



Functional mitral regurgitation in patients with heart failure and depressed ejection fraction

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Purpose of review

Functional mitral regurgitation (FMR) is a common complication of left ventricular dysfunction. It is now recognized as an important clinical entity and an independent predictor of poor prognosis in cardiomyopathy patients. In this review, we provide a comprehensive summary of the pathophysiology, latest imaging modalities, and diagnostic criteria for FMR. Additionally, we discuss the recent literature on the continuously evolving surgical and percutaneous treatment options.

Recent findings

The criteria for quantification of FMR on echocardiography were updated and are distinct from organic mitral regurgitation in the most recent American College of Cardiology/American Heart Association 2014 valve guidelines. Furthermore, the evolving role of MitraClip for potential treatment of FMR offers exciting prospects to treat high-risk symptomatic patients.

Summary

Our review serves to consolidate the current diagnostic and treatment modalities for FMR and provide a contemporary resource for clinicians while treating patients. Additionally, we identify the gaps present in our knowledge of FMR to guide further clinical investigation.

Keywords

echocardiography, functional mitral regurgitation, MitraClip

INTRODUCTION

Mitral regurgitation is a commonly encountered valvular lesion in modern clinical practice [1]. Mitral regurgitation can be further classified into organic (or primary) and functional (or secondary). Organic mitral regurgitation refers to regurgitant lesions resulting from disorders of the mitral valve apparatus, and common causes include degenerative disease, endocarditis, rheumatic disease, and papillary muscle rupture [2^{***}]. Functional mitral regurgitation (FMR), on the other hand, occurs secondary to left ventricular (LV) dysfunction and geometric alteration of an anatomically intact mitral valve apparatus. FMR is an important entity as it independently portends a poor prognosis in patients with depressed LV ejection fraction. However, its mechanism is incompletely understood and the treatment options remain controversial. The following section discusses the cause, pathophysiology, diagnostic evaluation, prognosis, and therapeutic approaches to FMR.

CAUSE AND PREVALENCE

FMR is a common complication of ischemic and nonischemic cardiomyopathy. Ischemic heart disease

is the most common cause of FMR. Prevalence of FMR is difficult to establish because of heterogeneity of the populations studied and variability in the diagnostic techniques. Studies have found the incidence of FMR to be anywhere between 20 and 50% within the first 30 days of a myocardial infarction (MI) [3–5]. FMR is more prevalent with inferior MIs (38%) as compared with anterior MIs (10%) potentially because of direct involvement of the mitral subvalvular apparatus [6]. In dilated cardiomyopathy, the prevalence is reported anywhere from 50 to 73% [7–9].

PATHOPHYSIOLOGY

To understand the pathophysiology, it is important to elucidate the complex anatomy and functioning of the mitral valve apparatus.

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KEY POINTS

- FMR poses a diagnostic and management challenge.
- FMR is a dynamic lesion dependent on loading conditions.
- Three-dimensional echocardiography is helpful in evaluating complex and multiple jets of FMR.
- Medical therapy is the first-line therapy in FMR.
- Surgical intervention may be considered in selected patients particularly while undergoing surgical revascularization.
- The role of percutaneous intervention is currently evolving in FMR.
- Percutaneous intervention may be considered in carefully selected high-risk symptomatic patients not responding to medical therapy.

The mitral valve apparatus consists of six structures, namely anterior and posterior leaflets, mitral annulus, chordae tendinae, papillary muscles (anterolateral and posteromedial), posterior left atrial wall, and LV wall [10]. The two leaflets have a roughly equal surface area but the posterior leaflet has a longer circumference than the anterior leaflet. The mitral leaflets come into contact at the ‘coaptation line’ in the annular plane. Normally, the combined area of the two leaflets is approximately two and a half times the area of the mitral orifice, providing significant overlap, known as ‘coaptation reserve’. The chordae tendinae arise from the papillary muscles and attach on to both the anterior and posterior leaflets. Chordae arising from the anterolateral papillary muscle attach to both leaflets in the region of the anterolateral commissure, while the chordae from the posteromedial papillary muscle attach to the region of the posteromedial commissure. This preferential chordal attachment to the commissural regions leaves the central portion of the mitral valve relatively chord free [11–13].

