close association with heart failure symptoms, and adverse impact on prognosis [2,4,9–11]. Recognition of the distinct ventricular and atrial phenotypes is critical, as they differ in anatomy, clinical course, and response to therapy and may thus require tailored diagnostic and interventional strategies [1–8]. Multimodality imaging, including transthoracic and transesophageal echocardiography, cardiac magnetic resonance, and computed tomography, has become indispensable not only for accurate quantification of MR severity but also for distinguishing between AFMR and VFMR and for procedural planning [3,9,10]. In parallel, management has evolved from a foundation of guideline-directed medical therapy (GDMT) to a broad spectrum of surgical and, increasingly, transcatheter interventions targeted to the specific mechanism of regurgitation [10,12–16]. This review synthesizes contemporary understanding of FMR, emphasizing the pivotal role of multimodality imaging and outlining current and emerging management strategies across the spectrum of ventricular and atrial phenotypes.

2. Epidemiology and Clinical Impact

FMR is one of the most prevalent forms of moderate-to-severe mitral regurgitation in adults, accounting for approximately 65% of cases in a community-based cohort [17]. The estimated prevalence of moderate-to-severe mitral regurgitation in the general adult population ranges from 0.46% to 2.3% [2,17,18], with FMR occurring more frequently among older individuals and those with comorbid conditions, such as heart failure or atrial fibrillation [2,19–21].

The clinical burden of FMR is significant. Compared to the general population and to patients with primary mitral regurgitation of similar severity, individuals with FMR experience markedly increased morbidity and mortality [2,4,9–11]. The five-year heart failure incidence can be as high as 80% in VFMR and 59% in AFMR [22]. All-cause mortality is significantly elevated, with reported risk ratios ranging from 1.88 to 3.45 across FMR subtypes [17,23–25]. Notably, severe FMR confers a graded increase in mortality across all heart failure phenotypes, with hazard ratios reaching as high as 7.5 in the most advanced cases [24–26]. Despite its high prevalence and adverse prognosis, FMR remains a challenge to diagnose and treat. Fewer than 10% of affected patients undergo surgical or transcatheter mitral interventions [15], underscoring the need for improved recognition and management of this condition.

3. Pathophysiology & Management Considerations of FMR

The mitral valve sits on a saddle-shaped annulus. There are 2 mitral valve leaflets, the anterior and posterior leaflets. There are chordae tendineae attached to each leaflet, which allow the mitral valve to perform its function during systole and diastole. FMR arises from perturbations in cardiac geometry of the saddle-shaped annulus and/or LV function that impair mitral valve competence despite structurally normal

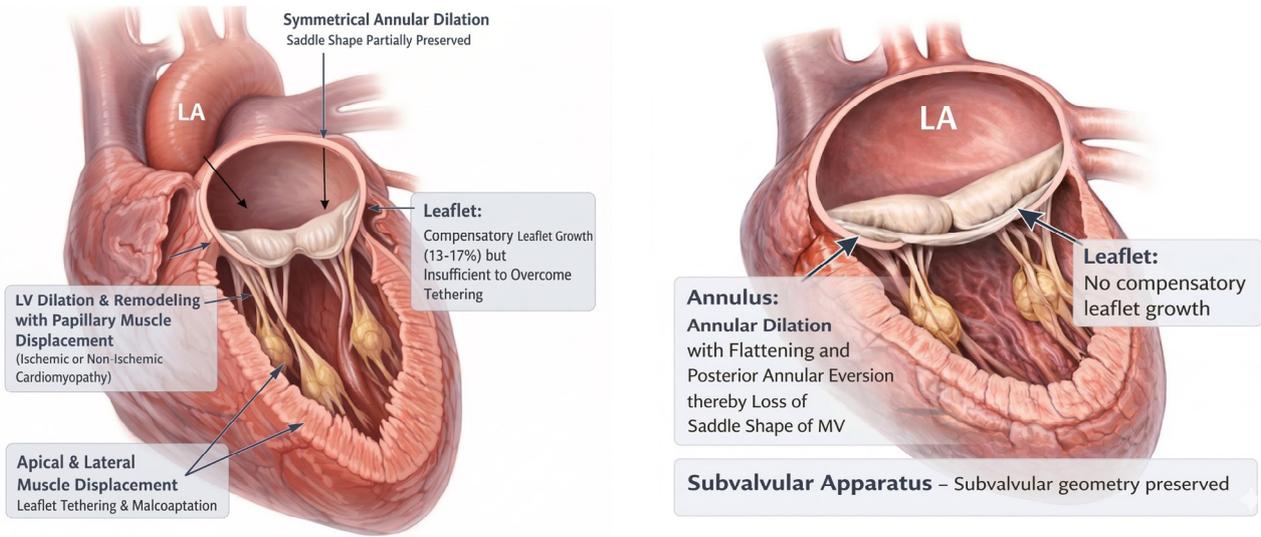
leaflets and sub-valvular apparatus [9]. On this basis, FMR can be further classified into three distinct phenotypes: VFMR, AFMR, and dual FMR [2,4,7,27–29]. VFMR is more common in males and is associated with left ventricular systolic dysfunction and ischemic heart disease [2,17,30–32], while AFMR is predominantly linked to AF and left atrial enlargement [19,27,33–36]. Dual FMR reflects the coexistence of atrial and ventricular mechanisms, in which both annular dilatation and leaflet tethering contribute to regurgitation, and may be encountered in advanced or long-standing cardiomyopathic and atrial remodeling [2,4,7,27–29]. Although their initiating mechanisms differ, all three phenotypes converge on a final common pathway: loss of effective leaflet coaptation due to an imbalance between tethering and closing forces [7,27,28,37]. Furthermore, FMR is a dynamic entity: its severity may fluctuate with loading conditions, heart rhythm, blood pressure, and ventricular synchrony [38–40]. Ultimately, a structurally normal mitral valve becomes incompetent due to its maladaptive mechanical environment [2], which clearly distinguishes FMR from primary (degenerative) mitral regurgitation, which is related to intrinsic issues with the mitral valve itself. The key mechanistic and clinical differences between VFMR and AFMR are detailed and summarized in Figure 1 and Table 1. Figure 2 details the differing management processes and considerations for VFMR and AFMR, which will be further elaborated in subsequent sections.

Table 1. Comparative Mechanistic and Clinical Characteristics of Ventricular vs. Atrial Functional Mitral Regurgitation.

	VFMR	AFMR
Primary geometric driver	LV dilation and remodeling due to ischemic or nonischemic cardiomyopathy with papillary muscle displacement	Left atrial enlargement with mitral annular dilation in the setting of chronic AF or HFpEF and preserved LV size
Imaging characteristics	LV dilation, increased LVEDV, papillary muscle angles widened, increased tenting height/area (~10 mm diameter \geq 40 mm, height/width ratio $<$ 0.15, in severe cases), eccentric jet.	Marked LA dilation ($>$ 60 mL/m ²), annular normal LV size/strain, central jet
Clinical associations	HFrEF, ischemic scar, LBBB	Chronic AF, HFpEF, older age
Prognosis	Higher mortality and HF hospitalization risk	Lower mortality and HF hospitalization risk; may progress to dual FMR
First-line management	GDMT for HFrEF; CRT if indicated	Rhythm control for AF, HFpEF management, afterload reduction if hypertensive
Device/interventional therapy	TEER or surgical repair/replacement in select cases after GDMT optimization	TEER or annuloplasty in select symptomatic patients
Key RCTs	COAPT, MITRA-FR, RESHAPE-HF2	No large RCTs specific to AFMR; most data from observational studies and subgroup analyses

Abbreviations: VFMR = Ventricular Functional Mitral Regurgitation; AFMR = Atrial Functional Mitral Regurgitation; LV = Left Ventricle; LA = Left Atrium; HFpEF = Heart Failure with Preserved Ejection Fraction; HFrEF = Heart Failure with Reduced Ejection Fraction; CRT = Cardiac Resynchronization Therapy; LVEDV = Left Ventricular End-Diastolic Volume; TEER = Transcatheter Edge-to-Edge Repair; RCT = Randomized Controlled Trial; COAPT = Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation; MITRA-FR = Multicenter Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients with Severe Secondary Mitral Regurgitation; RESHAPE-HF2 = Randomized Study of the MitraClip Device in Heart Failure Patients with Clinically Significant Functional Mitral Regurgitation.

Ventricular Functional Regurgitation Atrial Functional Regurgitation



Force Balance	Increase tethering forces and reduce closing forces due to LV dysfunction. "Double Hit" of increase tethering force from papillary Pull. Decrease closing force due to reduce LV contractility.	Force Balance	Preserve closing forces (normal LVEF) but loss of annular function.
Dynamic Behavior	Load & dys-synchrony dependent. If LBBB present, improvement with CRT. Improvement in afterload and decrease MR severity.	Dynamic Behavior	Sensitive to atrial rhythm and volume. Preferential for rhythm control to reduce MR severity.

Figure 1. Pathophysiological Mechanisms of Ventricular vs. Atrial Functional Mitral Regurgitation.

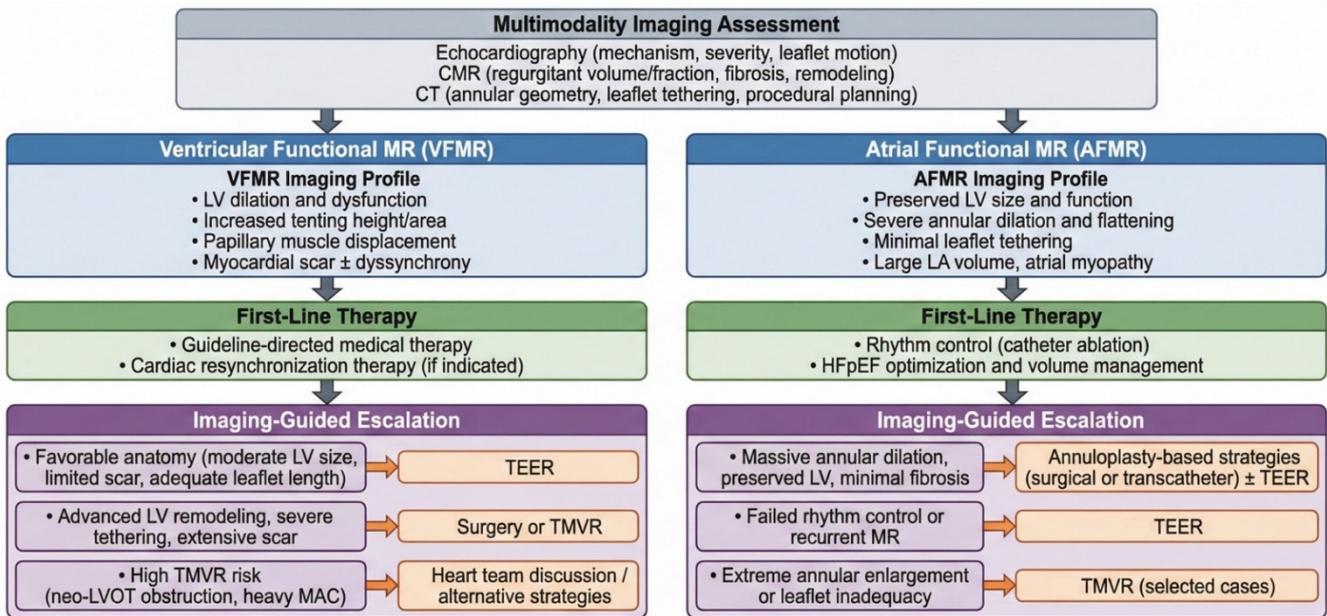


Figure 2. Management Process of Ventricular and Atrial Functional Mitral Regurgitation.

3.1. VFMR

VFMR typically occurs in the context of ischemic or nonischemic cardiomyopathy and reflects the downstream consequences of LV dilation, papillary muscle displacement, and mitral annular enlargement [2,41]. These geometric alterations result in apical and lateral displacement of the papillary muscles, leading to increased leaflet tethering and preventing proper coaptation [29,41,42]. Impaired LV contractility reduces closing forces, further exacerbating regurgitation, even in the absence of structural valve abnormalities [3,43].

A contemporary conceptual framework, first articulated by Grayburn et al., categorizes VFMR into proportionate and disproportionate subtypes, depending on the relationship between the effective regurgitant orifice area (EROA) and the extent of LV remodeling [44]. In proportionate VFMR, MR severity aligns with the degree of LV dilation and dysfunction, implying that regurgitation is primarily a reflection of advanced myocardial disease [44]. Management in these patients should focus on reversing or stabilizing LV remodeling through GDMT, cardiac resynchronization therapy (CRT), or mechanical circulatory support, as valve intervention alone is unlikely to significantly alter outcomes [45–47]. Disproportionate VFMR is characterized by MR severity that is excessive relative to the degree of LV dilation, a scenario where the EROA is much larger than would be expected based on the LV end-diastolic volume (LVEDV) [44]. Mechanistically, this often results from regional wall motion abnormalities, dyssynchrony, or asymmetric leaflet tethering [44]. Here, MR itself is thought to drive symptoms and adverse events, so directly addressing the valve lesion surgically or via transcatheter edge-to-edge repair (TEER), offers substantial prognostic benefit [48,49]. This dichotomy has substantial clinical implications; it provides a potential explanation for divergent results in landmark trials: MITRA-FR (dominated by proportionate MR and large ventricles) found no benefit from TEER [16], whereas COAPT (which selected for those with disproportionate MR and smaller LV volumes) demonstrated significant improvements in heart failure hospitalization and mortality [49].

However, this framework has sparked considerable debate, and emerging evidence raises questions about its clinical utility. Hagendorff et al. provide a pointed critique, questioning the physiological validity of “disproportionate” MR and arguing that regurgitant flow cannot meaningfully exceed the limits set by ventricular remodeling [50]. They advocate for a comprehensive echocardiographic assessment over reliance on EROA/LVEDV ratios [50]. Similarly, Ooms et al., in a multicenter registry, observed that although patients classified as having disproportionate FMR initially experienced more robust MR reduction after TEER, this benefit was not sustained and did not translate into better long-term outcomes compared to those with proportionate MR [51]. Furthermore, Kałmucki et al. recently demonstrated that mitral annuloplasty with the Carillon device resulted in MR reduction and LV reverse remodeling, irrespective of “proportionality”, with outcomes not dependent on the EROA/LVEDV relationship [52]. These findings undermine the predictive value of the framework for durable clinical benefit [53].

