

Review Article

Functional Mitral Regurgitation: Therapeutic Strategies for a Ventricular Disease

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ABSTRACT

Functional mitral regurgitation is a highly prevalent condition among patients with ischemic and dilated cardiomyopathies. Arising from remodeling of both the mitral valve annulus and the left ventricle, it is associated with high mortality and morbidity. In selected patients, cardiac resynchronization therapy helps to reduce functional mitral regurgitation, but surgical intervention remains the mainstay of therapy when medical therapy for left ventricular dysfunction has been inadequate. It is, however, associated with significant perioperative risks and does not alter long-term mortality. Percutaneous devices, and more recently the Mitraclip in particular, represent a promising alternative that can improve symptoms and ventricular remodeling with significantly lower periprocedural risk. (*J Cardiac Fail* 2014;20:252–267)

Key Words: Mitraclip, dilated cardiomyopathy, mitral valve surgery.

Functional mitral regurgitation (fMR) has been described as a ventricular disease characterized by restricted mitral valve (MV) leaflet motion in the setting of segmental wall motion abnormalities or dilated cardiomyopathies or by normal leaflet motion in the setting of annular dilatation and left ventricular (LV) dysfunction.¹ Classified according to the Carpentier system,¹ such regurgitation occurs in the absence of any anatomic leaflet, papillary muscle, or chordal abnormalities as might be seen with endocarditis, acute myocardial infarction (MI) and papillary muscle rupture, myxomatous degeneration, and rheumatic heart disease. It serves as a marker for poor clinical outcomes, including increased mortality rates and heart failure (HF) admissions compared with HF patients without MR,² but

it remains unclear whether fMR repair is beneficial to this ventricular-valvular disease paradigm. Increasingly, percutaneous approaches to correct fMR are being investigated as a potential alternative to surgical valvular interventions owing to the high surgical mortality and morbidity rates.^{3,4} The present review will examine data regarding post-procedure and long-term outcomes of fMR interventions and, in particular, compare outcomes of percutaneous devices compared with those of traditional surgical techniques. It will additionally focus on the rationale for using percutaneous interventions as first-line therapy for fMR.

Functional MR Arises From Remodeling of Both the MV Apparatus and LV

Functional MR complicates up to 30% of MI and is identified in 35%–50% of patients with HF.⁵ Of patients with an ejection fraction (EF) of <40%, 56.2% were found to have fMR and almost 30% had moderate or severe (3+ or 4+) MR.⁶

MV leaflet tethering that leads to fMR in both dilated and ischemic cardiomyopathy arises from papillary muscle displacement, whether due to increased LV sphericity⁷ or from remodeling of the posterior and inferior LV walls (Fig. 1).⁸ Characteristic echocardiographic findings include increased tenting, tethering length (ie, distance between the papillary muscle tips and the mitral annulus)^{7,9} and

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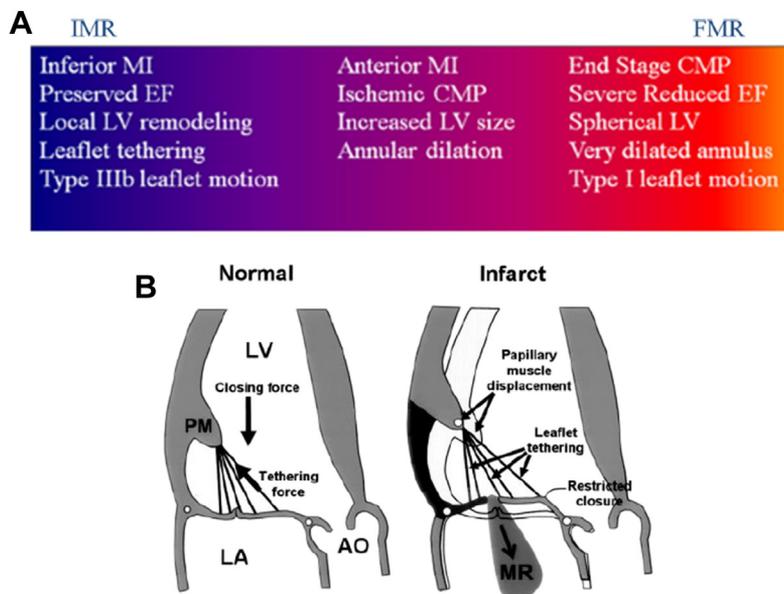


Fig. 1. Mechanism of functional MR. (A) Cause of MR considered as a spectrum, from “ischemic MR” after post-infarct remodeling, to fMR in a spherical LV. (adapted with permission from Timek et al. 2011).¹⁰ (B) Schematic of mitral regurgitation after myocardial infarction and remodeling of posterior and inferior LV walls. (adapted with permission from Liel-Cohen et al. 2000).⁸³ Ao, aorta; fMR, functional mitral regurgitation; IMR, ischemic mitral regurgitation; LA, left atrium; LV, left ventricle; MR, mitral regurgitation; PM, papillary muscle.

coaptation depth.¹⁰ Malcoaptation in particular occurs as the papillary muscles exert forces that are no longer perpendicular to the leaflets, which can themselves be stiffened and stretched.⁷ Transient decreases in LV pressure in early and late systole increase tethering and create dynamic changes in regurgitant flow.⁷

But fMR also arises from changes in mitral annular function and size. The MV annulus in dilated cardiomyopathy is flattened and demonstrates reduced circumferential contraction and reduced intercommissural folding.^{10,11} Annular dilatation in the septal lateral length is common in patients with anterior MIs^{10,11} and can lead to malcoaptation.¹⁰

The absolute regurgitant volume (RV) may be low in patients with fMR, as atrial pressures increase over time.⁸ Indeed, it appears that fMR portends a worse prognosis at levels of regurgitation that would be quantitatively graded as “moderate” by existing clinical guidelines for other types of MR, such as an effective regurgitant orifice area (ERO) of ≥ 20 mm² and an RV of ≥ 30 mL.^{12–14} Some investigators argue that such load-independent parameters will help to more accurately stratify patients and determine prognosis.¹⁴

However, current American College of Cardiology (ACC)/American Heart Association (AHA)¹³ and European Society of Cardiology (ESC)³ guidelines (Table 1) do not make a distinction in recommended diagnostic modalities or in classification schema for severity, between fMR and other etiologies of MR (Fig. 2). Indeed, investigators have used tools including traditional echocardiographic parameters, such as jet area/left atrial area ratio, vena contracta,⁷

color Doppler,⁴ and less frequently left ventriculography,⁶ to characterize fMR severity. Imaging modalities such as cardiac magnetic resonance imaging have not been sufficiently validated for consistent use in diagnosing or characterizing MR severity in general.⁸

There are conflicting data regarding the effect of fMR on rates of comorbid conditions, such as atrial fibrillation, with prevalence estimates ranging from 8%² to 15%¹² in retrospective studies. But complications such as pulmonary hypertension are clearly associated with increased fMR severity.⁸ Several investigators have demonstrated the relationship of fMR with poor outcomes such as mortality and hospital admissions. Functional MR in HF patients has been shown to be associated with a 50% composite rate of mortality and HF admissions at 3 years, compared with $\sim 30\%$ in HF patients without MR.² Specifically in patients with ischemic MR, 5-year total and cardiac mortality rates were increased ($62 \pm 2\%$ and $50 \pm 0\%$, respectively) compared with those without ($39 \pm 9\%$ and $30 \pm 0\%$, respectively).¹² Increasing severity of MR has been further identified as a predictor of death or transplantation in patients with EF $< 35\%$ ¹⁵ and associated with higher mortality rates and HF hospitalizations.^{12,16} However, even moderate MR in patients with acute MI and subsequent HF or LV systolic dysfunction has been shown to be an independent predictor of mortality and HF hospitalizations.¹⁷ Compared with mild MR, moderate MR reduced 5-year survival in patients with inferior wall motion abnormalities and coronary artery disease (CAD) to 73%, compared with 93% in those patients with mild MR.¹⁸