Mitral valve closure is a dynamic process, which occurs as a result of two simultaneous opposing yet balanced forces [14]. As the ventricular cavity contracts, the mitral annulus moves toward the apex. The ‘tethering forces’ produced by traction of the chordae tendinae secondary to papillary muscle contraction in systole draw the leaflets apically and prevent leaflet prolapse into the left atrium. Simultaneously, the opposing ‘closing forces’ generated by LV contraction drive blood up against the leaflets, leading to their coaptation. The mitral annulus also contracts during systole, decreasing the area required

for leaflet coaptation. The annulus is also important for maintaining normal leaflet stress.

An imbalance between the tethering and closing forces along with mitral annular deformation leads to malcoaptation of the leaflets and subsequently FMR. If the tethering forces overcome the closing forces, the leaflet coaptation occurs below the annular plane in the ventricular cavity [15]. If the closing forces are stronger, the leaflet coaptation occurs toward the left atrium. Based on the Carpentier classification (which describes mitral valve pathology based on a mechanistic approach), FMR mostly occurs because of type III b and less frequently type I dysfunction [16,17].

In ischemic/nonischemic cardiomyopathy the LV undergoes regional or global remodeling, respectively. As a result, the papillary muscles (normally situated parallel to the LV long axis and perpendicular to the mitral annulus) get apically and/or laterally. The normal perpendicular tension applied by the papillary muscle on the mitral valves transforms to a tangential force causing increased traction on the chordae. The altered tethering forces cause impaired systolic excursion of one or both the leaflets, leading to decreased coaptation and regurgitation [18,19]. The direction of the regurgitant jet depends on whether one or both of the papillary muscles are displaced. Closing forces also decrease as the LV systolic dysfunction develops and the LV transforms from a normally ellipsoid into a more spherical shape. Degree of LV distortion is a more important determinant of FMR than the LV dysfunction itself. Lastly, flattening of the saddle-shaped mitral annulus leads to increased leaflet stress, and mitral annular dilation, which is often asymmetric (greater involvement of the posterior annulus), leads to decreased coaptation [20,21].

The mitral apparatus in FMR has been shown to undergo remodeling over time. In a study by Debonnaire *et al.*, patients with FMR had larger leaflet areas, and degree of left ventricular ejection fraction (LVEF) was inversely related to the leaflet area. Additionally, the lack of coaptation reserve, defined in this study by the ratio of coaptation to leaflet area (coaptation index), was independently associated with significant mitral regurgitation [22^{***}]. Variability in the adaptive remodeling of the mitral valve apparatus may explain why patients with similar degrees of LV dysfunction have different severities of FMR.

Dynamic nature of functional mitral regurgitation

FMR is a dynamic lesion because of its dependence on ventricular loading conditions and timing of the

cardiac cycle. Therefore, when estimating FMR, loading conditions like blood pressure and drug treatments should be taken into consideration. The degree of FMR also varies throughout the cardiac cycle. It is greater in early and late systole and decreases in midsystole. This is because of the systolic variation of transmitral pressures, midsystolic decrease in the regurgitant orifice, and alteration in the balance between tethering and closing forces through the cardiac cycle [23,24].

DIAGNOSIS

A thorough history and physical examination are essential for the initial diagnosis. History of ischemic heart disease or symptoms of congestive heart failure may be helpful indicators. On physical examination, a pan systolic murmur of mitral regurgitation can be appreciated; however, it may be clinically silent.

Echocardiography is the mainstay of diagnosis for FMR. In addition to evaluating the severity of FMR, it is often helpful in differentiating between ischemic and nonischemic etiology. Different echocardiographic measures and techniques used for FMR are discussed in detail below.

Two-dimensional echocardiography

Color Doppler imaging

Color Doppler imaging is the initial and most common technique used for the diagnosis and semi-quantitative assessment. Severity of FMR is based on the size and extent of the regurgitant jet into the left atrium. Although this provides a quick assessment, it is not reliable for quantification, as it is affected by hemodynamic factors. Mitral regurgitation may be overestimated on color Doppler because of the aliasing/blooming artifacts from high-velocity mitral regurgitation jets, or underestimated in eccentric jets [25,26].