Rather than viewing these perspectives as mutually exclusive, a more integrative interpretation is that proportionality may serve as a heuristic to frame competing ventricular versus valvular drivers of disease, but not as a binary determinant of treatment eligibility. When EROA and LVEDV appear discordant, a stepwise, physiology-informed approach may be more clinically useful as listed in Figure 3 which includes the following steps: (1) confirm MR severity using multiparametric echocardiographic assessment, including vena contracta width, regurgitant volume, and dynamic loading conditions; (2) interrogate mechanisms of tethering and annular deformation, with attention to regional wall motion abnormalities, dyssynchrony, and leaflet geometry; (3) assess the extent of myocardial disease and reversibility using LV volumes, strain, and cardiac magnetic resonance where available; and (4) evaluate clinical trajectory and response to optimized GDMT. In this framework, markedly dilated ventricles with only modest EROA should prompt caution that MR predominantly reflects advanced myocardial pathology, whereas severe MR in the setting of relatively preserved LV size and focal tethering may reasonably support consideration of valve intervention despite apparent “disproportionality”.

Taken together, the proportionate–disproportionate framework is best regarded as an interpretive lens rather than a prescriptive algorithm. Patient selection for surgical or transcatheter mitral intervention should ultimately rest on comprehensive multimodality imaging, longitudinal assessment of ventricular remodeling, clinical status, and heart team deliberation, rather than on simplified ratios alone. Future prospective studies integrating imaging-derived phenotypes with treatment response are needed to refine

risk stratification beyond proportionality metrics and to identify patients most likely to derive sustained benefit from mitral valve intervention.

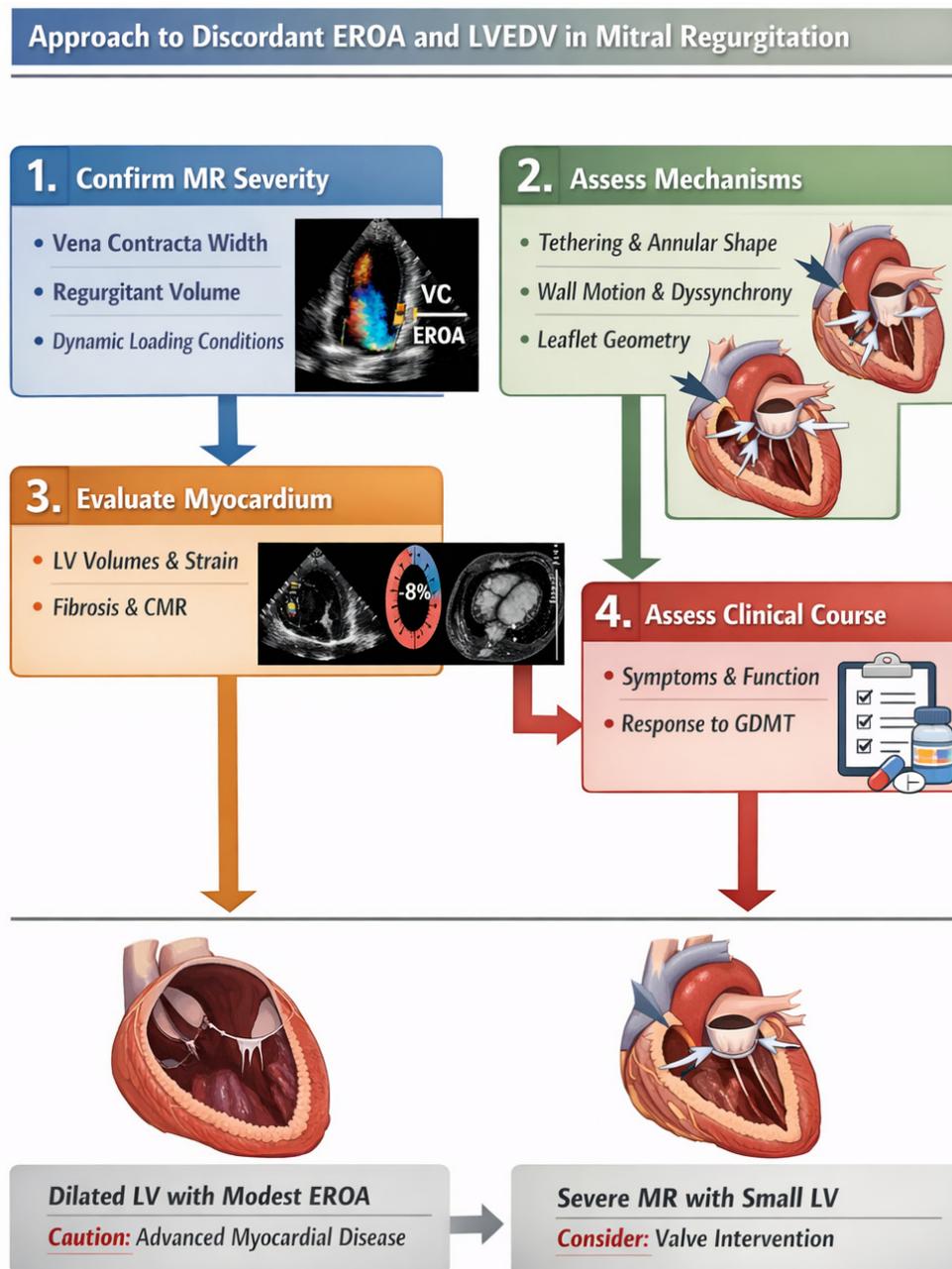


Figure 3. Approach to Ventricular Functional Mitral Regurgitation and Consideration of Management. Color Doppler: Red = flow toward the transducer, Blue = flow away from the transducer, Mosaic/mixed colors (yellow–green/orange) indicate turbulence and/or aliasing when velocities exceed the Nyquist limit (velocity scale). Global Longitudinal Strain from speckle-tracking echo: Red side = more myocardial shortening (*i.e.*, more negative strain, typically closer to normal/better contraction; e.g., around -18% to -22% for GLS), Blue side = less shortening (*i.e.*, less negative strain, closer to 0) or sometimes even positive strain (paradoxical lengthening/dyskinesis).

3.2. AFMR

AFMR occurs in the setting of preserved LV size and systolic function and is driven primarily by LA and mitral annular enlargement [4,28,35]. The most common etiologies are chronic AF and HFpEF [19,20]. Unlike VFMR, AFMR is not associated with papillary muscle displacement or LV dilation; rather, the pathological changes are atrial and annular in origin [4,22,28,35].

Chronic AF and/or elevated LA pressures lead to progressive LA dilation, which causes mitral annular enlargement and loss of its normal saddle shape [36,54–56]. The annulus becomes flattened and more planar, reducing leaflet coaptation and increasing the likelihood of central regurgitation [54–56]. Although the mitral leaflets are structurally normal, the annular dilation exceeds the compensatory capacity of the leaflets, resulting in a leaflet-to-annulus mismatch [57,58]. AF further compromises annular contractility, diminishing systolic annular shortening and thereby exacerbating regurgitation [59,60]. In some patients, posterior annular displacement may contribute to atrigenic tethering, compounding coaptation failure [34,54,56].

Not all FMR should be treated with the same algorithm. Given that the mechanistic of AFMR is due to atrial dilation, for the cohort with AFMR, treating the driver of atrial dilatation is of great importance. A proposed framework for the management of AFMR is listed as follows.

3.2.1. Step 1: Rhythm Control and HFpEF Optimization as First-Line Therapy

Given that AFMR is fundamentally driven by left atrial remodeling and dysfunction, therapeutic strategies that target the reduction of continuous adverse LA remodeling need to be considered at the forefront of management. Rhythm control, most commonly via catheter ablation, has emerged as a central therapeutic pillar in AFMR, with accumulating observational evidence demonstrating meaningful reductions in MR severity, left atrial volume, and annular dimensions, alongside improvements in diastolic function, natriuretic peptide levels, and functional status [7]. Importantly, MR improvement following successful rhythm control can reduce propensity for further atrial dilatation and loss of annular contraction in AFMR, rather than irreversible leaflet or ventricular pathology.

Although randomized data are lacking, several contemporary cohorts suggest that maintenance of sinus rhythm is associated with durable MR reduction and lower progression to dual FMR, particularly when intervention occurs before advanced atrial myopathy or severe annular dilation has developed [19]. These observations underscore the importance of early rhythm control in appropriately selected patients. Consistent with this concept, the Japanese Circulation Society assigns a Class IIa recommendation for catheter ablation in symptomatic patients with persistent atrial fibrillation and severe functional MR when sinus rhythm maintenance is considered achievable, highlighting atrial-directed therapy as a disease-modifying strategy rather than purely symptomatic management.

In cases of HFpEF that contribute to elevated LA pressure, guideline-directed therapy, including diuretics for volume optimization and aggressive blood pressure control, remains an essential adjunct.

3.2.2. Step 2: Indications for Escalation to Valve-Directed Intervention

Valve intervention should be considered in patients with persistent severe MR and NHYA class III–IV symptoms despite optimized rhythm control and medical therapy. Careful consideration of MR phenotype is critical to confirm atrial-predominant MR and to exclude advanced ventricular remodeling or mixed (dual) FMR, which is associated with worse outcomes and may not respond durably to atrial-focused strategies. Multimodality imaging is essential to identify patients in whom MR has become structurally entrenched and is less likely to regress with rhythm control alone.

3.2.3. Step 3: Selection of Interventional Strategy Based on Annular Pathophysiology and Atrial Substrate

For patients undergoing surgical intervention, such as mitral valve surgery, surgical mitral annuloplasty, when combined with a Cox-Maze procedure, is a viable interventional consideration for AFMR [61], as it simultaneously addresses annular dilatation and the underlying arrhythmic substrate. Observational data demonstrate substantially lower rates of recurrent MR when surgical annuloplasty is paired with atrial fibrillation ablation compared with annuloplasty alone, reinforcing the concept that isolated annular correction may be insufficient in the presence of ongoing atrial myopathy [61]. However, marked annular

enlargement may necessitate aggressive ring under-sizing, increasing the risks of mitral stenosis or annular dehiscence, and mitral valve replacement may be required in select cases. Concomitant repair of atrial functional tricuspid regurgitation should be strongly considered when present.

Transcatheter edge-to-edge repair (TEER) represents an effective alternative in patients at elevated surgical risk and has demonstrated high procedural success and symptomatic improvement in AFMR cohorts. TEER appears to perform more favorably in AFMR than in VFMR, likely owing to preserved LV function and minimal leaflet tethering. Nonetheless, because TEER does not directly address annular dilatation or atrial remodeling, its durability may be limited in patients with progressive atrial myopathy, emphasizing the importance of careful patient selection. It is important to have a robust heart team meeting to discuss, as the success of TEER procedures often depends on the center's success in treating mitral valve disease with TEER devices.

Direct and indirect transcatheter annuloplasty systems offer a more mechanistically aligned approach by targeting annular geometry and, in some cases, promoting left atrial reverse remodeling. While these strategies may achieve less immediate MR reduction than TEER, they may offer advantages in selected patients in whom atrial enlargement and annular dysfunction are the dominant drivers of regurgitation. Collectively, these considerations highlight that AFMR management should not default to annular intervention alone; rather, it should integrate rhythm control, atrial substrate modification, and valve therapy in a personalized, stepwise manner.

4. Clinical Features

The main symptoms of both VFMR and AFMR include exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, fatigue, and decreased exercise tolerance [32,42]. These symptoms reflect elevated left-sided filling pressures and pulmonary congestion resulting from both primary ventricular dysfunction and the superimposed regurgitant volume load [9,20,62]. Palpitations and light-headedness can also be present, especially when AF is the underlying rhythm [37]. On physical examination, a holosystolic murmur is often appreciated at the cardiac apex and may radiate to the axilla [2,37,63]. Additional findings typically reflect the severity of heart failure and include signs of volume overload, such as elevated jugular venous pressure, pulmonary rales, hepatomegaly, and peripheral edema [63]. Evidence of underlying left ventricular systolic dysfunction, such as a displaced apical impulse or a soft S1, may also be present [2].

FMR is associated with a high risk of heart failure hospitalization and mortality, with outcomes closely tied to MR severity [17,22,24,25]. It is essential to note that the degree of regurgitation is often dynamic, fluctuating with changes in preload, afterload, or cardiac rhythm, which underscores the importance of serial assessment under physiologic conditions [4,37]. While both FMR subtypes carry increased risk, VFMR is generally associated with higher rates of mortality and heart failure hospitalization than AFMR [17,22,64]. However, in some patients, persistent atrial overload from AFMR can lead to progressive cardiac remodeling and eventual ventricular dysfunction, resulting in a transition to a mixed or "dual FMR" phenotype [22,37].

5. Diagnostic and Prognostic Evaluation

5.1. Electrocardiography, Laboratory Tests, and Chest Radiography

Electrocardiography (ECG) provides valuable clues to the underlying etiology of FMR, although findings are not specific. In VFMR, ECG may reveal features of structural heart disease, including Q waves or ST-T wave abnormalities indicative of prior myocardial infarction, left bundle branch block, or nonspecific intraventricular conduction delays [31,65]. These abnormalities reflect underlying ischemic or nonischemic cardiomyopathy and may contribute to dyssynchrony that exacerbates regurgitation [65,66]. In AFMR, AF is the most common rhythm disturbance, presenting with absent P waves and an irregularly

irregular rhythm [4,28,35,58]. Alternatively, patients in sinus rhythm may exhibit P-wave changes consistent with left atrial enlargement, supporting the diagnosis of AFMR driven by atrial dilation [4,28,35,58].

Laboratory testing is largely non-specific in FMR. Elevated natriuretic peptides (BNP or NT-proBNP) are frequently observed in both VFMR and AFMR, reflecting elevated intracardiac pressures and neurohormonal activation associated with heart failure [67,68]. In more advanced cases, laboratory abnormalities related to end-organ dysfunction may emerge: impaired renal function due to cardiorenal syndrome and mild transaminase elevations due to hepatic congestion from right-sided heart failure [69,70]. However, these findings are not unique to FMR and should be interpreted in the broader clinical context.

