ASK THE EXPERTS

What Is the Role of Mitral Repair in Heart Failure?

Experts discuss treatment strategies for patients with mitral regurgitation progressing to heart failure.

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Congestive heart failure (CHF) is one of the leading causes of cardiovascular hospitalizations and mortality. In the United States alone, there are more than 5.8 million patients affected and more than 23 million patients worldwide.[1] This highly morbid condition carries a grim prognosis, with survival estimates of 50% at 5 years and 10% at 10 years.[1] Among the many complications of end-stage cardiomyopathy is functional mitral regurgitation (FMR), which affects nearly all heart failure patients to some degree and, once it presents, has a mean survival of 12 months.[2]

The pathophysiology of nonischemic MR is hypothesized to be due to progressive annular dilation from ventricular remodeling, leading to a spiral of volume overload, ventricular dilation, and further annular dilation. In FMR, this is caused by malcoaptation from progressive dilation and is a fundamental difference from ischemic MR.

Historically, patients with CHF were medically managed with aggressive diuresis and with surgery and mitral valve replacement (MVR), when deemed appropriate. However, both medical management and MVR carry poor long-term survival, and our current standard of care has shifted to mitral valve repair in those who continue to have symptoms and severe MR despite medical therapy. A durable repair with an undersized annuloplasty ring can be performed with low perioperative mortality and low rate of recurrence.[3] Furthermore, repair in the hands of a high-volume center shows improved ejection fraction, cardiac output, and end-diastolic volumes.[3] Yet, perhaps most importantly, is the large body of data supporting symptomatic improvement after mitral valve repair.

Despite this, many patients with CHF do not undergo interventions because of the perceived high perioperative mortality and lack of long-term benefits for survival and ventricular remodeling. Be that as it may, mitral valve surgery has been proven safe in patients with heart failure, carries a low rate of MR recurrence, and some

data would suggest benefits for long-term left ventricular (LV) structure and function.[4]

However, the many accompanying comorbidities can preclude surgery in many patients with heart failure. If the patient is not deemed a surgical candidate, other percutaneous means of correcting MR exist—all aimed at mimicking the fundamental principles of surgical correction. Within percutaneous approaches, the aim is to correct annular dilation or help directly remodel the left ventricle. One such option is MitraClip (Abbott Vascular), which creates a competent double-orifice valve and can be implanted in the catheterization laboratory. Other novel devices include VenTouch (Mardil Medical, Inc.) and the NeoChord system (NeoChord, Inc.), the latter of which is a transapical, beating heart approach to restore valvular competency. Regardless of the repair technique, the goal is to reduce the volume overload to the ventricle and thus reduce ventricular size.

CHF places an extreme burden on patients, providers, and the health care system and can portend a poor prognosis when MR presents. Therefore, surgical mitral valve repair should play a key role in the treatment strategy, with the goal being symptomatic relief and prevention of further LV dysfunction. When surgery is risk-prohibitive, we recommend consultation at a multidisciplinary structural heart center for consideration of minimally invasive and percutaneous techniques to repair the mitral valve apparatus.

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Secondary or FMR increases left atrial pressure, diminishes LV stroke volume, adds volume overload to a compromised left ventricle, and is associated with diminished survival. Surgical repair or replacement of the secondarily regurgitant mitral valve is associated with improved quality of life but does not improve survival and may be associated with a precipitous decline in LV systolic function.[1] The failing and dilated ventricle causing FMR may not tolerate surgery as well as the usually intact ventricle affected by degenerative MR (DMR). Surgical mitral repair is less effective and durable in the setting of FMR than DMR,[2] leaving residual MR similar to what was observed with MitraClip in the EVEREST II trial.[3] Finally, surgery may increase the complexity and risk of subsequent LV assist device or transplant surgeries. Although surgical mitral repair and replacement are important adjuncts to bypass surgery among patients with coronary artery disease, heart failure, and FMR, patients with FMR represent a small fraction of the patients undergoing stand-alone mitral surgery today, leaving a large unmet clinical need.