Table 1. ESC and ACC/AHA Guidelines for the Treatment of Functional MR

ESC guidelines for chronic functional MR ³	
Surgery is indicated in patients with severe MR undergoing CABG and LVEF > 30% (<i>Class I, Level of Evidence C</i>)	
Surgery should be considered in patients with moderate MR undergoing CABG (<i>Class IIa, Level of Evidence C</i>)	
Surgery should be considered in symptomatic patients with severe MR, LVEF < 30%, option for revascularization, and evidence of viability (<i>Class IIa, Level of Evidence C</i>)	
Surgery may be considered in patients with severe MR and LVEF > 30% who remain symptomatic despite optimal medical management (including CRT if indicated) and have low comorbidity, when revascularization is not indicated (<i>Class IIb, Level of Evidence C</i>)	
ACC/AHA guidelines for functional MR ¹³	
MV surgery is beneficial for patients with chronic severe MR and NYHA functional class II, III, or IV symptoms in the absence of severe LV dysfunction (defined as ejection fraction < 0.30) and/or end-systolic dimension > 55 mm (<i>Class I, Level of Evidence: B</i>)	
MV surgery is beneficial for asymptomatic patients with chronic severe MR and mild to moderate LV dysfunction, ejection fraction 0.30–0.60, and/or end-systolic dimension ≥ 40 mm (<i>Class I, Level of Evidence: B</i>)	
MV repair may be considered for patients with chronic severe secondary MR due to severe LV dysfunction (ejection fraction < 0.30) who have persistent NYHA functional class III–IV symptoms despite optimal therapy for heart failure, including biventricular pacing (<i>Class IIb, Level of Evidence: C</i>)	

ESC, European Society of Cardiology; ACC, American College of Cardiology; AHA, American Heart Association; MR, mitral regurgitation; CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; CRT, cardiac resynchronization therapy; MV, mitral valve; NYHA, New York Heart Association; LV, left ventricular.

What Are the Mechanisms by Which Current Therapies Target fMR?

There is no clear optimal strategy for the correction of fMR, because the literature points to mixed success of therapies targeting the mitral valve itself, ventricular remodeling alone, or a combination of both. Therefore, within a spectrum that includes medical therapy, cardiac resynchronization therapy (CRT), and surgical interventions, treatment selection depends on both disease severity and the degree of functional impairment.

Medical Therapies Aim to Reduce fMR and Reverse the Underlying Systolic LV Dysfunction

In both humans and animal models of fMR, vasodilator therapy (particularly nitroprusside) reduces fMR by decreasing ventricular filling pressures, systemic vascular resistances, and ventricular volumes.¹⁹ Unlike nitroprusside, hydralazine, which selectively vasodilates the arterial bed, significantly reduces MR but does not affect LV filling pressures.²⁰ By reducing volume overload and atrial

pressure, diuretics¹⁹ and nitrates²¹ have also been shown to reduce transmitral pressures, ERO, and regurgitant flow.⁹ The decrease in ERO is associated with reductions in LV end-diastolic, LA, and mitral annular dimensions,¹⁹ which can help to mitigate MV tethering. Afterload reduction can also prove to be useful, but only with concomitant measures to reduce tethering.⁹

Although the primary effect of angiotensin-converting enzyme (ACE) inhibitors on fMR appears to be related to vasodilation, beta-blockers (particularly atenolol and carvedilol) can decrease fMR by specifically mitigating LV hypertrophy and remodeling, lowering filling pressures, and improving contractility.^{5,9} However, although these therapies have been demonstrated to reduce fMR severity, they do not decrease its incidence in the setting of LV remodeling after MI.⁹ Thus, though targeting LV remodeling, medical therapy is limited in its ability to fully correct fMR.

CRT Can Reduce fMR Significantly

Unlike medical therapy, CRT specifically targets myocardial dyssynchrony, which can be especially

	Mitral Regurgitation		
	Mild	Moderate	Severe
Qualitative			
Angiographic grade	1+	2+	3–4+
Color Doppler jet area	Small, central jet (less than 4 cm ² or less than 20% LA area)	Signs of MR greater than mild present but no criteria for severe MR	Vena contracta width greater than 0.7 cm with large central MR jet (area greater than 40% of LA area) or with a wall-impinging jet of any size, swirling in LA
Doppler vena contracta width (cm)	Less than 0.3	0.3–0.69	Greater than or equal to 0.70
Quantitative (cath or echo)			
Regurgitant volume (ml per beat)	Less than 30	30–59	Greater than or equal to 60
Regurgitant fraction (%)	Less than 30	30–49	Greater than or equal to 50
Regurgitant orifice area (cm ²)	Less than 0.20	0.20–0.39	Greater than or equal to 0.40
Additional essential criteria			
Left atrial size			Enlarged
Left ventricular size			Enlarged

Fig. 2. Classifying MR severity. Adapted with permission from Bonow et al. 2008.¹³

pronounced in those patients with segmental wall motion abnormalities and contributes to fMR.²² Superimposed on therapy with ACE inhibitors and beta-blockers, CRT has been demonstrated to significantly reduce fMR at 3 and 6 months after implantation and concurrently to improve LV end-diastolic and end-systolic volumes.²³ In fact, CRT effects on fMR are both acute and long lasting, with decreased ERO in the 1st week after implantation²⁴ and a reduction of ≥ 1 grade in fMR in 49% of patients at 6 months after implantation.²⁵ In a small randomized trial evaluating transvenous ($n = 20$) versus surgical ($n = 20$) LV lead implantation in patients with challenging coronary sinus anatomy, fMR was reduced by almost 1 grade at 1 year in the surgical group and by less than half a grade in the percutaneous group.²⁶

Interestingly, van Bommel et al²⁵ found that compared with those patients whose fMR improved with CRT, fMR nonresponders (51% of the study population) demonstrated

similar improvements in LV end-systolic and end-diastolic volumes but a smaller magnitude of improvement in LVEF. Mechanisms of fMR reduction include activation at the papillary muscle insertion sites²⁵ and an increase in LV dP/dt, higher closing forces, and increased transmitral pressures during the isovolumic contraction phase of systole (Fig. 3A).^{5,9,24} Other potential contributions may stem from decreasing sphericity indices and MV annular size.²² The benefits of CRT on fMR may therefore be limited in those patients with significant scar burden, because the activation site may not be able to contribute as much to LV contractility.²⁵

CRT has thus proved to be especially beneficial in reducing fMR in the selected group of patients meeting implantation criteria regarding LVEF, QRS duration, and New York Heart Association (NYHA) functional class.²⁷ Importantly, CRT responders (as measured by decrease in fMR) demonstrate higher 1- and 2-year survival rates compared