Chest radiography offers supportive evidence of cardiac chamber enlargement and pulmonary congestion. Pleural effusions may be present in cases of volume overload [37,68]. Left ventricular enlargement is typically absent in AFMR, reflecting its preserved LV geometry [8,22,54,64]. These diagnostic tools, although not definitive, play a crucial role in the initial assessment and in guiding further imaging and risk stratification.

5.2. Echocardiography

Echocardiography serves as the cornerstone in the diagnosis and characterization of FMR, providing a direct view of the mitral valve apparatus and its interaction with surrounding cardiac structures [37,63]. A comprehensive echocardiographic examination, ideally combining 2D and 3D imaging, provides both hemodynamic grading and mechanistic insight [37,63]. Echocardiographic grading of MR severity requires a comprehensive, integrative approach, as no single parameter is definitive [37]. Figure 3 details the assessment of MR, both quantitative and semi-quantitative measures, as well as the guidelines of both ACC/AHA and ESC on MR severity thresholds.

As recommended by the ACC/AHA and ASE, this involves synthesizing qualitative parameters, such as valve morphology and color Doppler jet characteristics, with semiquantitative parameters like the vena contracta width (VCW; ≥ 0.7 cm for severe), pulmonary vein flow (systolic flow reversal is specific for severe MR), and a dense, triangular continuous-wave Doppler jet profile [37,63]. These are integrated with quantitative parameters, considered most specific, including regurgitant volume (RegVol; ≥ 60 mL for severe), regurgitant fraction (RF; $\geq 50\%$ for severe), and effective regurgitant orifice area (EROA; ≥ 0.40 cm² for severe) [37,63].

Despite these guidelines, accurately quantifying FMR remains challenging. The regurgitant orifice in FMR is often elliptical and dynamic, making the commonly used PISA method, which assumes a circular orifice, susceptible to underestimation [71]. Contemporary professional society guidelines generally agree on the importance of integrating quantitative and qualitative parameters when assessing FMR, differ in how rigidly EROA thresholds are applied, and how they inform TEER candidacy. The ACC/AHA guidelines define severe secondary MR using an EROA ≥ 0.40 cm² (or regurgitant volume ≥ 60 mL) [37], consistent with primary MR, yet emphasize that intervention decisions, particularly TEER, should be guided by symptom burden, response to GDMT, and patient selection criteria derived from COAPT rather than by EROA alone [12]. In contrast, the ESC/EACTS guidelines adopt lower quantitative thresholds for severe FMR (EROA ≥ 0.20 cm² or regurgitant volume ≥ 30 mL) [2]. The differences in EROA thresholds reflect the challenging aspects of MR assessment, given differences in mechanistic factors and the load-dependent nature of secondary MR, but both guidelines similarly stress comprehensive assessment and clinical context over isolated cutoffs. Recent studies suggest that an intermediate value of around 0.30 cm² may better correlate with adverse outcomes and response to therapy [72,73]. The ASE/EACVI recommendations further reinforce this integrative approach, cautioning against reliance on a single parameter, such as EROA, and advocating multiparametric grading that incorporates ventricular size and function, regurgitant jet characteristics, and dynamic behavior [74]. Taken together, these documents are aligned in recognizing the

limitations of rigid EROA thresholds in FMR and converge on the principle that TEER candidacy should be determined by a holistic evaluation of MR severity, ventricular remodeling, and clinical status rather than by any single quantitative metric. Figure 4 illustrates the multi-parametric transthoracic echocardiographic assessment used to grade severe AFMR, encompassing chamber enlargement, jet characteristics, and quantitative Doppler measurements.

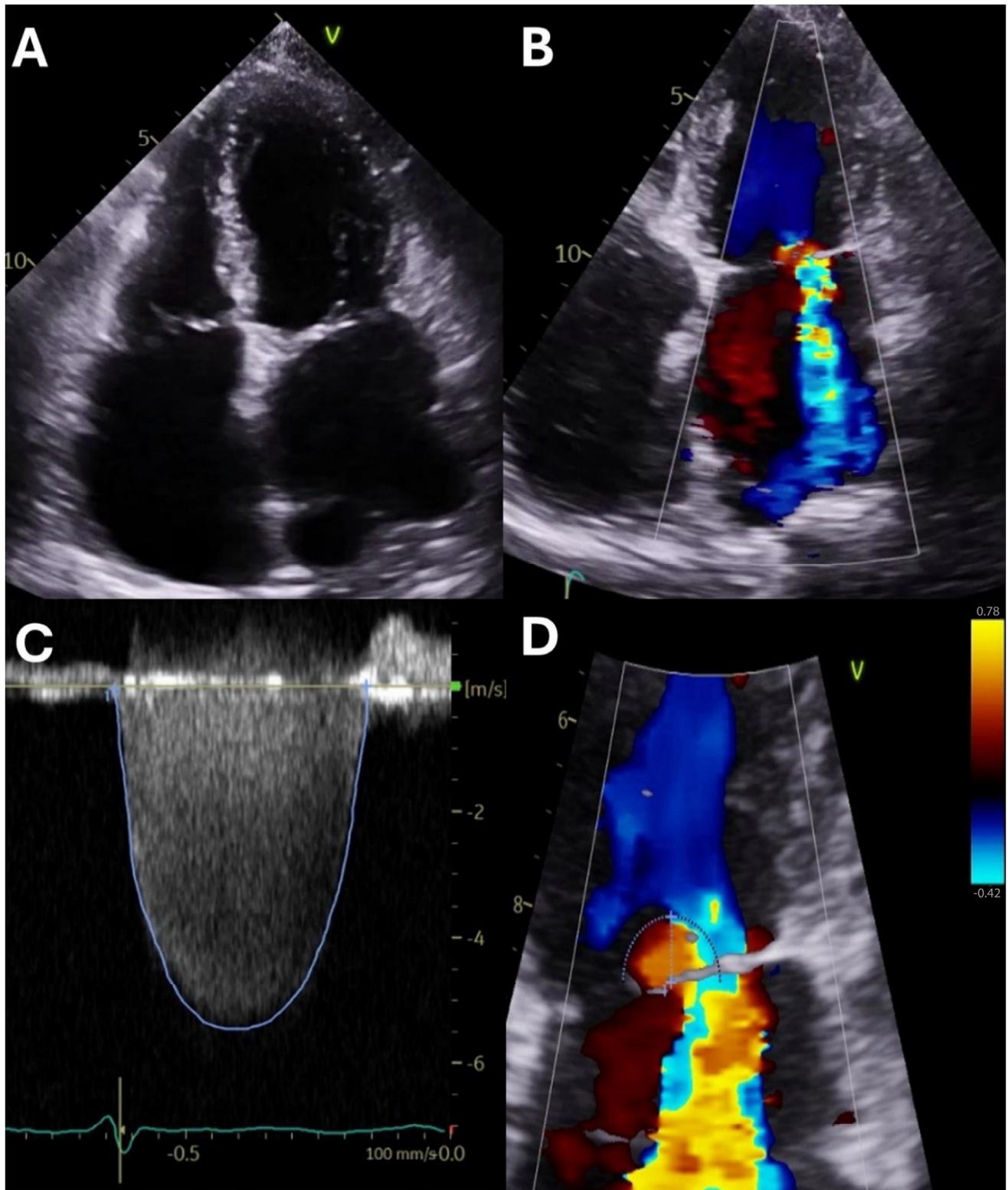


Figure 4. Transthoracic Echocardiographic Assessment of Severe Atrial Functional Mitral Regurgitation. (A) Apical four-chamber view demonstrating severe bi-atrial enlargement with marked dilation and flattening of the mitral annulus, consistent

with atrial functional mitral regurgitation. The numbers along the side (e.g., 5, 10) are depth markers (in mm). **(B)** Color Doppler imaging in the same view reveals a broad, centrally directed jet of severe mitral regurgitation. Red vs. blue represent opposite flow directions relative to the transducer (conventionally: red = toward, blue = away, depending on the machine's color map and orientation). Yellow/orange/mosaic colors indicate aliasing and turbulent/high-velocity flow (velocity exceeding the Nyquist limit). **(C)** Zoomed color Doppler view focused on the regurgitant orifice, showing a proximal isovelocity surface area (PISA) radius of 0.8 cm, supportive of significant regurgitant flow. The y-axis shows velocity (units shown as m/s). The horizontal baseline (0 m/s) separates flow directions (above vs. below baseline). The outlined envelope/contour (blue tracing) marks the spectral Doppler envelope used for measurement (e.g., peak velocity and/or velocity-time integral). The ECG trace at the bottom provides timing within the cardiac cycle. **(D)** Continuous-wave Doppler tracing across the mitral valve reveals a dense, holosystolic MR signal with a peak velocity of 5.5 m/s, consistent with elevated regurgitant volume and pressure gradient. This corresponds to an effective orifice regurgitant area (EROA) of 0.31 cm². The dashed circular/semicircular outline highlights the proximal flow convergence/isovelocity contour. The straight line/arrow indicates the measured radius/distance from the flow origin to the aliasing boundary. The vertical color bar at the right is the velocity color scale, showing the range and direction of encoded velocities (*i.e.*, the Nyquist limits and the color mapping).

Beyond grading, echocardiography is crucial for identifying the specific FMR mechanism [37,38]. In VFMR, the image typically shows a dilated or regionally remodeled left ventricle with apically and laterally displaced papillary muscles, leading to a tethered (Carpentier type IIIb) configuration [1–3,8,38]. Tenting parameters (height > 10 mm or area > 2.5 cm²) reflect this advanced distortion [1,3,38]. In contrast, AFMR is characterized by significant left atrial and annular enlargement (e.g., indexed LA volume > 34 mL/m²) in the setting of a preserved LV [7,22,28,38]. The annulus flattens and dilates, preventing the structurally normal leaflets from coapting, often creating a central regurgitant jet [4,7,41,75].

Assessment of LV and LA size, function, LV volumes, and LVEF and strain is central to this evaluation [37,38]. LA volume is a sensitive marker of chronic MR, as a normal LA size virtually excludes severe chronic MR [38,76]. Furthermore, LV global longitudinal strain (GLS) can detect early myocardial dysfunction before a decline in LVEF, while LA reservoir strain provides insight into atrial compliance; a reservoir strain below 18% indicates poor compliance, elevated pulmonary pressures, and a higher likelihood of failure with rhythm-control strategies [77–82]. This comprehensive chamber assessment is pivotal for applying the proportionate/disproportionate VFMR framework, which relies on the relationship between LVEDV and EROA to guide therapy [44,45].

Finally, specialized echocardiographic studies are used in specific clinical scenarios [44,63,83,84]. Stress echocardiography, preferably with exercise, is recommended when the severity of MR at rest does not correlate with clinical symptoms [40,63,85]. Key findings associated with adverse outcomes include a dynamic increase in MR severity (e.g., an EROA increase ≥ 13 mm²) or the development of pulmonary hypertension (PASP ≥ 60 mmHg) [40]. Transesophageal echocardiography (TEE) is essential when transthoracic echocardiography images are inconclusive and is mandatory for procedural planning and guidance [2,86]. TEE provides superior, high-resolution visualization of leaflet morphology, coaptation depth, and annular geometry (Figure 5) [2,86]. 3D TEE, in particular, offers a “surgical view” that is critical for assessing suitability for TEER and other transcatheter interventions [63,83,87]. During the MitraClip procedure, TEE is used for device navigation, guidance of transseptal puncture (e.g., measuring height from the annular plane), precise leaflet grasping, and assessment of the final post-deployment result [63,86]. This step-by-step guidance is critically important, as demonstrated in Figure 2.

To be clinically actionable, an echocardiographic report should document chamber dimensions, ejection fraction, annular size, leaflet tethering indices, and integrate multiple Doppler indices to estimate severity, explicitly stating which grading criteria were used. Most importantly, it should provide a mechanistic interpretation, concluding whether the regurgitation is predominantly ventricular, atrial, or mixed, as this narrative is essential for informing the management strategy.