Transcatheter mitral valve repair and replacement aim to be the first-line therapy for patients with heart failure exacerbated by FMR. Nonrandomized observational studies suggest that successful MitraClip repair in FMR is associated with improved walking distance, reduced heart failure hospitalization, improved quality of life, and reduced LV systolic and diastolic volumes.[4,5] The COAPT, RESHAPE-HF, and MITRA-FR trials will test these observations in a rigorous, prospective, randomized fashion (Table 1). Although mortality is a secondary endpoint in these trials, bedside observations of marked clinical benefit after MitraClip in many patients fuels optimism that MitraClip may also be associated with improved survival among patients with FMR (Table 2).

Enthusiasm for the MitraClip FMR trials must be tempered with realistic expectations. Investigators have learned much during these trials. Because transcatheter mitral valve repair is an invasive procedure, presumably with risks beyond those of medications, a conservative approach was selected for these early trials, limiting enrollment to those who failed to respond to coronary revascularization, aggressive guideline-directed medical therapy, and, if indicated, biventricular pacing. The remaining nonresponders qualifying for enrollment were often quite ill, perhaps beyond the reach of MitraClip to sufficiently impact primary clinical outcomes. MitraClip therapy was a relatively new procedure for many implanting physicians, but they continue to gain experience over time with ever-improving outcomes. The next-generation MitraClip NT (Abbott Vascular) and

TABLE 1. FMR RANDOMIZED TRIALS			
	COAPT	**MITRA-FR**	**RESHAPE-HF2**
No. of patients	555 at 85 sites in North America	288 at 22 sites	380 at 50 European sites
Control arm	GDMT ± CRT	GDMT ± CRT	GDMT ± CRT
FMR grade	≥ 3+ (EROA ≥ 30 mm^2 and/or Rvol > 45 mL by ECL)	Severe (EROA > 20 mm^2 + Rvol > 30 mL by ECL)	≥ 3+ (EROA ≥ 30 mm^2 and/or Rvol > 45 mL by ECL)
NYHA class	II, III, or ambulatory IV	II–IV	III or ambulatory IV
Other inclusion criteria	HF hospitalization within 12 mo or BNP ≥ 300 pg/mL or NT-proBNP ≥ 1,500 pg/mL within 12 mo; MV surgery not local SOC	HF hospitalization within 12 mo; not eligible for MV surgery	HF hospitalization < 12 mo or BNP ≥ 350 pg/mL or NT-proBNP ≥ 1,400 pg/mL < 90 days; ineligible for MV surgery
LVEF	≥ 20%–50%	≥ 15%–40%	≥ 15%–40%
LV volumes	LVESD ≤ 70 mm	–	LVEDD ≥ 55 mm
Efficacy endpoint	HF hospitalization 12 mo	Death or HF hospitalization at 12 mo	Death or HF hospitalization 12 mo
Safety endpoint	SLDA, device embolizations, endocarditis/mitral stenosis/device-related complications requiring nonelective cardiovascular surgery, LVAD, OHT	–	All-cause mortality, stroke, myocardial infarction, new renal replacement therapy, nonelective cardiovascular surgery for device-related complications
Duration of follow-up	5 y	2 y	1 y

Abbreviations: BNP, B-type natriuretic peptide; CRT, cardiac resynchronization therapy; ECL, echocardiographic core laboratory; EROA, effective regurgitant orifice area; FMR, functional mitral regurgitation; GDMT, guideline-directed medical therapy; HF, heart failure; LVAD, left ventricular assist device; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MV, mitral valve; NT-proBNP, N-terminal B-type natriuretic peptide; NYHA, New York Heart Association; OHT, orthotopic heart transplantation; Rvol, regurgitant volume; SLDA, single leaflet device attachment; SOC, standard of care.