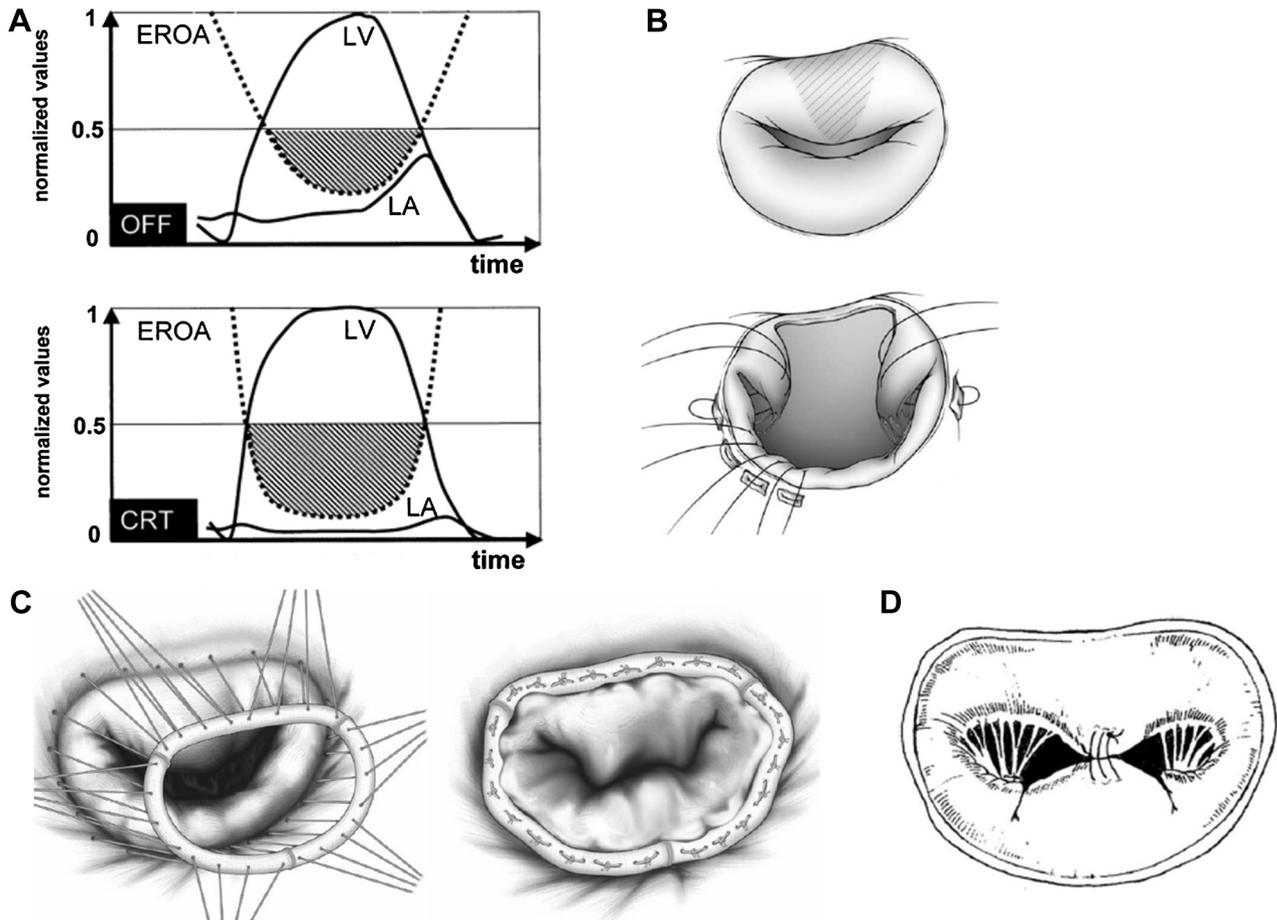


Fig. 3. Correction of fMR by CRT and MV surgery. (A) By increasing LV dP/dt, CRT promotes a faster rise in transmitral pressure (instantaneous pressure gradient between LV and LA), thus opposing the tethering forces that would keep mitral leaflets open in systole. The shaded area represents the amount of time that the effective regurgitant orifice area (EROA) remains at $< 50\%$ of its initial value. Solid lines represent chamber pressures and dashed lines represent absolute value of EROA. (Adapted with permission from Hung et al. 1999).⁸⁴ (B) MV replacement while sparing chordae and subvalvular structures. Only a small section of the anterior leaflet is resected. (Adapted with permission from Calafiore et al. 2004).⁴⁰ (C) MV repair using an undersized annuloplasty ring. (Adapted with permission from Badhwar et al. 2002).⁷⁰ (D) Edge-to-edge repair technique. (Adapted with permission from Fedak et al. 2008).⁶⁶

with nonresponders.²⁵ Whether other patients with fMR and EF <40% may benefit from CRT may be a worthwhile question to address in future CRT trials.

MV Surgery Improves Functional Status and LV Remodeling at Significant Perioperative Risk

Although MV surgical interventions include techniques for both valve repair and replacement, early literature has shown evidence of worsening LV function after MV replacement in patients with HF and MR. The proposed mechanism is correction of the “pop-off” mechanism into the left atrium from the LV.²⁸ Alternatively, some have argued that LV dysfunction after MV replacement arose from resection of the valve apparatus itself, particularly the chordae tendinae which help to support the LV’s structure and contractile function.²⁸ Both MV repair and chordal sparing techniques for MV replacement bypass this concern with preservation of LV function (Fig. 3B–D).

Our literature search protocol is detailed in Appendix 1. Surgical procedures for MV repair include annuloplasty and MV leaflet repair with techniques such as leaflet extension with the use of pericardial patches and edge-to-edge repair. In small case series²⁹ and retrospective studies,³⁰ some investigators have demonstrated lower MR recurrence rates by combining leaflet repair with annuloplasty. However, there have been no randomized trials to compare the effectiveness of different repair techniques.⁵ Recurrent MR is not an uncommon finding, but estimates vary widely, from 35% at 1 year after surgery⁵ to 50% at 5 years after surgery.³¹

Our review of the literature for surgical approaches to significant fMR (grade 3+–4+) with systolic dysfunction (preoperative EF usually 25%–35%) revealed primarily retrospective analyses of techniques including MV replacement, annuloplasty, and edge-to-edge repair.^{5,29–47} Concomitant procedures included coronary artery bypass grafting (CABG),^{29–32,34–37,40,47} tricuspid surgery,^{37,41}

maze procedure,⁴¹ and aortic surgery.⁴³ Overall at 1-year follow-up, MR is reduced from an average grade of 3+ to <1+, EF increases by 5%–10%, and NYHA functional class improves from 3 to 1.5–2. Postoperative mortality for patients with fMR remained high, at 8%–16% at 1 year, 15%–30% at 3 years, and 30%–65% at 5 years, with no clear mortality benefit of MV surgery compared with medication and CRT.⁵ Taken together, the data suggest that fMR can be reduced at a variable but substantial risk of mortality and morbidity, but without any demonstrable long-term mortality benefit over existing therapy.^{32–49}

The retrospective nature of these studies suggests that there is likely underreporting of the incidence and severity of adverse events. In our review of 15 of the most relevant surgical approaches to functional MR,^{4,30,33,35,39–41,43,44,46,47,50–53} reported events included mortality, bleeding, stroke, and renal failure. For our summary of adverse events (Tables 2 and 3), each rate was calculated based on a weighted average incorporating data from all studies that reported it. Overall, perioperative mortality was 3.4% but climbed to as high as 6% or greater in some cases of valve replacement in low EF.^{30,38,41,44,49} Bleeding requiring transfusion was reported in 40%–70% of cases, requiring reoperation in 1%–8%. Stroke rates were 2%–4% and that of renal failure almost 9% overall, although there was no clear definition of renal failure specified in any study. Importantly, in the one direct comparison of percutaneous approaches (Mitraclip) and surgery,⁵³ death, stroke, MI, need for urgent operation or blood transfusion, and renal failure occurred in only 15% of those randomized to the percutaneous approach, compared with 48% of those undergoing surgery. Taken together, the findings of our review suggest that compared with medical therapy and CRT, MV surgery is associated with high perioperative risks and unproven mortality benefit.