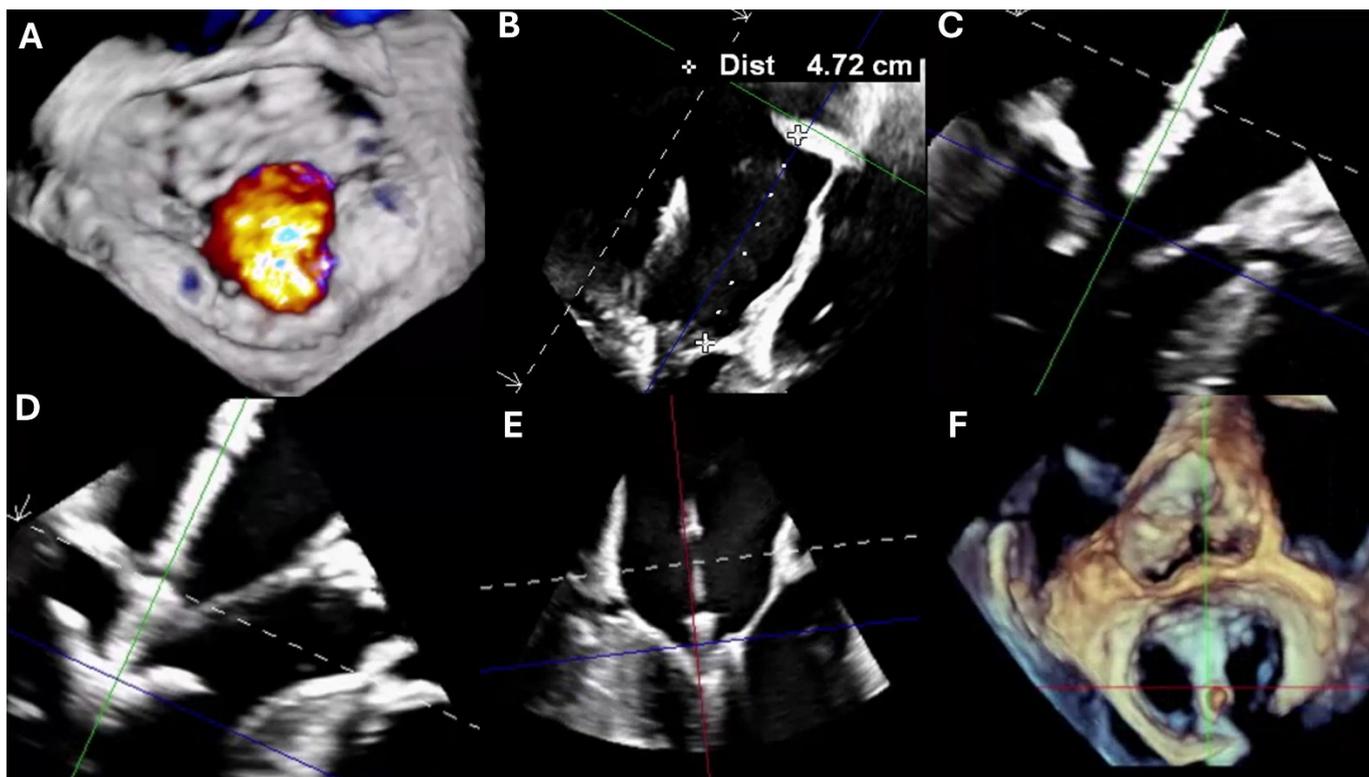


Figure 5. Transesophageal Echocardiographic Guidance During MitraClip Procedure for Severe Mitral Regurgitation. (A) Three-dimensional multiplanar reconstruction (MPR) of the mitral valve from the left atrial (surgeon’s) view demonstrating severe mitral regurgitation (aliasing/mosaic pattern consistent with high-velocity regurgitant flow). (B) Bi-caval TEE view showing successful transseptal puncture with a posterior and superior approach; height from the mitral annular plane measured at >4 cm, appropriate for clip delivery. (C) TEE long-axis view illustrating the MitraClip device crossing the mitral valve into the left ventricle. (D) Device arms fully opened within the left ventricle prior to leaflet capture. (E) Leaflet grasping with approximation of the anterior and posterior leaflets under real-time TEE guidance. (F) Final post-deployment result with stable clip position. Colored lines denote orthogonal 3D multiplanar reconstruction reference planes; white ‘+’ markers indicate caliper/cursor points; the ‘Dist’ line reports the measured transseptal height; dashed white lines outline the imaging sector/3D cropping or MPR slice limits; color Doppler shows the MR jet.

5.3. Cardiac Magnetic Resonance

Cardiac magnetic resonance (CMR) imaging offers a comprehensive, high-resolution, and reproducible assessment of both cardiac chambers and the mitral valve apparatus, making it an invaluable tool for evaluating FMR (Figure 6) [88–91]. As the reference standard for quantifying left ventricular and atrial volumes, systolic function, and remodeling, CMR plays an increasingly central role in the diagnosis, risk stratification, and longitudinal monitoring of patients with FMR [37,68,92,93].

One of the key advantages of CMR is its ability to quantify mitral regurgitant volume and fraction with high accuracy and low operator dependency [88,90]. This is achieved by subtracting aortic forward stroke volume, measured via phase-contrast velocity mapping, from the total left ventricular stroke volume derived from cine images [38,88,94,95]. The resulting regurgitant fraction ($\geq 35\%$ is often considered severe) is highly reproducible and particularly helpful when echocardiographic assessments are technically limited or yield discordant findings [78,96]. These volumetric parameters provide a robust estimate of MR severity and reflect its hemodynamic burden over time, thereby aiding in therapeutic decision-making [78,96].

Emerging 4D flow CMR techniques allow for direct visualization and quantification of complex regurgitant jets, including multiple or eccentric jets, and enable time-resolved assessment of regurgitant flow throughout systole [97]. While 4D flow offers theoretical advantages in capturing complex MR geometry, its use remains limited by longer acquisition times, post-processing complexity, and lack of

standardized thresholds [98]; thus, it is currently best viewed as complementary to established indirect volumetric methods rather than a replacement in routine clinical practice.

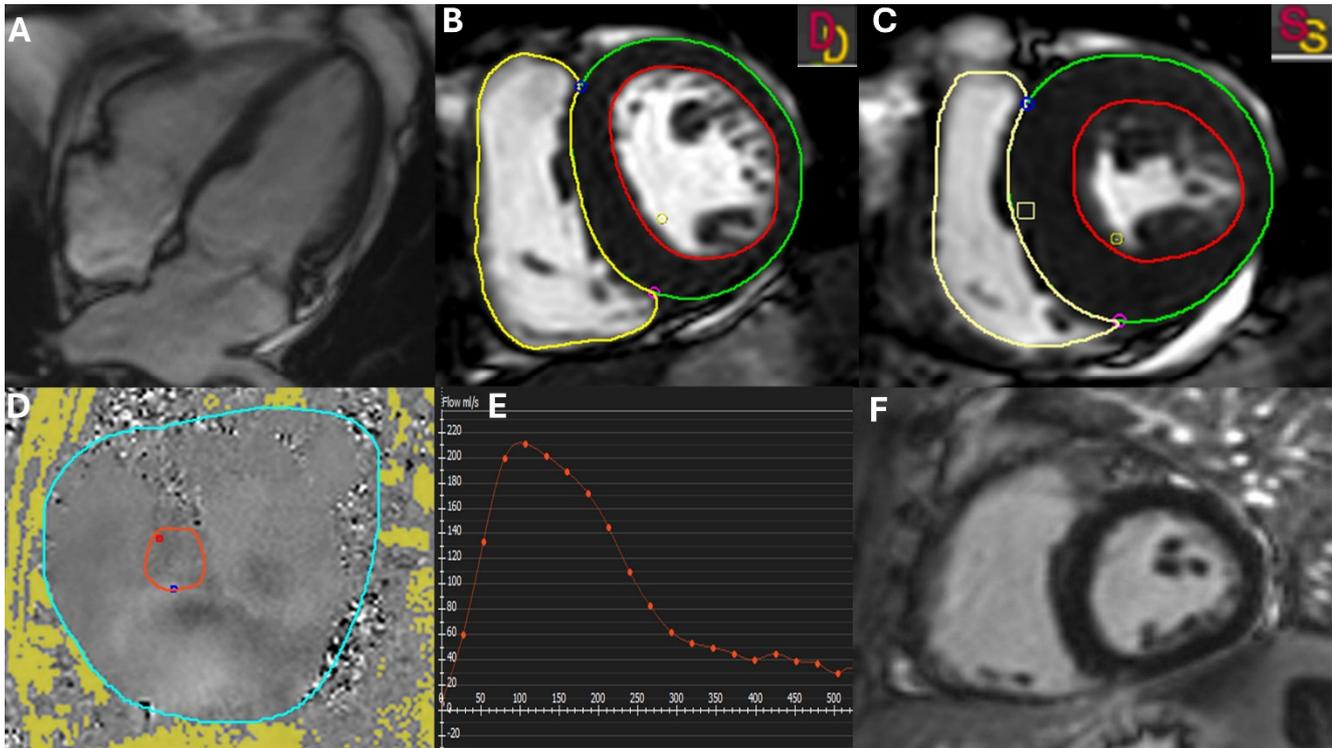


Figure 6. Cardiac Magnetic Resonance Evaluation of Mitral Regurgitation. (A) Cine four-chamber view demonstrating a systolic mitral regurgitant jet extending into the left atrium. (B,C) Short-axis stack at end-diastole (B) and end-systole (C) with manual contouring of the left ventricle to calculate end-diastolic volume (EDV), end-systolic volume (ESV), and stroke volume (SV). LV endocardial and epicardial contours are shown in red and green, respectively; the RV endocardial contour is shown in yellow. ED and ES frames are indicated (D = end-diastole; S = end-systole). (D) 2D phase-contrast flow imaging acquired at the sinotubular junction (STJ) for quantification of aortic forward flow. The aortic lumen ROI used for flow integration is outlined in red, and the reference/background (phase-offset correction) ROI is outlined in cyan. (E) Corresponding flow curve generated from (D) used to calculate regurgitant volume ($RV = \text{aortic flow} - SV$) and regurgitant fraction ($RF = RV/SV$). The orange curve/markers represent instantaneous aortic flow across the cardiac cycle (positive = forward flow). (F) Late gadolinium enhancement (LGE) imaging demonstrates no evidence of myocardial fibrosis or scar.

CMR is also exceptional at defining the underlying FMR mechanism [38,90,91]. In ventricular-driven FMR, it typically reveals left ventricular dilation, impaired systolic function, and regional wall motion abnormalities [1,41,99]. It can precisely visualize apical papillary muscle displacement and leaflet tethering, correlating well with echocardiographic findings [1,99]. In contrast, atrial-driven FMR exhibits a distinctly different pattern, characterized by significant left atrial and annular enlargement, while the left ventricle remains structurally and functionally preserved [4,7,58]. CMR may also visualize subtle forms of “atriogenic” leaflet tethering, in which posterior leaflet angulation arises from posterior annular displacement, reinforcing the mechanical nature of AFMR [38,90,91].

CMR’s most notable contribution is the characterization of myocardial tissue using late gadolinium enhancement (LGE) and T1 mapping techniques [68]. LGE detects replacement fibrosis (scar), which is typically focal and associated with prior infarction or advanced remodeling [100]. In FMR, the presence and extent of LGE are independently associated with adverse outcomes, including mortality and heart failure hospitalization [101]. For example, Wang et al. demonstrated that in both ischemic (ICM) and nonischemic (NICM) cardiomyopathy, LGE ($\geq 5\%$ in ICM or $\geq 2\%$ in NICM) predicted worse event-free survival, with the combination of high MR fraction and LGE conferring an additive risk [102]. Similarly,

Badau Riebel et al. found that replacement fibrosis detected by LGE was a strong independent predictor of adverse outcomes (HR 1.83) [103].

In addition, T1 mapping and extracellular volume (ECV) quantification enable the detection of diffuse interstitial fibrosis, which often precedes overt systolic dysfunction and is not visualized by LGE [104]. Elevated native T1 and ECV values are associated with adverse remodeling and worse prognosis in MR [105,106]. Badau Riebel et al. also demonstrated that interstitial fibrosis, as identified by T1 mapping, was an independent predictor of adverse outcomes (HR 1.61) [103]. The prognostic value of this tissue characterization is substantial: both replacement and interstitial fibrosis are associated with less improvement in LV function and symptoms after intervention [103,106]. These findings can thus inform the timing and selection of therapy, identifying high-risk patients who might benefit from earlier or alternative strategies [68,107].

Taken together, the strengths of CMR lie not only in its volumetric precision and reproducibility but also in its ability to integrate structural, functional, and tissue-based assessments in a single modality. As such, CMR serves as a valuable adjunct to echocardiography, particularly when discrepancies exist or when detailed anatomical and myocardial characterization is essential for guiding therapy. Its contributions are especially critical in distinguishing phenotypes of FMR, determining chronicity, and identifying candidates for valve-directed versus rhythm- or remodeling-focused therapies.

5.4. Computed Tomography

Cardiac computed tomography (CT) has emerged as a complementary modality for the structural assessment of FMR, providing high-resolution, three-dimensional visualization of the entire mitral apparatus—including the annulus, leaflets, chordae, and papillary muscles—with submillimeter spatial accuracy (Figures 7 and 8) [108]. While three-dimensional echocardiography remains central to FMR evaluation, CT is widely regarded as the reference standard for mitral annular quantification and offers unique advantages in characterizing complex mitral geometry [109]. Multiphase CT reconstructions allow precise assessment of annular area, inter-commissural and septo-lateral diameters, annular nonplanarity, leaflet length, tenting height, and papillary muscle position throughout the cardiac cycle [110,111].

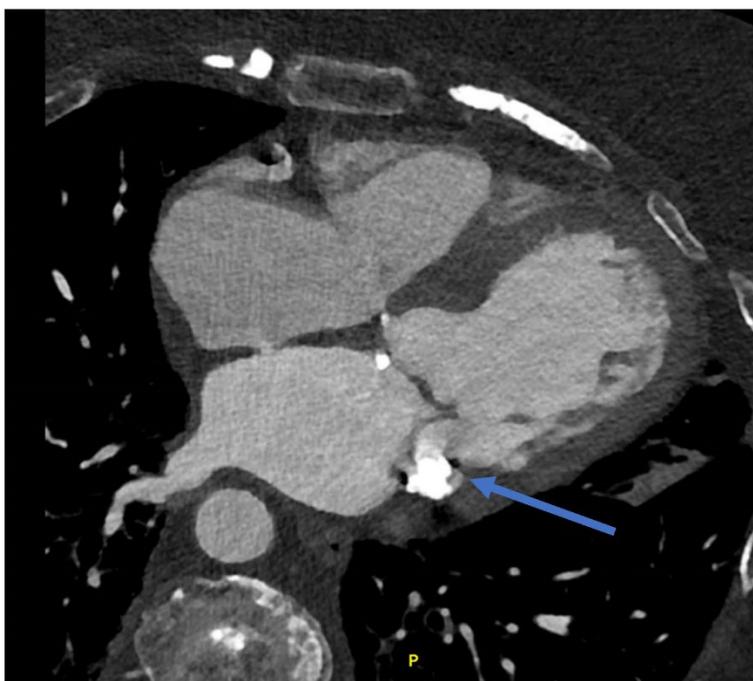


Figure 7. Cardiac Computed Tomography (CT) for Anatomy Evaluation. CT cardiac offers good temporal and spatial resolution for evaluation of cardiac structures and understanding the FMR mechanism and leaflet anatomy (including annulus, any mitral

annular calcification, relation to LVOT). This image shows left atrial dilatation and LV dilatation. There is evidence of mitral annular calcification (indicated by the blue arrow).