Vena contracta

The width of vena contracta is a more reliable quantitative approach, as it measures the narrowest part of the regurgitant jet passing through the valvular orifice. It reflects the effective regurgitant orifice area (EROA) and is less dependent on technical and loading conditions. Calculation of vena contracta relies upon the assumption that the regurgitant orifice is circular; however, in FMR it may be elliptical, leading to inaccurate estimation. At times multiple regurgitant orifices may be present along the closure line, which also limits its use, as they

cannot be added together. Due to the abovementioned limitation, the 2014 American College of Cardiology/American Heart Association (ACC/AHA) guidelines do not recommend using vena contracta in FMR [27,28].

Proximal isovelocity surface area

Proximal isovelocity surface area (PISA) is the recommended quantitative approach as it can be used reliably in both central and eccentric jets. Quantitation of FMR is important in patients with moderate to severe mitral regurgitation (especially asymptomatic) for determining the prognosis and treatment. PISA can be used to derive EROA and regurgitant stroke volume (R Vol). PISA is based on the assumption of hemispheric symmetry of velocity distribution proximal to the regurgitant lesion. In FMR flow convergence may be ellipsoid, which may also lead to inaccurate estimation. An EROA of greater than 20 mm² or R Vol of greater than 30 ml is considered severe per the 2014 ACC/AHA guidelines and is associated with an increased risk of cardiovascular events [29,30].

Other useful parameters on echocardiography include LV ejection fraction, wall motion abnormalities, coaptation depth, tenting area, annular dimension, left atrial size, and pulmonary artery pressure. These parameters help correlate cause and modality of treatment indicated. Reversal of pulmonary venous flow pattern is also helpful in consolidating the diagnosis of severe FMR.

By combining the abovementioned parameters, FMR can be categorized into four stages per the ACC/AHA guidelines that prognosticate and guide therapy: at risk of secondary mitral regurgitation, progressive secondary mitral regurgitation, asymptomatic severe secondary mitral regurgitation, and symptomatic severe secondary mitral regurgitation (Table 1). It is important to note that these guidelines differentiate between the diagnostic criteria for organic and FMR.

Stress echocardiography

Exercise or dobutamine stress echocardiography can be helpful in evaluating the impact of FMR on the functional capacity and the LV contractile reserve. Exercise echocardiography is particularly helpful in provoking hemodynamically significant mitral regurgitation in patients whose symptoms appear out of proportion to mitral regurgitation severity. Exercise results in increased preload, afterload, LV dyssynchrony, a more spherical ventricle and expansion of the mitral annulus [30]. Exercise-induced severe mitral regurgitation may identify patients at heightened risk for death or heart failure

Table 1. Stages of functional mitral regurgitation per the 2014 ACC/AHA Guidelines

Stages of functional mitral regurgitation			
Grade	Valve anatomy	Valve hemodynamics	Cardiac structure and function
A: at risk of MR	Normal valve leaflets, chords, and annulus in a patient with coronary disease or cardiomyopathy	No MR jet or small central jet area less than 20% LA on Doppler	Normal or mildly dilated LV size with fixed (infarction) or inducible (ischemic) regional wall motion abnormalities
B: progressive MR	Regional wall motion abnormalities with mild tethering of mitral leaflet	Small vena contracta less than 0.30 cm EROA less than 0.20 cm ²	Primary myocardial disease with LV dilation and systolic dysfunction Regional wall motion abnormalities with reduced LV systolic function
C: asymptomatic severe MR	Annular dilation with mild loss of central coaptation of the mitral leaflets	Regurgitant volume less than 30 ml Regurgitant fraction less than 50%	LV dilation and systolic dysfunction because of primary myocardial disease
D: symptomatic severe MR	Regional wall motion abnormalities and/or LV dilation with severe tethering of mitral leaflet	EROA at least 0.20 cm ² Regurgitant volume at least 30 ml Regurgitant fraction at least 50%	Regional wall motion abnormalities with reduced LV systolic function LV dilation and systolic dysfunction because of primary myocardial disease
	Annular dilation with severe loss of central coaptation of the mitral leaflets	EROA at least 0.20 cm ² Regurgitant volume at least 30 ml Regurgitant fraction at least 50%	HF symptoms because of MR persist even after revascularization and optimization of medical therapy Decreased exercise tolerance
	Regional wall motion abnormalities and/or LV dilation with severe tethering of mitral leaflet	Regurgitant volume at least 30 ml Regurgitant fraction at least 50%	Exertional dyspnea