Several recent meta-analyses and reviews have attempted to compare effects of valve replacement versus repair on

Table 2. Summary of Adverse Events After Mitral Valve Surgery

Adverse Event	Study References	Total No. of Patients in the Studies	Total No. of Events	Adverse Event Rate	95% CI
Death at 30 days	4, 30, 33, 35, 39–41, 43, 44, 46, 47, 50–53	2,355	80	3.4%	2.7%–4.1%
Myocardial infarction	35, 39, 40, 44, 52, 53	439	6	1.4%	0.3%–2.5%
CHF/low output syndrome	4, 33, 40, 52	227	18	7.9%	4.4%–11.4%
Atrial fibrillation (new onset)	50, 53	1,273	3	24.8%	22.5%–27.2%
Unspecified arrhythmia	4, 35, 50	270	79	29.2%	23.8%–34.7%
Stroke	33, 35, 39–41, 50, 52, 53	1,786	37	3.4%	2.5%–4.2%
Prolonged ventilation or other respiratory complication	4, 35, 39–41, 52, 53	637	69	10.8%	8.4%–13.2%
Bleeding					
Transfusion	33, 35, 39, 40, 50, 52, 53	1,665	695	41.7%	39.4%–44.1%
Reoperation for bleeding	4, 39, 50	1,304	69	5.3%	4.1%–6.5%
Infection					
Deep wound infection	53	216	2	0.9%	–0.4%–2.2%
Septicemia	4, 33, 35, 41, 50, 53	1,712	74	4.3%	3.4%–5.3%
Renal failure	4, 33, 35, 39, 40, 52	487	43	8.8%	6.3%–11.3%

CI, confidence interval; CHF, chronic heart failure.

Table 3. Primary and Secondary Outcomes of Trials Investigating Surgical Approaches to fMR

Trial	Type of Analysis	Intervention Studied	Primary Outcome	P Value	Secondary Outcome	P Value
Wu et al 2005 ⁴	Retrospective comparison	Medical treatment with or without MVA	Death, LVAD, or transplantation	NS		
de Bonis et al 2005 ³⁰	Nonrandomized prospective study	MVA with or without edge-to-edge repair	Overall actuarial survival (91.4 ± 4.12% vs 90.7 ± 7.64%)	NS		
Fattouch et al 2009 ³³	Randomized trial	CABG with or without MV repair	Recurrent MR grade 3–4+ (3.7% vs 21.7%) NYHA ≥II (15.5% vs 43.7%) LVESD (37 ± 7 vs 42 ± 2) LVEDD (52 ± 2 vs 56 ± 6) LVEF (48 ± 8% vs 45 ± 5%)	.02 .002 <.01 <.01 NS	In patients with mild to moderate residual MR (0 vs 65%): • Symptom limited exercise test (7% vs 29%) • Worsening MR grade and PA pressure during exercise (0% vs 62%)	N/A
Acker et al 2006 ³⁵	Analysis of randomized subgroup	MV surgery with or without Corcap	All-cause mortality (13.5% vs 15.9%) QOL scores, 6MWT, peak VO2 LVEF LVEDV (15.5 mL lower with Corcap) LVESV (14.6 mL lower with Corcap) MR severity LV sphericity index (higher with Corcap) Freedom from major cardiac procedures	NS NS NS .043 .044 NS .003 NS		
Calafiore et al 2001 ³⁹	Retrospective comparison	MV repair vs replacement in fMR	5-year survival (83 ± 3% vs 73 ± 30%) Improvement at 5 years, by ≥1 NYHA class (76 ± 6% vs 65 ± 51%) LV volumes and EF	NS NS NS		
Calafiore et al 2004 ⁴⁰	Retrospective comparison	MV repair vs replacement in ischemic cardiomyopathy	5-year survival (75.6 ± 6.7% vs 66 ± 60.5%) NYHA I–II (79.1% vs 60%) LVEF (40 ± 06% vs 31 ± 1%) LVEDV (98 ± 82 mL vs 158 ± 87 mL) LVESV (61 ± 18 mL vs 113 ± 39 mL)	NS NS N/A N/A N/A		
Geidel et al 2008 ⁴¹	Nonrandomized prospective study	MVA in nonischemic cardiomyopathy vs isolated MVA in ischemic cardiomyopathy vs MVA with CABG	Late survival Residual MR (lowest in MVA with CABG) NYHA class (highest in MVA with CABG) LVESV/LVEDV (highest in MVA with CABG) LVEF (highest in MVA with CABG)	NS .0001 .0004 .000001, 0.000019 .00001		
Gummert et al 2003 ⁴³	Retrospective case series	MVA, with subgroup analysis of ischemic vs nonischemic cardiomyopathy	Overall actuarial 5-year survival 66 ± 6% Lower actuarial 2-year event-free survival in ischemic cardiomyopathy (62 ± 24% vs 73 ± 3%)	— <.001		
Ngaage et al 2004 ⁴⁴	Retrospective case series	MV surgery in nonischemic cardiomyopathy	5-year survival 33%	—		
Rothenburger et al 2002 ⁴⁶	Retrospective case series	MV surgery in fMR	1-year survival 91% 5-year survival 77% 1-year freedom from heart failure admission 85% NYHA class (3.3 ± 3.8 to 2.1 ± 1.7) LVEF (23.1 ± 1.6% to 36 ± 6.8%)	— — — <.01 <.02		
Shah et al 2005 ⁴⁷	Retrospective case series	MVA in organic vs functional MR	1-year survival 94 ± 4% 5-year survival 70 ± 0% 5-year freedom from reoperation, transplantation, and death (61 ± 11% vs 54 ± 4%)	— — NS		

(continued on next page)

Table 3. (Continued)

Trial	Type of Analysis	Intervention Studied	Primary Outcome	P Value	Secondary Outcome	P Value
Modi et al 2009 ⁵⁰	Prospective series	Minimally invasive MV repair or replacement	Overall operative mortality 2.1% (repair) and 4.6% (replacement)	N/A		
Szalay et al 2003 ⁵¹	Retrospective comparison	MVA in ischemic vs nonischemic cardiomyopathy	2-year actuarial survival (85% vs 93%) 1-year NYHA class (1.7 ± 7.07 vs 1.8 ± 8.2) LVEF ($32 \pm 2.2\%$ vs $34 \pm 4.7\%$)	NS NS N/A		
Calafiore et al 2004 ⁵²	Retrospective comparison	MV repair vs replacement in ischemic and nonischemic cardiomyopathy	5-year freedom from death ($81.4 \pm 4.5\%$ vs $66.7 \pm 7.1\%$) Improvement at 5 years, by ≥ 1 NYHA class ($76.6 \pm 6\%$ vs $51.9 \pm 9.6\%$)	NS NS		
Feldman et al 2011 ⁵³	Randomized controlled trial	Percutaneous MV repair vs. surgical MV intervention	1-year freedom from death (6% each), reoperation for MV dysfunction (20% vs 2%), and 3+–4+ MR (21% vs 20%; overall, 55% vs 73%) 30-day major adverse events (composite, 15% vs 48%)	.007 <.001	LVEDD (-0.1 ± 1.6 cm vs -0.0 ± 0.6 cm) LVEDD (-0.4 ± 4.5 cm vs -0.6 ± 6.6 cm) LVESV (-5.5 ± 54.5 mL vs -5.6 ± 61.0 mL) LVEDV (-25.3 ± 38.3 mL vs -40.2 ± 25.9 mL) NYHA class III–IV (2% vs 13%) 6-month QOL score Physical component (higher in percutaneous arm) Mental component 12-month QOL score	NS .04 NS .004 .002 <.001 NS NS