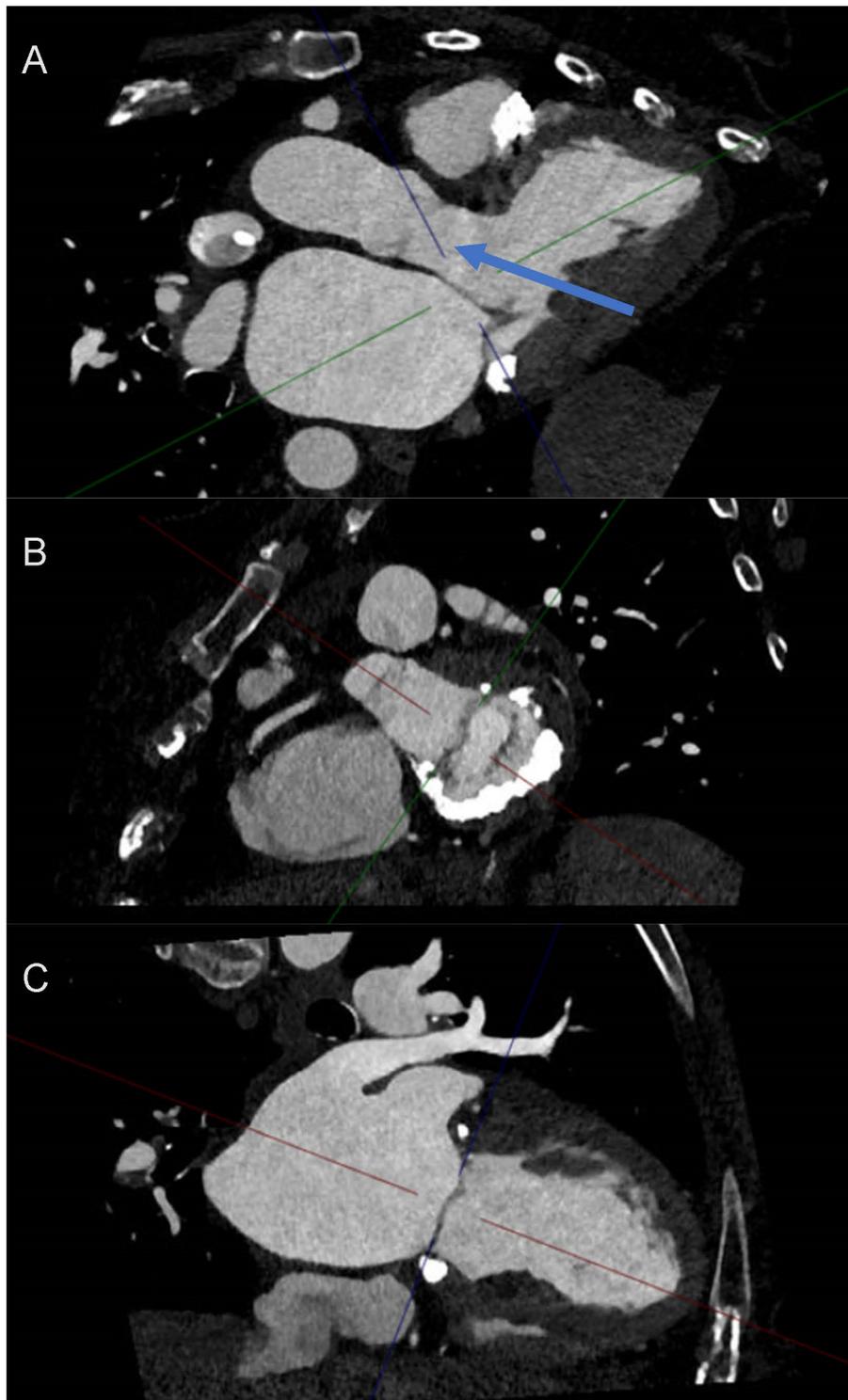


Figure 8. Use of Cardiac Computed Tomography in Functional Mitral Regurgitation Imaging. (A) 3 chamber view in relation to the mitral valve and the importance of evaluating LVOT (indicated by blue arrow) proximity to mitral valve intervention. (B) Short axis of mitral valve and appreciation of prohibitive anatomy for transcatheter or surgical intervention. This patient has significant mitral annular calcification, but the posterior leaflet still remains mobile. Loss of mitral valve saddle shape is predominantly due to the atrial functional mechanism. (C) 2-chamber view of the left atrium and left ventricle. Colored lines represent multiplanar reformation reference planes (crosshairs) displayed by the CT workstation.

Importantly, CT provides incremental value in phenotyping FMR mechanisms, particularly in differentiating ventricular from atrial functional MR. In VFMR, CT readily demonstrates LV dilation, papillary muscle displacement, leaflet tethering, and increased tenting geometry [22], whereas AFMR is characterized by marked annular dilatation, annular flattening, and preserved papillary muscle geometry in the setting of normal or near-normal LV size [4]. These distinctions are especially relevant in borderline or mixed phenotypes, where accurate mechanistic classification directly informs downstream management strategies.

CT is also indispensable for procedural planning of transcatheter mitral interventions [112,113]. In the context of transcatheter mitral valve replacement (TMVR), CT enables detailed prosthesis simulation, virtual valve deployment, and accurate calculation of the neo-left ventricular outflow tract (neo-LVOT). A projected neo-LVOT area $<2.0 \text{ cm}^2$ identifies patients at high risk for LVOT obstruction and strongly influences candidacy, device selection, and the need for adjunctive techniques such as intentional laceration of the anterior mitral leaflet (LAMPOON) [114,115]. The same datasets provide critical information on leaflet anatomy, annular dimensions, and the presence, distribution, and severity of mitral annular calcification (MAC), all of which impact the feasibility and durability of both TEER and TMVR [116,117]. In selected cases, CT planimetry of the anatomic regurgitant orifice area can further refine MR severity assessment, particularly when echocardiographic grading is limited by eccentric or multiple jets.

Finally, coronary computed tomography angiography (CCTA) plays an important adjunctive role in patients with suspected ischemic VFMR, where identification of significant coronary artery disease directly informs the need for concomitant revascularization as part of a combined surgical or hybrid strategy [32,100,118,119]. In contrast, broader assessment of extracardiac aortic pathology or general redo sternotomy planning, while valuable in selected surgical cases, is typically secondary to CT's primary role in defining FMR mechanism and guiding mitral-specific intervention.

In summary, cardiac CT offers unparalleled anatomical detail and quantitative precision for FMR evaluation, with particular strength in mechanistic phenotyping, transcatheter procedural planning, and ischemic substrate assessment. When integrated with echocardiography and cardiac magnetic resonance imaging, CT provides essential complementary information that directly informs patient selection and procedural strategy in contemporary FMR management (Table 2).

Table 2. Diagnostic Imaging Modalities for Functional Mitral Regurgitation.

Diagnostic Tool	Role in FMR Assessment	MR Severity Quantification	Strengths	Limitations	Best Clinical Use
Echocardiography (TTE/TEE, 2D/3D)	First-line modality for diagnosis, mechanistic classification (VFMR vs. AFMR), hemodynamic assessment, and longitudinal follow-up; essential for procedural guidance	Integrative multiparametric grading using qualitative (jet morphology), semiquantitative (vena contracta width, pulmonary vein flow), and quantitative measures (EROA, regurgitant volume, regurgitant fraction)	Widely available; real-time; assesses valve/ventricle/annulus; Doppler quantifies MR; 3D improves annular and leaflet geometry assessment	Image quality dependent; limited by acoustic windows; Doppler parameters affected by loading; 2D may underestimate complex jets; TEE semi-invasive	Initial diagnosis; serial follow-up; procedural guidance for TEER; dynamic assessment (stress echo)
Cardiac Magnetic Resonance (CMR)	Quantifies MR severity (regurgitant volume/fraction); precise LV/LA volumes; detects scar/fibrosis	Indirect volumetric method: LV stroke volume (cine) minus aortic forward flow (phase-contrast); regurgitant fraction $\geq 35\%$ often considered severe; 4D: direct time-resolved visualization and quantification of regurgitant jets	Gold standard for MR quantification; geometry-independent quantification; reproducible; accurate in eccentric or multiple jets; comprehensive LV/LA assessment; tissue characterization; 4D captures complex, multiplanar, and eccentric jets; full volumetric flow mapping	Limited availability; contraindications (e.g., devices); less spatial/temporal resolution for leaflets; not real-time for intervention guidance; longer acquisition time; 4D flow lacks standardized thresholds and widespread adoption	Discordant or inconclusive echocardiography; prognostic stratification; assessment of remodeling and intervention research settings with complex jet morphology
Computed Tomography (CT)	Anatomic assessment for intervention planning; annular sizing; access route	Not a primary modality for functional MR severity; optional anatomic regurgitant orifice planimetry in selected cases with complex jets; Neo-LVOT prediction; annular sizing; MAC burden assessment	Reference standard for annular geometry; excellent spatial resolution; distinguishes VFMR vs. AFMR anatomy; virtual valve deployment; accurate neo-LVOT calculation; device feasibility assessment	Lacks hemodynamic assessment; radiation and contrast exposure; static assessment of a dynamic process; does not quantify functional severity; requires specialized software	Phenotyping FMR mechanism; TMVR/TEER planning; annular and leaflet anatomy assessment

Abbreviation: TTE = Transthoracic echocardiography; TEE = Transesophageal echocardiography; 2D = Two-dimensional; 3D = Three-dimensional; MR = Mitral regurgitation; FMR = Functional mitral regurgitation; VFMR = Ventricular functional mitral regurgitation; AFMR = Atrial functional mitral regurgitation; LV = Left ventricle/ventricular; LA = Left atrium/atrial; EROA = Effective regurgitant orifice area; CMR = Cardiac magnetic resonance; CT = Computed tomography; TMVR = Transcatheter mitral valve replacement; TEER = Transcatheter edge-to-edge repair; MAC = Mitral annular calcification; neo-LVOT = Neo-left ventricular outflow tract; 4D = Four-dimensional.

5.5. Standardization of Imaging Assessment

As listed above, there are many imaging modalities that prove useful for FMR assessment. Table 2 summarizes the different modalities described above, along with their strengths and limitations in FMR assessment.

FMR is inherently dynamic, with severity varying substantially according to loading conditions, heart rate, rhythm, and ventricular–atrial interactions [2]. Changes in preload, afterload, and contractility can meaningfully alter regurgitant volume and effective regurgitant orifice area over short time intervals, contributing to variability across imaging studies and potential misclassification of severity [5]. Given this marked load dependence, careful standardization of imaging conditions is essential to ensure that measured MR severity reflects the patient’s “true” clinical state rather than transient hemodynamic perturbations [38]. Whenever feasible, MR assessment should be performed under stable, near–euvoletic conditions, ideally after optimization of guideline-directed medical therapy [37]. Imaging performed during acute decompensation, excessive diuresis, dehydration, or uncontrolled hypertension may either exaggerate or underestimate regurgitation severity and should be interpreted with caution [37].

Practical steps to optimize and standardize imaging assessment include: (1) avoiding MR quantification during periods of rapid volume shifts (e.g., immediately after aggressive diuresis or intravenous fluid administration) [37]; (2) documenting blood pressure, heart rate, and rhythm at the time of imaging [37]; and (3) ensuring adequate blood pressure control, as acute elevations in afterload can disproportionately increase regurgitant severity [37]. In patients with atrial fibrillation, averaging measurements over multiple cardiac cycles is essential, and echocardiographic assessment should ideally be performed at a controlled ventricular rate [37]. Medication status should also be considered and reported. Imaging obtained before initiation or up-titration of vasodilators, diuretics, or rhythm-control therapies may not reflect steady-state conditions [32]. When serial imaging is used to guide management decisions, efforts should be made to perform studies under comparable hemodynamic and pharmacologic conditions to allow meaningful longitudinal comparison [38]. Stress echocardiography further highlights the dynamic nature of FMR by unmasking exertional increases in regurgitation severity and pulmonary pressures that may not be evident at rest [38]. However, resting MR severity used to guide interventional decisions should be grounded in standardized, clinically representative conditions rather than extreme loading states [38].

Taken together, recognition of FMR dynamism must be coupled with deliberate standardization of imaging acquisition and interpretation. Explicit documentation of loading conditions and thoughtful patient preparation reduces the risk of misclassification, improves reproducibility, and enhances the clinical relevance of imaging-based decision-making.

6. Therapeutic Modalities for Functional Mitral Regurgitation

Treatment modalities for FMR vary significantly in patient selection, mechanism of action, supporting evidence, and clinical outcomes (Table 3). Figure 4 summarizes an imaging-guided management algorithm distinguishing VFMR from AFMR and illustrates how specific imaging phenotypes inform selection among medical therapy, TEER, surgery, and TMVR.

Table 3. Overview of Therapeutic Modalities for Functional Mitral Regurgitation.

Therapy	Typical Candidates	Mechanism	Key Evidence/Trials	Clinical Outcomes	Limitations
Medical and Device Optimization	All with FMR; first-line for HF _r EF; CRT for LBBB/QRS ≥ 150 ms; rhythm control for AFMR	GDMT (beta-blocker, RAASi, ARNI, MRA, SGLT2i), CRT, AF ablation in FMR	Multiple RCTs in HF _r EF; observational	Reduces MR severity by 40–45%, improves survival, and HF hospitalization	Many remain symptomatic; MR often persists
Surgical Repair or Replacement	Severe, symptomatic FMR refractory to GDMT, or if other cardiac surgery is indicated	Annuloplasty (repair) or chordal-sparing replacement	CTSN SMR; observational studies	No survival benefit over GDMT; repair: high recurrence; replacement: less MR recurrence	High perioperative risk; no clear survival benefit in isolated FMR
Transcatheter Edge-to-Edge Repair	Severe, symptomatic FMR, LVEF 20–50%, persistent symptoms after GDMT, not surgical candidate	MitraClip (edge-to-edge leaflet approximation)	COAPT, MITRA-FR, RESHAPE-HF2	COAPT/RESHAPE-HF2: reduce HF hospitalization and mortality, improved QoL. MITRA-FR: neutral	Benefit depends on MR/LV proportion, anatomy, operator experience
Indirect Coronary Sinus Annuloplasty	Symptomatic FMR, annular dilation, suitable coronary sinus anatomy	Carillon device (annular cinching via coronary sinus)	AMADEUS, TITAN, REDUCE-FMR	Reduces MR, LV volumes, improves 6-min walk distance	Anatomic variability, risk of circumflex impingement, less MR reduction than TEER
Direct Annuloplasty (Cardioband, Millipede)	Symptomatic FMR, annular dilation, high surgical risk, suitable anatomy	Percutaneous direct annular reduction	Cardioband feasibility, comparative studies	Reduces annular size, MR, improves NYHA/6-min walk distance; similar or better functional outcomes vs. TEER in select patients	Limited RCT data, device availability, learning curve
Transcatheter Mitral Valve Replacement	Severe, symptomatic FMR, high/prohibitive surgical risk, unsuitable for TEER/annuloplasty	Transcatheter bioprosthesis (Tendyne, Intrepid)	Tendyne, Intrepid, registries	High device success, near-complete MR elimination, improved symptoms	High procedural risk, LVOT obstruction risk; high early mortality in high-risk; limited long-term data

Abbreviations: FMR = functional mitral regurgitation; HF_rEF = heart failure with reduced ejection fraction; CRT = cardiac resynchronization therapy; LBBB = left bundle branch block; QRS = QRS duration; AFMR = atrial functional mitral regurgitation; GDMT = guideline-directed medical therapy; RAASi = renin-angiotensin-aldosterone system inhibitor; ARNI = angiotensin receptor-neprilysin inhibitor; MRA = mineralocorticoid receptor antagonist; SGLT2i = sodium-glucose cotransporter 2 inhibitor; MR = mitral regurgitation; HF = heart failure; TEER = transcatheter edge-to-edge repair; QoL = quality of life; LV = left ventricle; LVOT = left ventricular outflow tract.