TABLE 2. PRIMARY ENDPOINTS FOR MITRAL REPAIR TRIALS		
Trial	**Follow-Up**	**Primary Endpoint**
Cardioband Repair Registry	1 mo	Reduction in severity of MR
REDUCE FMR	1 y	Change in regurgitant volume
Carillon United States IDE	1 y	Composite of mortality, HF hospitalizations, 6MWT, and regurgitant volume
COAPT	1 y	Recurrent HF hospitalizations
MITRA-FR	1 y	All-cause mortality and unplanned HF hospitalizations
MATTERHORN	1 y	Composite of death, HF rehospitalization, reintervention, assist device implantation, and stroke
RESHAPE-HF2	1 y	Composite of recurrent HF hospitalizations and cardiovascular death
EVOLVE-HF	6 mo	6MWT
MITRA-CRT	1 y	Freedom from stroke, device embolization, emergent surgery/pericardiocentesis or procedural mortality, 6MWT, no readmissions for HF, transplantation, or mortality

Abbreviations: 6MWT, 6-minute walk test; FMR, functional mitral regurgitation; HF, heart failure; IDE, investigational device exemption.

Pascal (Edwards Lifesciences) devices are now undergoing clinical investigation (Figure 1).

The FMR MitraClip trials will evaluate MitraClip use as a strategy, but not necessarily as the only or best strategy. Additional devices, such as the Cardioband (Edwards Lifesciences) and Carillon (Cardiac Dimensions, Inc.) devices aim to diminish FMR through transcatheter mitral annular reduction and may be used either alone or in conjunction with leaflet approximation to optimally repair the mitral valve

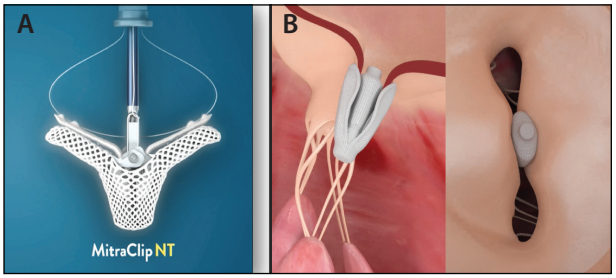

Figure 1. The MitraClip NT (A) and Pascal (B) devices.

(Figure 2). Numerous transcatheter mitral replacement valves are being developed and clinically tested at this time.

FMR is a disease of the ventricle complicated by distortion and malfunction of the mitral valve. An ever-growing list of medical, surgical, and transcatheter therapies are dramatically improving and extending the lives of our heart failure and FMR patients. Such patients are best cared for by teams of heart failure physicians, imaging experts, electrophysiologists, cardiovascular surgeons, and interventional cardiologists in a comprehensive valve program with committed expertise in all aspects of their care.[6]

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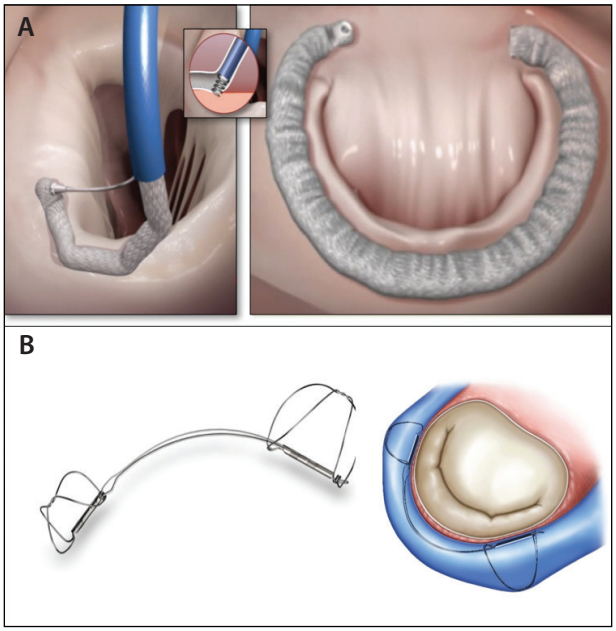

Figure 2. The Cardioband (A) and Carillon (B) devices.