CABG, coronary artery bypass graft; fMR, functional mitral regurgitation; LVAD, left ventricular assist device; LVEDD, left ventricular end diastolic dimension; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic dimension; LVESV, left ventricular end systolic volume; MR, mitral regurgitation; MVA, mitral valve annuloplasty; 6MWT, 6-minute walk test; N/A, not available; NS, not significant; NYHA, New York Heart Association functional class; QOL, quality of life.

mortality and function. In their prospective study of 267 patients who underwent MV surgery, Zhao et al⁵⁴ found a slightly higher improvement in NYHA functional class at 3 and 12 months after valve repair. Of note, 45.9% of patients undergoing MV repair had EF \leq 55%, compared with 55.7% of those undergoing MV replacement. A recent meta-analysis⁵⁵ showed significantly higher short- and long-term mortality with MV replacement. But patient populations vary greatly between individual studies, and patients with greater comorbidities more often undergo valve replacement rather than repair.⁵⁶ In a randomized trial designed to evaluate the effect of valve replacement versus repair for patients with severe ischemic MR, investigators found no significant difference in LV end-systolic volume index or survival at 12 months, although recurrent MR rates were higher in those patients undergoing MV repair.⁵⁷

Surgical Ventricular Reconstruction and Isolated Revascularization Produce Mixed Outcomes in fMR

There is some debate as to whether fMR contributes to worsening baseline LV dysfunction. Some investigators argue that the LV initially compensates for the increased

volume load of fMR with eccentric hypertrophy and higher compliance and eventually decompensates with increasing LV sphericity.^{5,10} Others posit, however, that the LV dysfunction must be progressive regardless of fMR. In their animal model of ischemic MR, for example, Guy et al⁵⁸ demonstrated improved LV function and a lower degree of remodeling in animals in which they had placed an external ventricular constraint device than in those undergoing MV annuloplasty alone.

Surgical ventricular reconstruction (SVR) aims to excise myocardial scar, achieving the original elliptical shape of the ventricle and narrowing the widened base of the heart,⁵⁹ particularly in patients with anterior wall infarctions, aneurysms, or severely dilated LVs.⁶⁰ Techniques used include LV aneurysm exclusion, excision, or plication (Fig. 4A).⁵ SVR has been shown in patients with anterior wall MIs to reduce LV dimensions,^{60,61} papillary muscle width, and tenting area, thereby reducing MR despite increasing LV sphericity in the long term.^{62,63} Some investigators have shown, however, that a combined surgery for CABG and SVR had a higher operative mortality (5.7%) than CABG alone (2.6%) and produced no difference in 3-year survival

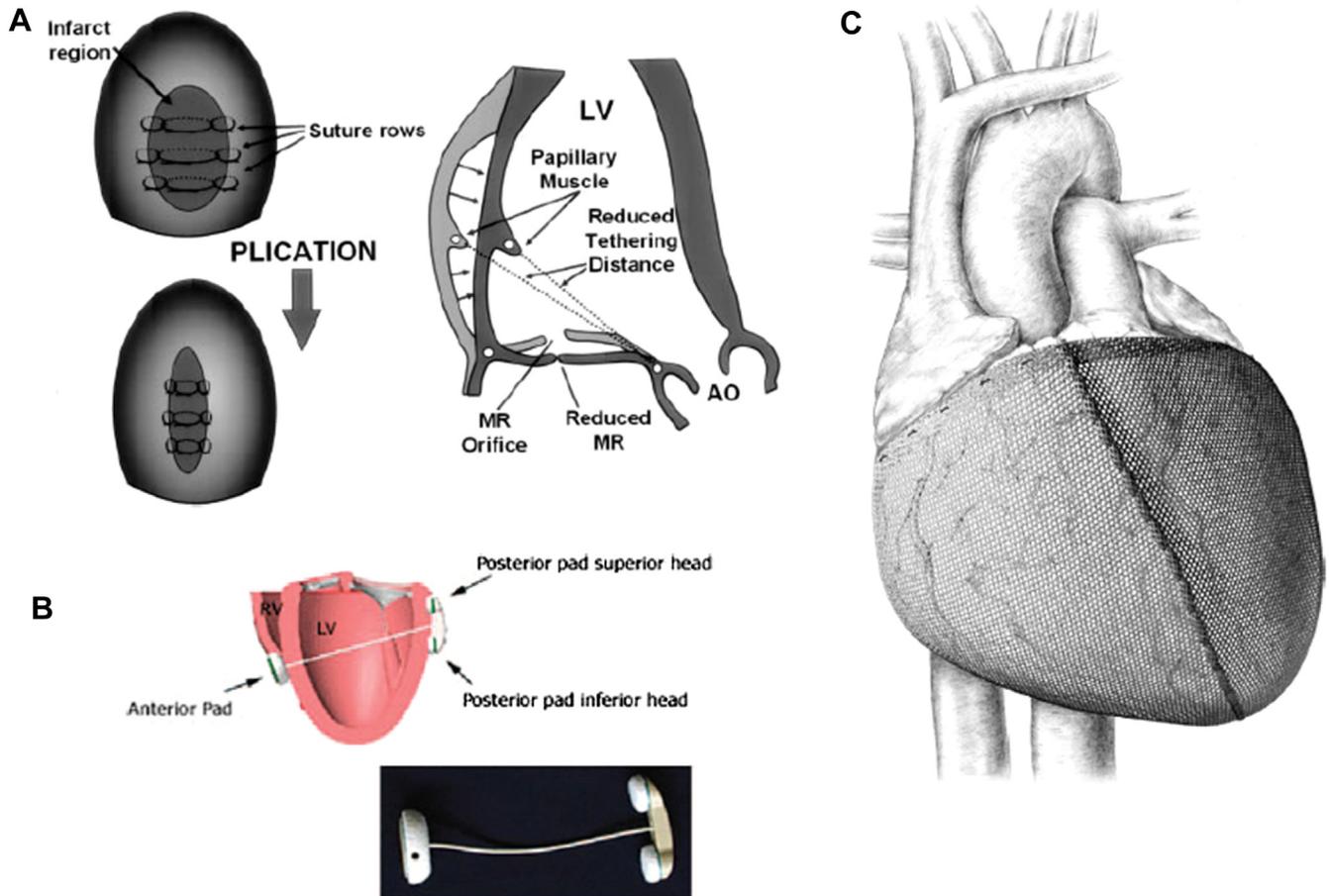


Fig. 4. Techniques for surgical ventricular reconstruction and restraint. (A) Infarct plication (adapted with permission from Liel-Cohen et al. 2000).⁸³ (B) The Coapsys device helps reverse LV remodeling and reduce fMR. (Adapted with permission from Fedak et al. 2008).⁶⁶ (C) The CorCap Cardiac Support Device helped reduce LV dimensions and improve sphericity indices. (Adapted with permission from Mann et al. 2004).⁶⁵

rates.⁶³ Although there have been no prospective studies comparing the effects of MV surgery alone with the combination procedure of valve surgery and SVR, a review of 12 papers describing valve surgery in HF patients found that the combination procedure allowed for more consistent reduction in fMR.⁵

With the underlying LV dysfunction as the target, some investigators argue that revascularization alone can reverse LV remodeling in ischemic cardiomyopathy and thus correct moderate fMR.⁶⁴ In their retrospective study of 107 patients with CAD and fMR, Kang et al³² found that postoperative MR was significantly reduced in 93% of patients undergoing CABG with MV ring annuloplasty, compared with 66% of those who underwent isolated CABG. However, operative mortality was higher for the combined procedure (12% vs 2%; $P = .03$), and there was no difference in the 5-year actuarial survival rate. With older age and atrial fibrillation identified as predictors of operative mortality, the authors suggested that MV repair in these populations with moderate fMR should be avoided. Conversely, in a small randomized trial of CABG alone ($n = 54$) versus CABG with MV repair (annuloplasty; $n = 48$), Fattouch et al³³ demonstrated significantly lower operative mortality rates (1.8% vs 4.1%, respectively; P values not provided) with significant improvements in NYHA functional class, LV dimensions, and pulmonary arterial pressures for those patients undergoing the combined procedure. Importantly, only 40% of patients undergoing isolated CABG showed improvement in postoperative MR, whereas none of the patients in the combined surgery arm had recurrent MR of $>1+$. Interestingly, in their retrospective study of 390 patients with $3+–4+$ ischemic MR, Mihaljevic et al³⁴ found no difference in long-term postoperative functional status or mortality between patients undergoing CABG or CABG with MV ring annuloplasty.