EROA, effective regurgitant orifice area; HF, heart failure; LA, left atrium; LV, left ventricular; MR, mitral regurgitation.

hospitalization. Increase in EROA by greater than 13 mm² on exercising is a poor prognostic sign associated with increased risk of cardiovascular events [31–33]. Stress echocardiography also helps to evaluate the presence of viable myocardium, which may guide revascularization in ischemic FMR. The 2014 ACC/AHA guidelines consider Doppler echocardiography useful in establishing the etiology of FMR (stages B to D) and/or to assess myocardial viability, which in turn may influence management of functional MR (Class I, level of evidence C) [2^{***}].

Three-dimensional echocardiography

Three-dimensional echocardiography can provide detailed images of the mitral valve apparatus and is considered superior to two-dimensional echocardiography. It can directly measure the vena contracta and EROA. This imaging technique is particularly helpful in noncircular orifices and for multiple regurgitant jets.

Transesophageal echocardiography

Transesophageal echocardiography (TEE) modality is often helpful in deciphering the cause and mechanism of FMR. As the mitral apparatus is clearly visualized, it can be used to make specific measurements like the coaptation length, coaptation depth, and tenting area, which are integral in guiding percutaneous and surgical treatment options (discussed below). It should be noted that the severity of FMR may be impacted by the hemodynamic effects of sedation or anesthesia during a TEE.

Cardiac magnetic resonance imaging

Cardiac magnetic resonance offers a precise method for characterizing mitral regurgitation severity by quantifying the EROA and R Vol [34,35]. It can also be helpful in determining the cause of FMR based on characterization of LV. However, it is reserved for cases where diagnosis is unclear on echocardiography because of its high cost.

Cardiac catheterization

Invasive evaluation of FMR may be indicated in selected few cases where noninvasive imaging is equivocal/nondiagnostic and further hemodynamic assessment is warranted.

PROGNOSIS

FMR is an independent predictor of poor prognosis in cardiomyopathy patients. Increasing severity of

FMR is associated with a stepwise increase in mortality. Some studies even suggest that mild, clinically silent FMR impacts mortality [36,37]. A large study on post-MI patients found 1-year mortality in mild, moderate and severe FMR to be 10, 17, and 40%, respectively [38]. A 3-year follow-up survival of FMR patients post-percutaneous coronary intervention in Ellis's study echoed similar results, with a specifically higher mortality in FMR patients with ejection fraction less than 40% [39].

MANAGEMENT AND TREATMENT OPTIONS

FMR can be managed medically, surgically, and percutaneously. However, the indications and timing of invasive treatment options remain controversial because of the lack of randomized clinical trials.

Medical treatment

All patients with FMR and systolic heart failure should receive guideline-directed medical therapy for heart failure, which includes angiotensin-converting enzyme (ACE) inhibitors (or angiotensin II receptor antagonists), β -blockers, aldosterone antagonists, and diuretics [40]. These drugs have been shown to provide symptom relief, improve cardiac function, and decrease mortality in systolic heart failure. Studies have also found that β -blockers and ACE inhibitors improve FMR by positive ventricular remodeling [41–44].

Cardiac resynchronization therapy

Resynchronization therapy has been shown to greatly benefit patients with FMR and depressed ejection fraction. By restoring LV resynchronization and improving LV contractility, cardiac resynchronization therapy (CRT) leads to increased closing forces and reduced tethering forces. It has also been shown to restore annular geometry.