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The mitral valve is the most complex cardiac valve with a large orifice area that maintains competency at higher pressures than any other valve in the heart. The unique design of the annulus, leaflets, and subvalvular apparatus allows the valve to function in synchrony with atrial and ventricular contractions. The function and geometry of the left atrium and LV play an integral part in the effective functioning of the mitral valve. MR can result from primary mitral valve structural pathologies or due to secondary problems of structural and functional abnormalities of the left atrium and LV.

The management of severe primary or DMR focuses on addressing the defective valve in symptomatic patients or asymptomatic patients with LV dilation (LV end-systolic diameter > 40 mm) or systolic dysfunction (LV ejection fraction [LVEF] ≤ 60%) (class I indication).[1] Mitral valve repair is generally preferred to MVR in primary MR when possible. For patients who are at high/prohibitive risk for surgery, percutaneous mitral valve repair with MitraClip has emerged as an accepted management strategy.

The EVEREST II trial enrolled low- to moderate-risk patients with severe DMR and demonstrated that mitral valve surgery was associated with lower rates of residual ≥ 3+ MR (0% vs 19%) at 1 year with similar mortality at 2 years (11%) compared to MitraClip.[2] This study also established the safety of MitraClip for patients with severe DMR, with lower rates of bleeding requiring > 2 units of packed red blood cells (13% vs 45%; *P* < .001) or any major adverse event (15% vs 48%; *P* < .001) compared to surgery. A retrospective review of the registries involving high/prohibitive-risk patients, EVEREST HRR and REALISM, identified a subset of prohibitive-risk DMR patients (N = 127) and further supported the safety and efficacy of MitraClip in this patient population, with a 73% reduction in hospitalization after the MitraClip procedure and positive LV remodeling at 1 year.[3] Based on these data and the lack of effective medical therapies for DMR, the US Food and Drug Administration approved MitraClip for symptomatic severe DMR in patients at prohibitive surgical risk (class IIb indication).[1] Thus, for DMR, the majority of patients have a defined treatment pathway.

Secondary or FMR is caused by LV dysfunction, including alterations in LV geometry around the mitral valve annulus, changes in the orientation of the papillary muscle and mitral valve annulus, and reduced mitral valve closure forces resulting in failure of leaflet coaptation. FMR confers a worse prognosis than DMR, as outcomes are often driven by the underlying LV dysfunction. The management of severe FMR is complex due to the heterogeneity of the causes and anatomic considerations that result in valvular incompetence. Guideline-directed medical therapy for LV dysfunction is a cornerstone of treatment of FMR. Cardiac resynchronization therapy has been shown to improve MR and should be pursued in patients who meet guideline-based indications for cardiac resynchronization therapy.[4] For patients with severe FMR and nonischemic cardiomyopathy, data to guide management are scarce. Although the ACORN trial was the first to suggest the safety of mitral valve surgery in this patient population, a dedicated trial to address the safety and efficacy of mitral valve surgery in patients with nonischemic cardiomyopathy (SMMART-HF) was aborted due to a lack of enrollment.[5] Acknowledging the absence of clinical trial data, American Heart Association (AHA)/American College of Cardiology (ACC) guidelines recommend that surgery be considered for chronic severe FMR in patients undergoing coronary artery bypass grafting or aortic valve surgery (class IIa) or those with persistent symptoms despite guideline-directed medical therapy (class IIb).