6.1. Medical and Device Optimization

Medical and device-based optimization forms the foundation of management in FMR, with the overarching goals of relieving symptoms, reducing mitral regurgitant volume, and delaying or potentially avoiding invasive intervention [21,120]. Both the American College of Cardiology (ACC) and the Heart Failure Association of the European Society of Cardiology (ESC-HFA) emphasize that therapy should begin with comprehensive GDMT for heart failure, with escalation to device or interventional strategies reserved for patients who remain symptomatic despite optimal medical management [9,14,47].

In patients with FMR and reduced ejection fraction, GDMT represents the first-line approach [68]. According to joint recommendations from the ACC, American Heart Association (AHA), and Heart Failure Society of America (HFSA), all eligible patients should receive a combination of the following: a beta-blocker, a renin-angiotensin system inhibitor (ARNI preferred, or ACEi/ARB if ARNI is not tolerated), a mineralocorticoid receptor antagonist (spironolactone or eplerenone), and a sodium-glucose cotransporter 2 inhibitor (SGLT2i) [68]. These agents not only improve survival and reduce heart failure hospitalizations but have also been shown to directly impact the severity of FMR in many cases [63]. By promoting reverse remodeling, these medications reduce left ventricular volumes and loading conditions and improve geometry, often leading to a reduction in regurgitant severity [68].

Device-based therapies are crucial adjuncts in selected patients [2]. In particular, cardiac resynchronization therapy (CRT) is indicated for individuals with an LVEF $\leq 35\%$, sinus rhythm, left bundle branch block, and a QRS duration of ≥ 150 ms [121–123]. CRT improves left ventricular synchrony, facilitates reverse remodeling, and has been shown to reduce the degree of FMR [2,46,124–126]. For patients with AFMR complicated by AF, rhythm control strategies, including antiarrhythmic medications and catheter ablation, can reduce left atrial size and improve annular function, thereby mitigating the severity of regurgitation [7,127,128].

In ischemic FMR, coronary revascularization (either PCI or CABG) plays a crucial role [74]. Many patients with moderate ischemic MR experience MR improvement after revascularization alone, especially with CABG, which is associated with better event-free survival compared to PCI [129,130]. Concomitant mitral annuloplasty with CABG further improves outcomes in selected patients [130,131]. Decision-making should be multidisciplinary, considering comorbidities, operative risk, and individual patient factors [74,132].

6.2. Surgical Interventions

Surgical treatment for FMR is generally reserved for patients who remain symptomatic despite maximally optimized GDMT and, when appropriate, CRT [32,133]. According to current ACC/AHA recommendations, surgery is indicated in patients with severe FMR, whether of ventricular or atrial origin, primarily when concomitant cardiac surgery, such as coronary artery bypass grafting (CABG), is already planned [32]. Isolated mitral surgery for FMR is less commonly performed due to the lack of a proven survival benefit and the high rates of recurrence [32]. Therefore, patient selection is a nuanced process that requires a multidisciplinary approach [32,37,134].

The management of Ischemic FMR (VFMR) has been heavily influenced by two landmark randomized trials from the Cardiothoracic Surgical Trials Network (CTSN) published in *The New England Journal of Medicine*, which clarified the role of surgery in both moderate and severe disease (Table 4) [135,136]. For moderate ischemic MR, the trial by Smith et al. (2014) randomized 301 patients undergoing CABG to receive either CABG alone or CABG plus mitral valve repair (restrictive annuloplasty) [135]. At one year, the addition of mitral repair did not improve survival or left ventricular reverse remodeling [135]. While the combined group had less residual MR, this did not translate into improved clinical outcomes [135,136]. Furthermore, the addition of repair increased operative time, hospital length of stay, and the risk of

neurologic events and arrhythmias [74,135,136]. Consequently, for patients with moderate ischemic MR, CABG alone is generally considered sufficient, as revascularization often reduces MR severity without the added morbidity of valve intervention [2,32,74,135,137]. For severe ischemic MR, the choice between repair and replacement was addressed by Acker et al. (2014) and Goldstein et al. (2016) [138,139]. This trial randomized 251 patients to either restrictive mitral annuloplasty (RMA), using a downsized rigid ring, or chordal-sparing mitral valve replacement [138]. The results highlighted a critical distinction between functional and primary MR [2]. Unlike primary MR, where repair is superior, in FMR, repair demonstrated poor durability [2,138,139]. At two years, the repair group had a significantly higher rate of recurrent moderate-to-severe MR (58.8% vs. 3.8%) and more heart failure-related adverse events compared to the replacement group [139]. However, there was no significant difference in survival between the two strategies [138,139]. These findings have shaped contemporary technical considerations. Repair remains an option for patients with mild tethering and less advanced ventricular remodeling, potentially favored in younger patients (<65 years) to avoid the risks of prosthetic valves [140]. However, because repair failure is driven by ongoing ventricular remodeling and leaflet tethering, chordal-sparing replacement is now generally preferred for patients with predictors of repair failure [2,32]. These predictors include a tenting height >10 mm, a posterior leaflet angle >45°, or significant infero-basal wall motion abnormalities [3,37]. Replacement in these high-risk anatomies provides a more durable correction of MR and fewer heart failure readmissions [2,139].

In contrast to the ventricular phenotype, AFMR requires a different surgical logic. Because the leaflets are typically structurally normal and regurgitation is driven by annular dilatation, isolated ring annuloplasty is highly effective and durable [27,141–145]. In the largest contemporary series, annuloplasty alone yielded a five-year survival rate of approximately 75% with low recurrence rates [141,142,144,145]. However, surgical success in AFMR often requires addressing the accompanying atrial pathology; standard practice includes concomitant Cox-Maze ablation and rhythm control strategies for atrial fibrillation, such as ablation or reducing afterload conditions that may contribute to elevated left ventricular/atrial filling pressures [111,142,143,146].

In summary, surgical management of FMR is mechanism specific. While AFMR is reliably treated with annuloplasty, moderate ischemic VFMR is often best managed with revascularization alone, and severe VFMR frequently necessitates valve replacement to ensure durability. Regardless of the technique, the decision to operate must weigh the limited survival benefit against the risks, prioritizing symptom relief and quality of life.

Table 4. Key Randomized Controlled Trials of Surgical Intervention for Functional Mitral Regurgitation.

Year	Trial (N)	Intervention	Comparator	Primary Outcome	Result Summary	Quality Considerations
2014	CTSN Moderate IMR Trial (N = 301)	CABG + mitral valve repair (restrictive annuloplasty)	CABG alone	LVESVI at 2 years	No significant difference in LVESVI (41.2 vs. 43.2 mL/m ²) or survival (10.0% vs. 10.6% mortality). Combined procedure reduced recurrent moderate-to-severe MR (11.2% vs. 32.3%, <i>p</i> < 0.001) but increased neurologic events and supraventricular arrhythmias.	Multicenter RCT from CTSN; stopped early after interim analysis showed no benefit in the primary endpoint; patients had moderate IMR (effective regurgitant orifice area 0.2–0.4 cm ²)

2014	CTSN Severe IMR Trial (N = 251)	Chordal-sparing mitral valve replacement	Restrictive mitral annuloplasty (downsized rigid ring)	LVESVI at 2 years	No significant difference in LVESVI or survival (19.0% vs. 23.2% mortality, $p = 0.39$). Replacement had significantly lower recurrent moderate-to-severe MR (3.8% vs. 58.8%, $p < 0.001$), fewer heart failure-related adverse events ($p = 0.05$), and fewer cardiovascular readmissions ($p = 0.01$).	Multicenter RCT from CTSN; patients had severe IMR (mean effective regurgitant orifice area 0.4 cm ²); concomitant CABG was performed when indicated
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Abbreviations: CTSN = Cardiothoracic Surgical Trials Network; IMR = Ischemic mitral regurgitation; CABG = Coronary artery bypass grafting; LVESVI = Left ventricular end-systolic volume index; MR = Mitral regurgitation; RCT = Randomized controlled trial.

6.3. Transcatheter Interventions

6.3.1. Transcatheter Edge-to-Edge Repair (TEER)

TEER has become a cornerstone intervention for selected patients with FMR who remain symptomatic despite maximally optimized GDMT [12,32,37]. Applicable to both VFMR and AFMR subtypes, TEER offers a less invasive alternative to surgery for patients with prohibitive operative risk [32,37].

The American College of Cardiology recommends TEER in patients with severe, symptomatic FMR and a left ventricular ejection fraction (LVEF) between 20–50%, left ventricular end-systolic dimension <7.0 cm, pulmonary artery systolic pressure <70 mmHg, and effective regurgitant orifice area (EROA) ≥0.3 cm², aligning with the inclusion criteria of the landmark COAPT trial [32,37]. These recommendations are made in the context of a multidisciplinary heart team decision, informed by comprehensive multimodality imaging to ensure anatomical suitability, specifically adequate leaflet length, coaptation depth, and a mitral valve area ≥4.0 cm², using anatomical criteria originally derived from the EVEREST trials (though notably, EVEREST II primarily studied degenerative MR) [37].

The procedure is performed under general anesthesia with continuous transesophageal echocardiography (TEE) and fluoroscopic guidance [74,147]. Devices such as the MitraClip (Abbott) are advanced transseptally across the mitral valve, where the anterior and posterior leaflets are grasped at the origin of the regurgitant jet, creating a double-orifice valve that reduces regurgitation [2,147]. Multiple clips may be deployed as needed to optimize the result [74,147]. The clinical evidence base for TEER in FMR is defined by three pivotal randomized trials, MITRA-FR, COAPT, and RESHAPE-HF2, which yielded differing results driven by distinct patient selection strategies (Table 5) [2,12,13,15,37,68,123,148].

Table 5. Key Randomized Controlled Trials of TEER for Functional Mitral Regurgitation.

Year	Trial (N)	Intervention	Comparator	Primary Outcome	Result Summary	Quality Considerations
2018	MITRA-FR (304)	TEER (MitraClip) + GDMT	GDMT alone	Composite of all-cause death or unplanned HF hospitalization at 12 months	No significant difference (54.6% vs. 51.3%, HR 1.16, 95% CI 0.73–1.84)	Broad MR inclusion, larger LV volumes, less severe MR, and less intensive GDMT
2018	COAPT (614)	TEER (MitraClip) + GDMT	GDMT alone	HF hospitalization at 24 months	Significant reduction (35.8% vs. 67.9%, HR 0.53, 95% CI 0.40–0.70); all-cause mortality also reduced (29.1% vs. 46.1%, HR 0.62, 95% CI 0.46–0.82)	Rigorous GDMT, more severe MR, smaller LV, strict selection, high procedural success

2024	RESHAPE-HF2 (505)	TEER (MitraClip) + GDMT	GDMT alone	Composite of first/recurrent HF hospitalization or CV death at 24 months	Significant reduction (rate ratio 0.64, 95% CI 0.48–0.85, $p = 0.002$); improved KCCQ-OS, lower recurrent HF hospitalizations	Broader MR severity, international sites, robust endpoints, and low device-related adverse events

Abbreviations: TEER = Transcatheter edge-to-edge repair; MR = Mitral regurgitation; GDMT = Guideline-directed medical therapy; HF = Heart failure; LV = Left ventricle/ventricular; CV = Cardiovascular; HR = Hazard ratio; CI = Confidence interval; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire–Overall Summary score.

The MITRA-FR trial randomized 304 patients with severe FMR and heart failure to MitraClip plus medical therapy versus medical therapy alone [16]. The trial found no significant difference in the composite endpoint of all-cause death or unplanned heart failure hospitalization at 1 or 2 years [16]. A critical analysis of the cohort reveals that MITRA-FR patients had larger LV volumes but less severe MR (mean EROA 0.31 cm²) relative to that ventricular size, a phenotype often described as “proportionate” MR [44,45,149]. Furthermore, the optimization of GDMT prior to enrollment was less stringent than in subsequent trials [45,150]. These factors suggest that in patients where MR is merely a biomarker of advanced ventricular disease rather than a driver, valve intervention may be futile [10,16].

In contrast, the COAPT trial enrolled 614 patients with symptomatic heart failure and moderate-to-severe or severe FMR who remained symptomatic despite a rigorous “run-in” period of maximally tolerated GDMT [48,151]. In this cohort, TEER with MitraClip led to significant reductions in heart failure hospitalizations (HR 0.53) and all-cause mortality (HR 0.62) at 24 months compared to GDMT alone, with durable benefits observed up to 36 months, along with improved quality of life [48,151]. The COAPT population differed fundamentally from MITRA-FR: patients had more severe MR (mean EROA 0.41 cm²) but less severe LV dilation [44]. This “disproportionate” MR phenotype implies that the valvular lesion contributed excessively to the pathophysiology, making it a prime target for repair [44].