Given the lack of clear randomized trials to assess the best surgical approach to moderate ischemic MR, the Cardiothoracic Surgical Trials Network is currently enrolling patients with ischemic MR into a randomized trial comparing strategies of CABG and MV repair with CABG alone. Follow-up is intended for 2 years after randomization, and the primary end point is change in LV end-systolic volume index. Secondary end points include effects on MR severity, functional status, and mortality.⁶⁵

Ventricular Restraint Combined With MV Surgery Improves Survival and Reverses LV Remodeling

Investigators have considered combined surgical procedures to address both the MV annular dilatation and underlying ventricular dysfunction that lead to fMR.⁶⁶ The Coapsys device (Fig. 4B), for example, includes posterior and anterior pads on the epicardial surface of the LV that are connected via a transventricular splint. Implanted without cardiopulmonary bypass, the device can be tightened to reduce papillary muscle and annular width.⁶⁷ In their prospective study of 165 patients with MR and

CAD, Grossi et al⁶⁸ randomized patients to CABG with or without MV repair, and each arm to then control or treatment with Coapsys. Both treatment and control arms showed significant reverse remodeling and reduced MR grade at 2 years, but patients treated with the Coapsys device had significantly higher 2-year survival rates (87%) compared with control (77%). The trial was terminated prematurely because of lack of funding.

Another example is the Corcap Cardiac Support Device (Fig. 4C), a fabric mesh that is positioned around the heart and passively reduces LV wall stress.⁶⁶ In a randomized trial, investigators randomized patients with HF and MR to MV surgery with or without the Corcap device.⁶⁶ With median follow-up of 22.9 months, all patients who underwent MV surgery had reduced LV dimensions and increased LVEF and sphericity indices.³⁵ Those who had the Corcap implanted had higher improvements in these indices.³⁵

Should We Consider Percutaneous MV Interventions?

Surgical interventions on the MV, LV, or both have thus been shown to improve fMR and LV remodeling but not mortality, and they are accompanied by high perioperative risk. Their uncertain benefits provide more impetus to consider less invasive percutaneous devices that may repair the MV but with fewer adverse perioperative outcomes such as bleeding, stroke, renal failure, and MI.⁶⁹ Furthermore, earlier outcome measures of efficacy, such as functional capacity and LV dimensions, may prove to be complementary to traditional end points such as mortality in applying percutaneous approaches to target fMR in the lower-EF cohort.^{69,70}

At present, percutaneous devices target only repair of the MV, not correction of LV remodeling. Surgical literature shows that isolated MV repair for fMR helps to reverse LV remodeling but does not significantly improve mortality rates, which range as high as $62 \pm 2\%$ at 5 years.^{2,12,18} Badhwar et al,⁷¹ for example, conducted a prospective study of 150 patients with dilated cardiomyopathy (EF 8%–24%) who underwent MV annuloplasty and found improvements in EF, LV dimensions and sphericity, cardiac output, and RV at 2 years. Actuarial survival rates at 1, 2, and 5 years were 82%, 71%, and 57%, respectively. In their retrospective analysis of 54 patients with dilated cardiomyopathy and severe MR undergoing MV repair, Bonis et al⁷² found an actuarial survival of $69 \pm 9.8\%$ at 6.5 years, along with freedom from significant MR ($\geq 3+$) of $89.1 \pm 1.7\%$. Mean EF increased and LV dimensions decreased at follow-up.

Working from mostly single-center retrospective studies^{5,9} and patient populations that vary widely in demographics,^{5–8} comorbidities, and even definitions of MR severity,¹⁴ ACC/AHA¹³ and ESC³ guidelines regarding isolated valve surgery for fMR suggest only that MV surgery may be considered in patients with EF $<30\%$ with

symptoms refractory to medical therapy and CRT. Factors arguing against surgical approaches to fMR could include the higher operative mortality compared with organic MV disease, high recurrence rates after repair, and the lack of demonstrable survival benefit.^{3,4,45}

Edge-to-Edge Repair (Mitraclip) Corrects fMR With Significantly Lower Periprocedural Risk

The Mitraclip (Fig. 5A) creates a double orifice by bringing together the free edge of the anterior and posterior leaflets.⁶⁹ Deployment immediately increases cardiac output and stroke volume while decreasing LV end-diastolic pressure.^{73,74} After device deployment, end-diastolic wall stress decreases, although to a greater extent in patients with organic MR compared with fMR,⁷⁴ and end-systolic wall stress (corresponding to LV afterload) increases in both groups. Patients with fMR (ie, with low EF) comprised only 21% and 27%, respectively, of the first prospective cohort study (EVEREST I)⁷⁵ and randomized trial (EVEREST II)⁵³ involving the Mitraclip. However, Maisano et al's⁷⁶ subsequent review of registry patient selection

found that the majority of patients in whom the Mitraclip was being deployed suffered from fMR.

In EVEREST I, the investigators successfully implanted the Mitraclip in 79 of 107 patients. Feldman et al⁷⁵ demonstrated MR reduction to at most 2+ grade in 74% of patients, and 66% were free of recurrent MR of $\geq 2+$, death, and need for surgical intervention at 12 months. Importantly, only 21% of the patients had fMR, although there was no difference in outcomes compared with those with degenerative MR. Adverse events included partial detachment of the device and recurrent MR in 9%, bleeding complications (4.6%), 1 prolonged mechanical ventilation, 1 periprocedural stroke, and 1 post-procedural death. One patient required a second MV surgical repair after inadequate percutaneous repair and failure of the first surgical repair.