Acutely, CRT decreases FMR at rest and at exercise and is a favorable predictor of long-term response and survival [45–48]. The EROA has been shown to decrease by approximately 40%; however, improvement in the degree of MR is not predictable [49]. A study by Van Bommel *et al.* suggests that FMR improved in only half of the patients after CRT [51].

Long-term follow-up demonstrates sustained benefit by decreasing the LV dimension, LV geometry, and mortality in patients with moderate to severe FMR [50,51]. However, it remains to be understood whether CRT improves the prognosis in FMR independently of its effects on LV dysfunction.

Surgical management

When medical management of FMR is not adequate for control of symptoms, surgical management aims at restoring competency of the mitral valve. The benefit of surgical intervention in FMR remains unclear because of the lack of prospective randomized trials comparing surgery with medical therapy. Therefore, surgical intervention for FMR typically occurs in concert with coronary artery bypass graft (CABG) because of lack of strong evidence.

Existing data reveal contradicting results with respect to survival benefit for surgical intervention on FMR [52,53,54]. In the recent Randomized Ischemic Mitral Evaluation (RIME) trial, patients with moderate ischemic mitral regurgitation randomized to mitral valve (MV) repair and CABG had improved functional capacity and greater reverse LV remodeling at 1 year compared with CABG alone [55]. In another observational study, at 4.7-year follow-up, patients undergoing MV surgery had a higher event-free survival in a propensity-adjusted model [53]. However, long-term follow-up was lacking in the trial and patients with LVEF less than 30% were excluded. On the contrary, the Cardiothoracic Surgical Trials Network (CTSN) trial evaluating the same question failed to show any significant benefit in LV dimensions or survival between the two groups at 1- and 2-year follow-up despite improvement in the degree of FMR [56,57]. Smaller nonrandomized studies have shown improvement in symptoms and quality of life after MV repair; however, the mortality benefit over medical management remains unanswered [54,58,59].

In patients without coronary disease, the data are even more limited and the survival benefit of MV surgery is yet to be demonstrated [60,61]. The timing of the surgery remains controversial. Larger preoperative LV dimensions and longer duration of symptoms were associated with less reverse remodeling, indicating that benefit of surgery is greatest at an earlier stage [62].

Mitral valve repair versus replacement

Mitral valve annuloplasty involves placement of an undersized prosthetic ring at the mitral annulus to decrease the mitral annular area and increase leaflet coaptation [54], whereas, mitral valve replacement entails replacing a mitral valve with a mechanical or bioprosthetic valve. Although the merits of MV repair over replacement are well documented for organic mitral regurgitation, data for FMR are not as distinctive.

Initial studies found MV repair to have better outcomes (increased ejection fraction and decreased LV wall stress) and lower mortality compared with

replacement. However, nowadays, with the advent of valve replacement with subvalvular preservation (chordal sparing surgeries), studies have found a decrease in early mortality and similar outcomes [63–67]. It is noteworthy that annuloplasty does evade the complications of valve replacement, including the need for anticoagulation.

Current data suggest that MV repair is associated with a lower perioperative mortality, whereas replacement is associated with lower rates of FMR recurrence. The first ever randomized trial evaluating repair versus replacement in ischemic mitral regurgitation by Acker *et al.* demonstrated no significant difference with respect to LV reverse remodeling or survival at 12 months [60]. In this study, replacement provided a more durable correction of mitral regurgitation, but there was no significant difference in composite of major adverse cardiac or cerebrovascular events, functional status, or quality of life at 1 year [68]. The observed 30-day rate of death was higher in the replacement group (4%) versus repair (1.6%). A meta-analysis of 12 studies with 2508 patients echoed similar results. Mitral valve repair had seven times increased odds of recurrence of more than 2+ mitral regurgitation compared with replacement, but surprisingly, the incidence of reoperation was similar between the two groups [69].

Studies have postulated that annuloplasty in FMR may cause functional mitral stenosis (especially with exercise) because of relatively restricted mitral valve opening. Postoperative studies have demonstrated elevated pulmonary artery systolic pressures in repair compared with replacement [70]. However, clinical implications of this finding remain to be determined.