Most recently, the RESHAPE-HF2 trial has expanded the evidence base. It included 505 patients with moderate-to-severe FMR (mean EROA 0.25 cm²) and symptomatic heart failure [13]. TEER significantly reduced first and recurrent heart failure hospitalizations and cardiovascular death at 24 months, with consistent benefits across subgroups [13,148,152]. Notably, the benefit was pronounced in patients with recent heart failure hospitalizations [148,152]. The results of RESHAPE-HF2 support the broader application of TEER, suggesting that clinical benefit extends to patients with MR severity that may be lower than the strict COAPT thresholds, provided they remain symptomatic despite medical therapy [13,152].

Real-world data, specifically regarding AFMR, also demonstrate encouraging outcomes. Registry data indicate procedural success rates ranging from 87% to 94%, with durable symptomatic improvement. In the Spanish Mitraclip series, 94% of AFMR patients had MR reduced to grade $\leq 2+$, and 80% improved to a NYHA functional class I–II at 12 months [153,154]. The MITRA-TUNE registry reported mid-term MR recurrence in only 11% [155–157]. However, anatomical phenotype matters: patients with “hamstrung” or atriogenic tethering, characterized by massive atrial enlargement causing marked posterior leaflet angulation, often experience higher residual MR and worse outcomes, highlighting the need for careful anatomical screening [157,158].

Technological evolution continues to refine these outcomes. Beyond the MitraClip, the Edwards PASCAL system offers novel design features, including independent leaflet capture and a central spacer, which enable enhanced adaptation to complex anatomy [15,159]. In the CLASP study, PASCAL achieved MR grade $\leq 2+$ in 96% of cases with a 92% one-year survival rate [160]. A head-to-head analysis from the CLASP IID randomized trial demonstrated non-inferiority of PASCAL compared to MitraClip in both safety (3.4% vs. 4.8% major events) and efficacy, with numerically higher rates of trace or no MR at six months (87% vs. 84%) [161–163].

Successful procedural planning relies heavily on 3D TEE and CT to assess jet location, leaflet length, and annular dimensions [164,165]. In VFMR, broad central jets may necessitate multiple clips, whereas AFMR often requires centrally placed devices, unless atrio-genic tethering is present [164]. Residual trans-mitral gradients > 5 mmHg, severe annular calcification, and flail gaps > 10 mm remain relative contraindications [37,166]. Following TEER, particularly in AFMR, aggressive rhythm control may offer additional remodeling benefits; however, this effect diminishes in the setting of extensive atrial fibrosis [19,166]. Overall, TEER offers higher procedural success and lower morbidity than surgery, positioning it as the preferred intervention for appropriate candidates [12,15,152].

6.3.2. Indirect Coronary-Sinus Annuloplasty

Indirect coronary sinus annuloplasty represents a minimally invasive, anatomically guided strategy for treating FMR, exploiting the proximity of the coronary sinus (CS) and the great cardiac vein to the posterior mitral annulus [167,168]. Among available technologies, the Carillon Mitral Contour System is the most extensively studied device [13,52,167,169–172]. It is deployed percutaneously via the right internal jugular or femoral vein and implanted within the coronary sinus, where it applies circumferential tension to reduce the septal-lateral annular dimension, thereby enhancing leaflet coaptation and mitigating mitral regurgitation [167,169,170].

The physiological rationale for this technique lies in the unique anatomical relationship between the coronary sinus and the adjacent mitral annulus [173–175]. By anchoring and “cinching” the coronary sinus, the posterior annulus can be effectively constricted without entering the left atrium or ventricle [174]. However, this anatomical relationship varies among patients, and pre-procedural imaging plays a crucial role in determining procedural feasibility [176]. Optimal outcomes are associated with a coronary sinus-to-annulus distance of less than 7.8 mm and an angle of less than 14.2° , as determined by pre-procedural cardiac CT angiography [177]. In addition, the proximity of the coronary sinus to the left circumflex artery raises the risk of coronary compression, making detailed anatomic evaluation and intraprocedural monitoring essential to avoid vascular complications [173–175].

Clinical trials and pooled analyses have consistently shown that the Carillon device reduces MR severity, facilitates left ventricular reverse remodeling, and improves functional capacity, particularly in patients with proportionate FMR, in which annular dilation is the dominant pathophysiologic mechanism (Table 6) [13,167,170–172,178]. In this subgroup, indirect annuloplasty reduces left ventricular volumes and enhances forward stroke volume, providing symptomatic relief without the need for left heart access [52]. Among patients with AFMR, the technique has also proven safe and effective, demonstrating reductions in left atrial volume and improvements in NYHA functional class; however, the degree of MR reduction may be less dramatic than with TEER [142,144,176]. Importantly, the procedural success rate is high, and major adverse events are relatively infrequent if patients are appropriately selected [169,176,179].

Table 6. Clinical Studies of Transcatheter Direct Annuloplasty Devices for Functional Mitral Regurgitation.

Annuloplasty Type	Year Trial (N)	Intervention	Comparator	Primary Outcome	Result Summary	Quality Considerations
Indirect	2009 AMADEUS (48)	Carillon device	None (single arm)	MR reduction (echo), 6MWD, QoL	Significant reduction in MR (22–32% by echo), improved 6MWD and QoL at 6 months, 13% 30-day major adverse event rate	Early feasibility, small n, anatomical exclusion, procedural learning curve
Indirect	2012 TITAN (53)	Carillon device	Device recapture (non-implant)	Change in regurgitant volume, LV volumes, 6MWD	Significant reduction in MR and LV volumes, improved 6MWD in implant group vs. recapture; 1.9% 30-day major adverse event	Non-randomized, device recapture as comparator, moderate sample size
Indirect	2022 Rottländer et al. (41)	Carillon device	MitraClip	MR reduction, LA volume, NYHA class	Both safe/feasible; MitraClip greater MR reduction, Carillon greater LA volume reduction at 12 months	Retrospective, single-center, small n, AFMR focus
Direct	2016 Maisano et al. (31)	Cardioband	None (single arm)	Technical success, annular reduction, MR grade at 30 days	100% device delivery; significant annular reduction; MR ≤ 2+ in 88% at 30 days; no device/procedure-related deaths	Early feasibility, high-risk, short follow-up
Direct	2016 Nickenig et al. (31)	Cardioband	None (single arm)	Annular reduction, MR grade, NYHA, 6MWD at 6–7 months	Annular septolateral dimension ↓ > 30%; MR ≥ 3+ from 77% to 13.6%; NYHA III/IV from 95.5% to 18.2%; 6MWD ↑; 9.7% mort. at 7 months	Feasibility, moderate sample, no control, short follow-up
Direct	2016 Nickenig et al. (71)	Direct annuloplasty system	None (single arm)	Device success, MR reduction, LV remodeling at 6 months	Device success 70%; MR grade ↓ by mean 1.3; annular and LV dimensions ↓; 6MWD and NYHA improved; 12.2% mortality at 6 month	Feasibility, moderate sample, no control, short follow-up
Direct	2019 Messika-Zeitoun et al. (60)	Cardioband	None (multicenter)	Technical/device/procedural success, MR, NYHA, QoL, 6MWD at 1 year	Technical success 97%; device/procedural 72/68%; MR ≤ 2+ in 61% (95% of echo-followed); NYHA I/II 79%; QoL, 6MWD improved; 87% survival at 1 year	Multicenter, moderate n, no control, device modification mid-study

Abbreviations: MR = Mitral regurgitation; NYHA = New York Heart Association (functional class); 6MWD = 6-min walk distance; QoL = Quality of life; LV = Left ventricle/ventricular; ↓ = Decrease; ↑ = Increase.

However, the anatomical suitability of the coronary sinus remains a major determinant of procedural efficacy [168,173,175,176]. Not all patients have favorable CS anatomy, and suboptimal alignment or excessive CS annulus separation can limit the capacity for effective annular remodeling [173,175,176,180]. As such, comprehensive multimodality imaging, including echocardiography, cardiac CT, and, where necessary, coronary angiography, is indispensable for case planning [38,83,181]. In recognition of this, both the American Society of Echocardiography and the European Association of Echocardiography recommend detailed pre-procedural evaluation to assess MR severity, annular geometry, and the spatial relationship of the coronary sinus to both the mitral annulus and coronary arteries [38,83,181].

In summary, indirect coronary sinus annuloplasty is a promising, catheter-based intervention for patients with FMR, particularly those with annular-dominant pathology, including both proportionate VFMR and atrial FMR. It offers a safe and less invasive alternative to direct mitral interventions, especially in patients with contraindications to TEER or surgery. While early results are encouraging, ongoing clinical trials and longer-term follow-up are necessary to fully define its place in the therapeutic algorithm, particularly in relation to emerging transcatheter and surgical techniques.

6.3.3. Direct Annuloplasty (Cardioband, Millipede)

Direct annuloplasty techniques aim to replicate the surgical principle of annular reduction through a fully transcatheter approach [182]. This strategy directly targets annular dilatation, a central pathophysiologic driver in both atrial and select forms of ventricular FMR [182]. Among the devices currently under clinical evaluation, Cardioband (Edwards Lifesciences) and Millipede represent the most advanced platforms [182,183].

The Cardioband system is an adjustable, transcatheter direct annuloplasty device designed to mimic the effect of surgical ring annuloplasty [182,183]. Under combined fluoroscopic TEE guidance, the device is delivered transvenously and sequentially anchored along the posterior mitral annulus, from the lateral to the medial fibrous trigone [147,184,185]. Once in place, the band is cinched in the beating heart, dynamically reducing the septolateral annular dimension until optimal regurgitation reduction is achieved, while carefully monitoring trans-mitral gradient to avoid iatrogenic stenosis [184]. This real-time adjustability allows for individualized optimization of leaflet coaptation and hemodynamics [147,184,186]. Clinical studies have demonstrated that Cardioband implantation is both feasible and safe in high-risk patients, resulting in significant reductions in annular area, mitral regurgitation grade, and left ventricular volume, as well as improvements in NYHA class, exercise capacity, and quality of life at 6 to 12 months (Table 5) [184,185,187]. Device success rates across studies range from 70% to 97%, with most patients achieving moderate or less moderate MR at 1 year [185,187]. In a multicenter feasibility study involving 60 high-surgical-risk patients with moderate-to-severe secondary FMR, Cardioband achieved 87% one-year survival, 66% freedom from heart failure rehospitalization, and 78% freedom from mitral reintervention, with sustained MR reduction and symptomatic improvement [187]. Follow-up registries have confirmed durable MR $\leq 2+$ at 12–24 months, with the degree of annular shrinkage correlating with the clinical response [185,187]. Ideal candidates for Cardioband therapy exhibit predominantly annular dilatation, preserved leaflet mobility, and an effective mitral valve area greater than 4.0 cm² [182,183]. Relative contraindications include heavy posterior annular calcification, inter-commissural gaps > 1 cm, and basal ventricular aneurysms, which may impair anchor seating or limit efficacy [182,183].

The Millipede annuloplasty system employs a modular approach, providing a semi-rigid, complete Nitinol ring with eight adjustable anchors, each of which can be repositioned to achieve symmetrical annular capture and reshaping [188]. The system incorporates intracardiac echo guidance, offering precise visualization during deployment [188]. In the first-in-human feasibility study involving seven patients, Millipede achieved a 31% reduction in septolateral annular diameter, with baseline MR grades of 3–4+ reduced to $\leq 1+$ at both discharge and 30 days post-procedure, without any major periprocedural

complications [188]. While large-scale data is still pending, the design allows for resheathing and resizing, offering potential advantages in anatomically complex or heterogeneous annular geometries [188]. The system is also compatible with future TMVR, positioning it as a versatile platform for staged or combined interventions [188].

As with all transcatheter mitral therapies, comprehensive pre-procedural imaging is essential for patient selection and procedural planning [37,189]. Both the American Society of Echocardiography and the European Association of Cardiovascular Imaging emphasize detailed evaluation of annular geometry, leaflet motion, and MR severity using echocardiography and cardiac CT [37,189]. Direct annuloplasty is generally most effective in patients with AFMR or milder forms of VFMR, where leaflet tethering is limited [144,166,190]. In contrast, for patients with advanced ventricular remodeling and a tenting height greater than 10 mm, edge-to-edge repair or combined strategies may be more suitable [29,37]. The hemodynamic goals of direct annuloplasty include achieving a residual trans-mitral gradient <5 mmHg and limiting residual MR to no more than mild [191]. In AFMR, where annular dilation is often atrial in origin and may be reversible, post-procedural rhythm control and hemodynamic unloading are critical adjuncts to promote sustained reverse remodeling and functional improvement [166].

In summary, direct annuloplasty with devices such as Cardioband and Millipede offers an anatomically precise, minimally invasive therapy for selected patients with FMR, particularly those with annular-dominant pathology and preserved leaflet motion. While current data support safety and early efficacy, randomized trials remain ongoing. IDE studies comparing Cardioband and Millipede with medical therapy, edge-to-edge repair, or combination strategies will be essential in defining their long-term durability, impact on remodeling, and appropriate place within the evolving treatment algorithm for FMR. As device design, imaging integration, and operator experience continue to advance, direct annuloplasty is poised to become a key tool in personalized, mechanism-driven mitral valve therapy.

6.3.4. TMVR

TMVR is an emerging therapeutic option for patients with severe FMR who are at high or prohibitive surgical risk and are either unsuitable for transcatheter repair or have failed prior repair attempts [192–194]. TMVR offers a mechanistically definitive solution, replacing the native mitral valve with a bioprosthetic implant that eliminates regurgitation regardless of underlying annular or subvalvular distortion, an important advantage over repair-based strategies, whose success may be limited by complex or severely remodeled anatomy [195–197]. Currently available TMVR platforms include transapically delivered devices, such as the Tendyne valve (Abbott) and the Intrepid valve (Medtronic), as well as fully transseptal systems, like the Sapien M3 and Evoque valves, which are under investigation in pivotal trials [162,198,199]. These systems are designed to anchor securely within the mitral annulus and accommodate the dynamic, elliptical, and noncalcified anatomy characteristic of FMR [196].