MR in the setting of ischemic cardiomyopathy has been studied more extensively. Chordal-sparing MVR is preferred to mitral valve repair in patients with symptomatic, chronic, severe ischemic MR due to a lower incidence of recurrent MR at 2-year follow-up (58.8% vs 3.8%; *P* < .001) (class IIa).[1,6,7] In the EVEREST II trial, FMR patients had similar outcomes in the composite endpoint of freedom from death, MV surgery, reoperation, or residual ≥ 2+ MR in both surgical and MitraClip groups at 1 and 4 years.[2]

Multiple European and North American registries have since shown high procedural success rates, low in-hospital mortality, and significant improvements in LV dimensions and New York Heart Association (NYHA) functional class in high/prohibitive-surgical-risk patients who received the MitraClip.[8-10] Three large randomized controlled trials—COAPT (United States and Canada), RESHAPE-HF (European Union), and MITRA-FR (France)—are currently underway to evaluate MitraClip versus guideline-directed medical therapy in patients with ≥ 3+ secondary MR and NYHA II–IV symptoms and depressed LVEF at prohibitive surgical risk. COAPT and MITRA-FR have finished enrolling patients, with results expected in late 2018.

Numerous other percutaneous mitral valve repair devices with initial safety and efficacy data such as the Cardioband, Carillon, and Mitralign (Mitralign, Inc.) annuloplasty systems are likely to begin enrollment in pivotal clinical trials in the near future. The expansion of transcatheter MVR experience also shows promise for several systems, including the Tendyne (Abbott Vascular), CardiAQ (Edwards Lifesciences), Caisson (LivaNova plc), Intrepid (Medtronic), and NaviGate (NaviGate Cardiac Structures, Inc.). Owing to the anatomic and etiologic heterogeneity inherent to MR, especially in FMR patients, it is unlikely a "one size fits all" approach will be successful, but as interventionalists, this is a very exciting time with numerous emerging technologies vying to be added to the armamentarium for managing this expanding high-risk patient population with limited options.

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Treatment of MR in the presence of LV dysfunction depends on whether the mitral valve etiology is degenerative versus functional. According to both ACC/AHA and European Society of Cardiology (ESC) guidelines, it is a class I indication to repair severe DMR in the presence of LV dysfunction. Per current guidelines, transcatheter mitral repair would be reserved for patients with DMR who are at high surgical risk.

The tougher question is regarding the role of surgical or transcatheter repair in patients with severe FMR due to LV dysfunction. Per the ACC/AHA and ESC guidelines, surgical repair or replacement for severe symptomatic FMR despite maximal medical therapy would be a class IIb indication, recommended by some experts but not by most. In the United States, transcatheter repair of FMR is not approved by the US Food and Drug Administration. In Europe, the majority of patients receiving transcatheter mitral repair with MitraClip are high-risk patients with symptomatic severe FMR. At 5 years, transcatheter MitraClip therapy for severe FMR can decrease MR, improve CHF symptoms, and decrease the rate of hospitalization for CHF.[1]

Available data suggest that surgery for severe FMR can improve MR and CHF symptoms despite no survival benefit.[2] However, recurrence of MR is greater after surgical repair of FMR than for degenerative mitral repair or for functional mitral replacement.[3] Patients with ejection fraction < 20%, significant restriction of mitral valve coaptation, and/or posterobasal aneurysms may have less recurrent MR with mitral replacement compared to surgical mitral repair. Despite the lack of guideline enthusiasm for surgical repair of FMR, some surgical series have seen relatively little recurrent MR in selected FMR patients.[2]

Medical science advances, and human practitioners are subject to fashion. At present in the United States, the percentage of patients with FMR referred for surgical or transcatheter repair may be at an all-time low. FMR, which constituted approximately 50% of mitral valve repairs 20 years ago, is only 5% of current surgical series.[4] It is likely that the American experience will follow that of Europe with increasing use of transcatheter repair of FMR in medium- to high-risk patients. It is also likely that subsets of patients will be identified who will receive at least symptomatic benefit from surgical mitral repair or replacement. Yet, other patients will be identified who are best managed by addressing the LV dysfunction, either with transplantation, ventricular assist devices, or other means such as stem cell therapy.

Just as we now know that FMR and DMR are different diseases, we eventually will realize that FMR patients are themselves diverse and may require more individualized therapy rather than lumping them all into one FMR group. ■

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