Mitral valve anatomy is an important factor for deciding between replacement and repair [63,67,71]. The 2015 position statement from the European Society of Cardiology describes mitral valve characteristics that predict recurrent mitral regurgitation after undersized annuloplasty (Table 2) [72]. Additional predictors of poor outcomes after annuloplasty include multiple/complex jets [71].

The 2014 ACC/AHA valve guidelines state that mitral valve surgery is reasonable [Class IIa, level of evidence (LOE): C] for patients with chronic severe secondary mitral regurgitation who are undergoing CABG or aortic valve replacement. They also make two weaker recommendations that mitral valve surgery may be considered for patients with chronic moderate secondary mitral regurgitation who are undergoing other cardiac surgery (Class IIb, LOE: C) and that mitral valve surgery may be considered for severely symptomatic patients [New York Heart Association (NYHA) class III/IV] with chronic severe

Table 2. Echocardiographic predictors of repair failure or recurrent mitral regurgitation after undersized annuloplasty

Coaptation depth greater than 1 cm
Systolic tenting area greater than 2.5 cm
Posterior mitral leaflet angle greater than 45°
Distal anterior mitral leaflet angle greater than 25°
LV end-diastolic diameter greater than 65 mm
LV end-systolic diameter greater than 51 mm
End-systolic interpapillary muscle distance greater than 20 mm
Systolic sphericity index 0.07

LV, left ventricular.

secondary mitral regurgitation despite optimal medical therapy (Class IIB, LOE: B) [2[■]].

Less common surgical procedures include ventricular resection of akinetic or dyskinetic areas to restore the ventricular volume and enhance post-procedural reverse remodeling [73]. In patients with increased anterior chordal tethering ('seagull sign') on echocardiography, chordal resection in addition to annuloplasty demonstrated less mitral regurgitation persistence, improved ejection fraction, and lower NYHA class [74[■]]. Edge-to-edge repair in addition to annuloplasty has been shown to have encouraging outcomes, including increased durability. Repositioning of the papillary muscle at the tip or the base has also been performed, especially in FMR because of ischemic cause [62]. Finally, in patients with extensive ventricular dilatation and low likelihood of reverse remodeling, two external cardiac support devices [CorCap (Acorn Cardiovascular, Inc., St Paul, MN) and Coapsys device (Myocor Inc., Maple Grove, USA)] have been studied to reshape the LV [75,76]. However, neither of the external cardiac devices has been incorporated into routine practice given lack of convincing benefit.

Percutaneous approach

MitraClip is a percutaneous clip attached to the mitral valve leaflets via transfemoral venous access and transseptal puncture under TEE guidance. The clip is designed to grasp the free edges of the mitral leaflets, simulating a surgical edge-to-edge repair. Currently, it is Food and Drug Administration approved only for severe primary mitral regurgitation in patients at prohibitive risk for surgery; however, it has received European Conformity (CE) mark approval (for both primary and secondary mitral regurgitation) in Europe. In the first and only randomized trial evaluating the efficacy of MitraClip versus surgical repair [Endovascular Valve Edge-to-Edge Repair Study II (EVEREST II)] in low-risk patients, MitraClip was not found to be superior

in the FMR subgroup for reducing mitral regurgitation, but demonstrated safety [77]. As patients ineligible for surgery are typically high risk and would benefit from percutaneous interventions, the EVEREST II High-Risk Registry was evaluated. In a prospective analysis of 246 FMR patients, Glower *et al.* demonstrated that high-risk patients can be successfully treated with the MitraClip, with morbidity and mortality less than that predicted for surgery [78[■]]. At 12 months, the MitraClip arm had significant reduction in mitral regurgitation, improvement in heart failure symptoms, reduction of heart failure hospitalization, and reduction of LV dimensions. These results suggest that high-risk patients may achieve significant improvement in quality of life with relatively little morbidity. The safety and efficacy reported in this study was similar to the ACCESS-Europe A Two-Phase Observational Study of the MitraClip System in Europe (ACCESS-EU) postmarketing registry [78[■],79]. From the EVEREST-II High-Risk Registry, Whitlow *et al.* [80] demonstrated that in 50 patients with severe FMR there was reduction in the degree of mitral regurgitation and the 30-day mortality was not different from that of a concurrent comparator group receiving standard medical therapy. A large registry has also demonstrated safety in elderly patients (age >76 years) with LV dysfunction similar to their younger counterparts (procedural success in 95% of patients, with no procedure-related deaths) [81].