Clinical studies of TMVR have demonstrated high procedural success rates, reaching up to 97%, with near-complete elimination of mitral regurgitation in most patients (Table 7) [191,192,194,200]. Improvements in symptoms, exercise capacity, and quality of life are typically sustained through 1 to 2 years of follow-up [191,192,194,200]. In the CTSN trial, moderate-to-severe MR recurred in 32.6% of patients who underwent surgical repair, compared to only 2.3% after valve replacement, despite similar survival rates and comparable degrees of left ventricular reverse remodeling [139,193]. These findings underscore the durability advantage of replacement, particularly in anatomies prone to recurrent tethering or annular dilation. In one prospective study of high-risk patients, TMVR reduced heart failure hospitalizations from 1.3 to 0.5 events per year, with 93% of survivors exhibiting no residual MR at two years [139,193]. However, despite these promising outcomes, early mortality remains substantial, particularly within the first 90 days, reflecting the advanced clinical status of patients typically selected for this therapy [193,194,200].

TMVR is not without challenges. Potential complications include obstruction, prosthetic thrombosis, paravalvular leak, and difficulty anchoring the device in the setting of heavy mitral annular calcification [201–203]. Pre-procedural planning is critical, with multimodality imaging playing a central role [204,205]. Cardiac computed tomography (CT) is used to evaluate annular dimensions, simulate device deployment, and, crucially, estimate the neo-left ventricular outflow tract (neo-LVOT) area [114,116,117,206]. A neo-LVOT $<2.0 \text{ cm}^2$ is strongly associated with increased risk of LVOT obstruction [206,207]. As a result, ongoing randomized trials, most notably SUMMIT and APOLLO, are evaluating TMVR in comparison with transcatheter edge-to-edge repair to determine its relative safety, efficacy, and appropriate clinical niche [195,208].

In summary, TMVR currently remains reserved for patients with severe symptomatic FMR who are not candidates for surgery or edge-to-edge repair, and its use is predicated on a multidisciplinary heart team assessment and advanced imaging-based procedural planning. As device technology matures, imaging integration improves, and operator experience expands, the role of TMVR is expected to broaden, potentially offering a durable, anatomically agnostic treatment option for an increasing number of patients with FMR.

To assist clinicians in navigating these interventional strategies, Table 8 provides a clinical guide for selecting the most appropriate therapeutic approach based on the dominant imaging phenotype and the underlying pathophysiology of FMR.

Table 7. Clinical Studies of Transcatheter Mitral Valve Replacement for Functional Mitral Regurgitation.

Year	Trial (N)	Intervention	Comparator	Primary Outcome	Result Summary	Quality Considerations
2015	Abdul-Jawad Altisent et al. (3)	Fortis TMVR (transapical)	None (case series)	Procedural success, MR reduction, 6-mo outcomes	100% device success, no major complications, all alive at 6 month, NYHA ≤ II, no HF readmission	Compassionate use, very high surgical risk, small n, short follow-up
2017	Muller et al. (30)	Tendyne TMVR (transapical)	None (feasibility)	Device success, MR reduction, 30-day safety	93% device success, 0 acute deaths/strokes, 1 death at 13d, 75% NYHA I/II at 30d, 1+ MR in 1 pt	Early feasibility, high surgical risk, short follow-up
2018	Bapat et al. (50)	Intrepid TMVR (transapical)	None (pilot)	Device success, MR reduction, 30-day safety	96% device success, 14% 30-day mortality, 79% NYHA I/II at follow-up, all mild/no MR	High/extreme risk, short follow-up, pilot study
2019	Sorajja et al. (100)	Tendyne TMVR (transapical)	None (feasibility)	Technical success, 1-yr survival, MR reduction	96% technical success, 6% 30d mortality, 72% 1-yr survival, 88.5% NYHA I/II, 73% KCCQ ↑ ≥ 10 pts	High/prohibitive risk, nonrandomized, 1-yr follow-up
2021	Muller et al. (100)	Tendyne TMVR (transapical)	None (prospective)	2-yr all-cause mortality, HF hospitalization, MR reduction	97% device success, 39% 2-yr mortality (44% in first 90d), HFH 0.51/yr vs. 1.3/yr pre-TMVR, 93% no MR at 2 yr	High surgical risk, nonrandomized, 2-yr follow-up
2023	Ludwig et al. (97) TMVR, 97 GDMT)	TMVR (CHOICE-MI registry, mostly transapical)	GDMT (COAPT control)	2-yr HF hospitalization, mortality, MR reduction	2-yr HFH 32.8% TMVR vs. 54.4% GDMT (HR 0.59); 2-yr mortality similar (36.8% vs. 40.8%); all TMVR ≤ 1+ MR	Propensity-matched, registry vs RCT control, device heterogeneity, high risk

Abbreviations: TMVR = Transcatheter mitral valve replacement; MR = Mitral regurgitation; NYHA = New York Heart Association (functional class); HF = Heart failure; HFH = Heart failure hospitalization; KCCQ = Kansas City Cardiomyopathy Questionnaire; GDMT = Guideline-directed medical therapy; RCT = Randomized controlled trial; ↑ = Increase.

Table 8. Imaging-Guided Interventional Decision-Making in Functional Mitral Regurgitation.

Dominant Imaging Phenotype	Key Imaging Findings	Pathophysiologic Interpretation	Preferred Therapeutic Strategy	Rationale
Advanced VFMR with severe tethering and myocardial disease	<ul style="list-style-type: none"> Tenting height > 10 mm or tenting area > 2.5 cm² (echo/CT) Marked LV dilation (↑ LVEDV/LVESV) Extensive LGE (>5% ischemic or >2% nonischemic) and/or high ECV (CMR) 	Ventricular-dominant disease with irreversible remodeling and reduced closing forces	Surgery (chordal-sparing replacement) or TMVR in high-risk surgical candidates	TEER durability is limited when tethering and scar burden are extensive; valve replacement offers more complete and durable MR elimination
Disproportionate VFMR with preserved myocardial viability	<ul style="list-style-type: none"> Severe MR relative to LV size (EROA disproportionately high vs. LVEDV) Moderate tethering without extreme annular dilation Minimal or absent LGE, low ECV 	Valvular lesion is a major driver of symptoms and outcomes	TEER (MitraClip or PASCAL) after optimized GDMT ± CRT	MR reduction improves outcomes when myocardium remains responsive and remodeling is potentially reversible

VFMR with electrical dyssynchrony	<ul style="list-style-type: none"> • LBBB, QRS \geq 150 ms (ECG) • Mechanical dyssynchrony and dynamic MR (echo) • Modest scar burden 	Functional MR amplified by electromechanical delay	CRT first, reassess MR; TEER if MR persists	CRT can restore synchrony, reduce tethering, and obviate valve intervention in responders
Ischemic VFMR with revascularizable myocardium	<ul style="list-style-type: none"> • Regional wall motion abnormalities • Viable myocardium on CMR (limited transmural LGE) • Significant CAD on CCTA or angiography 	MR partially driven by ischemia and regional remodeling	CABG \pm mitral intervention (repair or replacement depending on tethering severity)	Revascularization may reduce MR; severe tethering favors replacement over repair
Classic AFMR with annular-dominant disease	<ul style="list-style-type: none"> • Massive LA enlargement (LA volume index $>$ 60 mL/m²) • Marked annular dilation and flattening (CT/3D echo) • Preserved LV size and function • Minimal or no LGE/ECV 	Annular-driven MR with preserved ventricular mechanics	Annuloplasty (surgical or transcatheter) \pm TEER; rhythm control	Annular reduction restores coaptation; TEER adjunctive if residual MR persists
AFMR with atriogenic tethering (“hamstrung” posterior leaflet)	<ul style="list-style-type: none"> • Posterior annular displacement • Posterior leaflet angulation despite normal LV • Central or eccentric MR 	Combined annular dilation and atrial-induced leaflet mal-coaptation	Annuloplasty-first strategy, cautious use of TEER	Isolated TEER may leave residual MR due to persistent annular pathology
Mixed/Dual FMR	<ul style="list-style-type: none"> • LA and LV enlargement • Annular dilation + leaflet tethering • Variable fibrosis burden 	Combined atrial and ventricular mechanisms	Individualized Heart Team approach: TEER vs surgery vs TMVR	Single-modality therapy is often insufficient; imaging defines dominant driver
End-stage remodeling with prohibitive anatomy for repair	<ul style="list-style-type: none"> • Extreme annular dilation • Severe MAC • Predicted neo-LVOT $<$ 2.0 cm² (CT simulation) 	Unsuitable for repair strategies	TMVR (selected cases) or palliative GDMT	CT-guided planning essential to avoid LVOT obstruction

Abbreviations: VFMR = ventricular functional mitral regurgitation; AFMR = atrial functional mitral regurgitation; MR = mitral regurgitation; LV = left ventricle; LA = left atrium; EROA = effective regurgitant orifice area; LGE = late gadolinium enhancement; ECV = extracellular volume; CRT = cardiac resynchronization therapy; TEER = transcatheter edge-to-edge repair; TMVR = transcatheter mitral valve replacement; CABG = coronary artery bypass grafting; CAD = coronary artery disease; \uparrow = increase.

7. Future Directions

The management of FMR has reached a critical juncture. While the success of TEER in highly selected patients has definitively demonstrated the prognostic importance of reducing MR, the conflicting results of landmark trials such as COAPT and MITRA-FR underscore a fundamental challenge: the lack of a universally applicable patient selection tool. Consequently, the future of FMR care is rapidly evolving, with a focus on enhanced, personalized risk stratification, the adoption of innovative technologies, and a deeper understanding of disease heterogeneity.

A primary research objective is to refine the timing and criteria for intervention. Recent studies, including RESHAPE-HF2 and MATTERHORN, suggest a paradigm shift toward earlier use of TEER in well-selected, symptomatic patients, moving beyond the current approach of only intervening after GDMT has failed. This emphasis on earlier, individualized intervention makes it critical to clarify whether FMR is primarily a driver or merely a marker of heart failure progression, as this distinction dictates which patients will derive the greatest benefit from valve intervention versus intensified medical therapy alone. To achieve this precision, future algorithms must move beyond traditional parameters to incorporate dynamic assessment from stress echocardiography and detailed myocardial tissue characterization from CMR, which enables the identification of viable versus scarred myocardium.

Artificial intelligence (AI) is emerging as a critical enabling technology in this effort [209,210]. AI-based tools are already being applied to automate chamber segmentation, annular geometry assessment, and volumetric analysis across echocardiography, CMR, and CT, reducing inter-operator variability and improving reproducibility of MR severity grading [211]. In echocardiography, deep learning algorithms can automatically quantify ventricular and atrial volumes, strain, and regurgitant jet parameters [212], while AI-assisted CT and CMR workflows facilitate annular sizing, neo-LVOT prediction, and myocardial scar quantification for procedural planning [213]. By harmonizing quantitative imaging across modalities, AI has the potential to address longstanding limitations in FMR phenotyping and trial generalizability.

Ultimately, future research must extend beyond procedural success to evaluate the durability of reverse remodeling, patient-centered outcomes, and cost-effectiveness. As diagnostic complexity and therapeutic options continue to expand, integrating advanced imaging, AI-assisted analytics, and clinical expertise within a multidisciplinary Heart Team framework will be essential to delivering individualized, evidence-based care for patients with functional mitral regurgitation.

8. Conclusions

FMR remains a highly prevalent and morbid condition, inextricably linked to adverse outcomes in patients with both HF_rEF and preserved (HF_pEF) ejection fraction. As detailed throughout this review, FMR is not a singular entity, but a spectrum defined by two mechanistically distinct subtypes: VFMR, driven by LV remodeling and leaflet tethering, and AFMR, caused by left atrial LA and annular dilation. This heterogeneity mandates a mechanism-specific approach to evaluation and management as detailed in Figure 2 (Management process of FMR).

The central clinical dilemma, determining which patients with severe secondary MR benefit from valve intervention, has been partially resolved by the landmark COAPT trial, which demonstrated that in highly selected patients, aggressive MR reduction with TEER improves prognosis. However, the discordant results with MITRA-FR underscore that the field has moved beyond simply treating all severe MR to identifying the specific mechanical and myocardial environment in which intervention is beneficial. Patient selection is paramount.

Multi-modality imaging is therefore indispensable for precision medicine in FMR. Echocardiography serves as the diagnostic cornerstone, grading severity and identifying the primary mechanism, while CMR provides the gold standard for volumetric quantification and, critically, myocardial tissue characterization

via late gadolinium enhancement and T1 mapping. Furthermore, CT offers unparalleled anatomical detail, making it essential for pre-procedural planning, particularly for TMVR. These imaging data sets enable the application of advanced risk stratification tools, such as differentiating FMR phenotypes to the proportionate/disproportionate VFMR framework, which helps rationalize the divergent results observed in therapeutic trials. Effective management, as summarized in our comparative Tables 1 (Mechanistic Characteristics) and 2 (Diagnostic Modalities), defined a carefully integrated approach.

Ultimately, FMR care is rapidly transitioning from a one-size-fits-all model to an individualized model. First-line therapy remains robust, which includes GDMT, followed by the judicious consideration of transcatheter or surgical therapies for persistent, symptomatic MR. Future efforts, guided by the multidisciplinary Heart Team, will focus on integrating artificial intelligence, next-generation devices, and refined risk stratification to target earlier, more individualized interventions that maximize myocardial recovery and substantially improve the long-term outcomes for this challenging patient population.

Statement of the Use of Generative AI and AI-Assisted Technologies in the Writing Process

The authors used Google Gemini and ChatGPT 5.2 to generate ideas for visualizing and presenting the illustrations described in the paper. Grammarly was used to improve grammar and edit paragraphs in the manuscript. After using these tools, the authors reviewed and made necessary edits to the content, taking full responsibility for the final article published.

Author Contributions

Conceptualization, T.K.M.W. and S.-W.L.; Methodology (literature search strategy), S.-W.L.; Validation (critical review of arguments), J.E.R., Y.-F.T., C.T. and T.K.M.W.; Investigation (literature collection), S.-W.L. and J.E.R.; Resources, T.K.M.W.; Writing—Original Draft Preparation, S.-W.L.; Writing—Review & Editing, S.-W.L., J.E.R., Y.-F.T., C.T. and T.K.M.W.; Visualization, S.-W.L.; Supervision, T.K.M.W.; Project Administration, T.K.M.W.; Funding Acquisition, T.K.M.W.

Ethics Statement

Not applicable. This is a review article that synthesizes and summarizes previously published literature and does not involve any new studies with human participants or animals performed by any of the authors.

Informed Consent Statement

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