In the trial comparing Mitraclip with MV repair or replacement (EVEREST II),⁵³ 279 patients with $\geq 3+$ MR were randomized 2:1. Patients with fMR comprised 27% of the study population. Fifty-five percent of patients undergoing percutaneous repair were free from death, repeated valve surgery, and recurrent significant MR

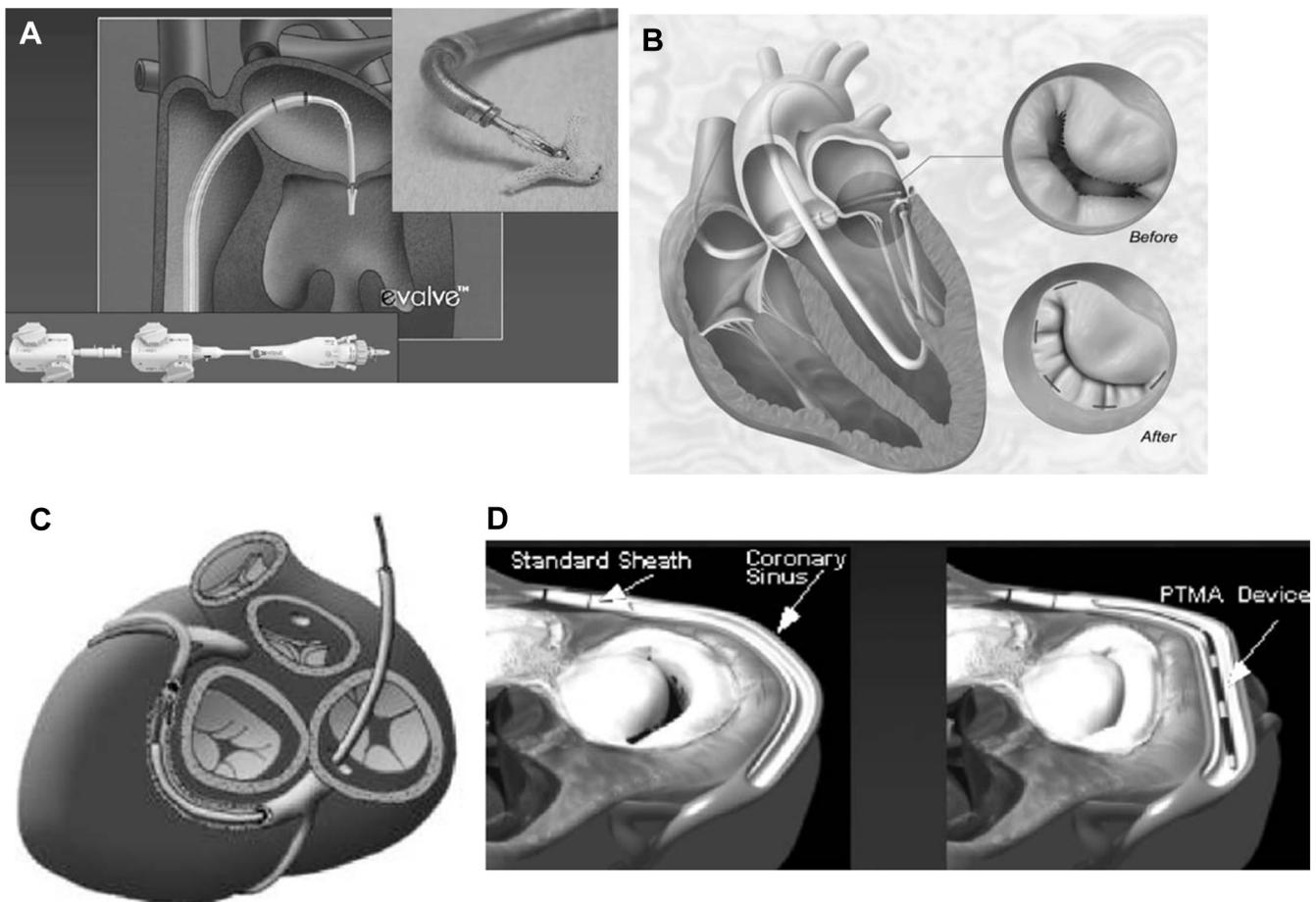


Fig. 5. Percutaneous techniques for correction of fMR. (A) The MitraClip grasps both anterior and posterior leaflet edges, creating a double orifice and reducing mitral regurgitation. (B) The expandable stents of the MONARC device are positioned in the great cardiac vein and coronary sinus ostium and help remodel the septal-lateral dimension of the mitral annulus. (C) Magnets in the CARILLON device are positioned in the coronary sinus and behind the posterior mitral valve leaflet to guide anchors that remodel the mitral valve annulus. (D) The Viacor system displaces the posterior mitral annulus by using tensioning nitinol rods. Adapted with permission from Mack 2006.⁶⁸

($\geq 3+$) at 12 months, compared with 73% of patients undergoing MV surgery ($P = .007$). LV dimensions and EF improved in both groups, but to a significantly greater extent in patients undergoing surgical correction. Furthermore, in the intention-to-treat population, only 3% of patients had persistent MR of $\geq 3+$ after surgical intervention, compared with 19% after the Mitraclip (P values not available). Importantly, the primary safety end point of death, stroke, MI, need for urgent operation or blood transfusion, and renal failure occurred in only 15% of those randomized to the percutaneous approach, compared with 48% of those undergoing surgery ($P < .001$).⁵³ The difference was driven primarily by higher likelihood of blood transfusions with surgery.

Interestingly, specific comparisons between the degenerative and fMR patients in EVEREST II⁵³ have shown that fMR patients are sicker, with higher frequencies of CAD, MI, atrial fibrillation, and cerebrovascular disease.⁷⁷ Although the Mitraclip produced similar reductions in MR, improvements in NYHA functional class, and LV reverse remodeling with no difference in major AEs at 30 days, 1- and 2-year mortality rates were much higher in patients with fMR (7.9% and 22.1%, respectively) compared with patients with organic MV disease (1% and 2.1%, respectively). Nonsurgical high-risk candidates who underwent Mitraclip implantation experienced significant improvements in NYHA functional class, chronic HF admissions, and LV reverse remodeling, but there were notable complications.⁷⁷ Almost 21% suffered death, stroke, MI, renal failure, or prolonged mechanical ventilation at 30 days. Residual MR of $> 2+$ was found in 18% at 1 year.

Two other smaller studies focusing on fMR patients (NYHA functional class III and IV, mean EF $27.1 \pm 1.7\%$ and $19 \pm 9\%$, respectively) found improvements in NYHA functional class and LV reverse remodeling, with 30-day mortality ranging from 4.2% to 6%^{78,79} and a cumulative survival of 81% at 6 months.⁷⁹ This compares favorably with a 3-year mortality rate ranging from 35% to 70% in NYHA functional class III patients who are CRT “non-responders”⁷⁸ and a 1-year mortality rate of 75% in NYHA functional class IV patients on optimal medical therapy.⁸⁰ The COAPT trial (Clinical Outcome Assessment of the Mitraclip Percutaneous Therapy for Patients at High Surgical Risk) will specifically address the question of whether the percutaneous approach in a high-risk patient population with LV dysfunction and fMR performs better than standard of care therapy. Nevertheless, given its high mortality and morbidity, it is not clear whether this intervention should be used in a patient population for whom mechanical circulatory support or heart transplantation can provide far better outcomes.

There Have Been No Direct Comparisons of Coronary Sinus Cinching Devices With Surgery

Alternative percutaneous devices have focused on the mitral annulus instead of the leaflets. Coronary sinus (CS) cinching devices can help remodel the posterior mitral

annulus in particular.^{67,69} Some investigators estimate that up to 70% of patients may have anatomy favorable for the deployment of such devices—ie, a short enough distance between the CS and the posterior mitral annulus.⁶⁹ However, the various prospective studies for each device have used various efficacy end points to assess fMR severity and different safety endpoints.

The Monarc device (Fig. 5B) decreases the septal-lateral dimension of the mitral annulus over 3–4 weeks after implantation. Its 2 ends are positioned in the great cardiac vein and the CS ostium.⁶⁹ In a feasibility study, it was safely implanted in 59 of 72 patients (patients with CRT were excluded), but the procedure was complicated by compression of the obtuse marginal artery in 15 patients and MIs in 2 patients.⁸¹ The primary safety end point was freedom from death, tamponade, and MI, and 91% of patients met this at 30 days. Only 22 matched echocardiograms were performed at 1 year, and 50% of them demonstrated ≥ 1 grade reduction in MR. The study was not powered to assess changes in LV dimensions or EF.⁸¹

The Carillon device (Fig. 5C) uses magnets in the CS and behind the posterior MV leaflet to help guide anchors across the annulus into the left atrium. The device uses these anchors to reduce the posterior annular diameter by 2–3 cm and the septal-lateral diameter by 0.5–1.0 cm.⁶⁷ In the first feasibility trial, the device was successfully implanted in 30 of 48 patients,⁸² with a 13% major AE rate at 30 days, including death, MI, CS dissection or perforation, device embolization, and surgery or PCI. At 6 months, quantitative parameters of fMR (including regurgitant jet area/left atrial area, vena contracta, ERO, and RV) demonstrated decreases of 32%, 25%, 32%, and 31%, respectively, but there were no significant changes in LV dimensions.