However, the long-term durability of this device is not well known. The EVEREST II trial suggested that initial postprocedural success predicted sustained effects at 4 years. On the contrary, a recent observational prospective study concluded that recurrence of mitral regurgitation at 4 years was not uncommon and that initial success did not predict sustainability. When compared with surgical repair, recurrent mitral regurgitation (more than or equal to 3+) was higher in the MitraClip group, but there was no difference between mortality or reoperation between the two groups [82[■]].

A meta-analysis of 875 patients undergoing MitraClip for FMR demonstrated net improvement in 6-min walk test and NYHA functional class, reverse LV remodeling, and low rates of procedural cardiac deaths at 9-month follow-up [83[■]].

No randomized trials have compared MitraClip with medical therapy; however, in a nonrandomized propensity-matched analysis 60 patients treated with MitraClip were found to have superior outcomes in terms of overall survival, cardiovascular survival, and lower cardiac readmissions compared with medical therapy [84[■]].

The 2013 ACCF/AHA heart failure guidelines provide a Class IIB (LOE: B) recommendation to

consider MitraClip in carefully selected symptomatic patients with severe secondary mitral regurgitation despite guideline directed medical therapy [40]. The 2014 ACCF/AHA valvular heart disease guidelines, recommended MitraClip for primary mitral regurgitation in symptomatic patients at prohibitive risk for MV surgery Class IIb (LOE: B) but make no recommendations for FMR patients [2^{***}] because of lack of strong evidence. The current ongoing Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation is evaluating the efficacy of MitraClip in FMR, and the results will help to better understand the role of MitraClip in FMR.

Percutaneous annuloplasty

Coronary sinus annuloplasty can be performed by placing a device in the coronary sinus to create tension in the mitral annulus given the proximity of the two structures. This causes the mitral annulus to decrease in size, enhancing the coaptation. The device can be repositioned or removed. The prospective single-arm CARILLON Mitral Annuloplasty Device European Union Study (AMADEUS) demonstrated decreased mitral annular diameter and mitral regurgitation grade and improvement in quality of life at 24 months. The Transcatheter Implantation of Carillon Mitral Annuloplasty Device (TITAN) trial (prospective nonrandomized) studied this device in FMR and demonstrated improvement in mitral regurgitation grade, EROA, and R Vol. Additionally, patients had sustained improvement in 6-min walk test, functional class, and quality of life at 24 months. However, given its proximity to the left circumflex coronary artery and increased gap between the mitral annulus and coronary sinus in dilated hearts, the device is yet to gain popularity. The Carillon device (Cardiac Dimensions Inc., Kirkland, WA, USA) received CE mark approval in Europe in 2011 [85,86].

The Mitralign system (Mitralign Inc., Tewksbury, MA, USA) has been developed for delivery at the mitral annulus via transventricular approach. Early animal studies demonstrated safety and feasibility of the device, and several patients have had successful percutaneous implants. Percutaneous mitral valve annuloplasty has also been attempted with Cardioband (Valtech Cardio Ltd., Or Yehuda, Israel) but is yet to be tested in clinical trials.

CONCLUSION

FMR is an important clinical entity as it is independently associated with poor prognosis in patients

with reduced ejection fraction. Given the dynamic nature, quantification can often be challenging; however, a detailed evaluation is pertinent for prognostication and guiding treatment. Optimal medical treatment for heart failure, including CRT, is the initial recommended treatment, as it greatly improves symptoms and survival. In carefully selected patients who do not respond to medical treatment, surgical and catheter-based interventions may be considered after carefully weighing the risks and benefits. In the future, prospective-randomized trials are essential to further clarify the timing and long-term benefit of invasive strategies.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

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