Nitinol rods in the Viacor PTMA (percutaneous transvenous mitral annuloplasty) system (Fig. 5D) apply incremental stiffness to the posterior mitral annulus to reduce the septal-lateral diameter with the use of real-time echocardiography to assess fMR.⁶⁹ In their feasibility study of 19 patients, Sack et al⁸³ found that the PTMA device reduced fMR severity grade from 3.2 ± 2.6 to 2.0 ± 0.0 in 13 patients with a mean reduction of 4.0 ± 0.2 mm in the septal-lateral diameter. No major AEs were noted.

Summary

Functional MR is a marker of poor clinical outcomes, including death and hospitalizations, in patients with HF. Standard medical regimens specifically target HF (including beta-blockers, ACE inhibitors, and perhaps hydralazine, nitrates, and diuretics) but also help with reducing afterload and preload in fMR. CRT can provide significant reductions in fMR, but not all HF patients are candidates, and of potential candidates, not all respond to therapy. MV surgery significantly reduces or eliminates fMR, reduces LV dimensions, and improves symptoms, but it is also associated with periprocedural complications, such as mortality, bleeding, stroke, and renal dysfunction,

Table 4. Summary of Treatment Strategies for fMR

Technique	Benefits Beyond Reducing fMR Severity	Limitations	Target Patients
Medications		Limited in patients with hypotension, poor renal function Do not lower filling pressures	All patients with fMR
Vasodilators (hydralazine, ACE inhibitors)			
Diuretics, nitrates	Promote reverse remodeling		
Beta-blockers	Promote reverse remodeling		
CRT	Promotes reverse remodeling	Potentially limited utility if significant scar burden	Currently only indicated if EF <40%, QRS >120 ms, and NYHA >II
MV surgery			
MV repair	Improves LVEF Improves NYHA class.	No clear long-term mortality benefit compared with medication and CRT. Significant perioperative morbidity. Recurrent MR is common.	Patients with severe fMR who require concomitant CABG or other valve surgery
Chordal-sparing MV replacement	Definitively addresses fMR.	No randomized trial to compare outcomes of repair vs replacement.	
Surgical treatment of LV			
Ventricular reconstruction or restraint	Reduce LV dimensions and MV tenting area. More consistent fMR reduction if combined with MV surgery.		Patients who require concomitant CABG or other valve surgery
Isolated revascularization		Unclear (in moderate fMR) if any incremental benefit of combining with MV surgery	Patients with moderate fMR
Heart transplant/ventricular assist device	Improved long-term survival for transplant candidates		Patients with severe LV dysfunction, minimal viability, or poor revascularization targets
Percutaneous approach			
Mitraclip	Improves cardiac output and stroke volume. Decreases LV filling pressures. Improves NYHA class. Compared with MV surgery, lower rates of periprocedural adverse outcomes (see Table 1)	Higher rates of persistent MR after deployment compared with MV surgery. No randomized trial focusing only on fMR patients. In high-risk fMR cohort, no randomized trial comparing outcomes with medical therapy.	Patients with severe fMR and EF <30%
CS cinching		No evidence of LV reverse remodeling. So far only feasibility studies have been published	

ACE, angiotensin-converting enzyme; other abbreviations as in [Tables 2](#) and [3](#).

and provides no clear long-term mortality benefit. Areas of uncertainty regarding MV surgery include the relative benefits and risks of MV repair versus replacement, and whether isolated MV surgery should be recommended for moderate fMR.

Current ACC/AHA and ESC guidelines do not provide clear recommendations for optimal therapy of fMR in the low-EF population (Table 1). In particular, the question remains whether this high-risk group would be ultimately better served, if possible, with options such as mechanical circulatory support and heart transplantation.

Percutaneous approaches to fMR represent a novel strategy that may minimize periprocedural risk while improving functional status and LV reverse remodeling. Two main areas of investigation include the Mitraclip and CS cinching devices. Mitraclip is the only device that has been compared with MV surgery in a randomized trial, successfully treating 72% of patients at 12 months, compared with 88% of patients for surgery. Of these patients, only 27% had LVEF <60%, and all had to have LVEF >25% and LV end-systolic dimension <55 mm. Notably, 15% of patients in the percutaneous arm suffered an adverse outcome, compared with 48% in the surgical arm.

Importantly, there are as yet no completed randomized control trials specifically targeting the fMR population that compare the effects of the Mitraclip with surgical intervention, nor, in patients deemed to be too high risk for surgery, comparing Mitraclip intervention and medical therapy with or without CRT. Although only 27% of enrolled patients had fMR, large numbers of fMR patients have received the device, as reported in subsequent registry studies. In such selected patients, although perioperative and 1-year mortalities remain high, the Mitraclip has been shown to significantly improve LV dimensions, EF, and NYHA functional status. It remains to be seen whether the Mitraclip is feasible in patients with LVEF <25% and more dilated LV.

Taken together, the findings of this review suggest a stepwise escalation of treatment in symptomatic patients with fMR that is refractory to medical therapy and CRT (Table 4). With the overarching goal of improving functional status and LV remodeling in a population already at high mortality risk from underlying LV dysfunction, the decision for surgical versus percutaneous treatment depends on appropriate risk stratification and the need for concomitant surgeries such as CABG or other valve interventions. As with the current trials in the Cardiothoracic Surgical Trials Network, this treatment paradigm using percutaneous MV interventions will need to be validated through randomized trials that specifically focus on patients with fMR.

Disclosures

L.C. is Vice President for Clinical Affairs at Guidant Delivery Systems, which is currently developing devices for percutaneous intervention in fMR.

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Appendix 1

Literature Search Methods and Selection Criteria

A series of literature searches were performed of Pubmed (<http://www.ncbi.nlm.nih.gov/pubmed>) to identify published literature related to the topic of fMR and the efficacy and risks of available treatments. If the search term “mitral regurgitation” is entered into Pubmed, there are 25,084 hits. Therefore, it is necessary to impose limits to arrive at the most relevant references.

Search Terms

Searches were performed with the following sets of search terms:

1. Functional Mitral Regurgitation.
2. Mitral Regurgitation AND Percutaneous.
3. Heart Failure AND Functional Mitral Regurgitation.

Limits

For each of these searches, the following limits were placed:

- Species: Humans.
- Types of reports: Clinical Trial or Meta-analysis or Randomized Controlled Trial or Review.
- Language: English.

- Other: Has an abstract.
- Dates: Published within 10 years.

In addition, we specifically searched for guidelines for treatment of fMR provided by the AHA, ACC, and ESC.

Finally, we also reviewed information in *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*, 9th Edition (2011), which is the most recently published and thorough textbook of cardiology.

Literature Findings

The number of papers identified for each of the search terms and search limits listed above were as follows:

1. Functional Mitral Regurgitation: 216.
2. Mitral Regurgitation AND Percutaneous: 143.
3. Heart Failure AND Functional Mitral Regurgitation: 111.