

Surgical and Transcatheter Mitral Valve Repair for Severe Chronic Mitral Regurgitation: A Review of Clinical Indications and Patient Assessment

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Significant mitral regurgitation (MR) is an increasingly common disorder affecting nearly 10% of the US population aged >75 years and is associated with increased morbidity and mortality in the setting of left ventricular (LV) dysfunction and heart failure symptoms. Mitral valve repair or replacement improves morbidity and mortality in appropriate clinical contexts, but determination of optimal timing of these therapies can be clinically challenging. Consequently, nearly 50% of patients meeting an indication for mitral valve surgery are not referred. Premature exposure to operative risk and limitations in durability are factors that may delay surgery. Conversely, high predicted operative mortality and severe frailty limit other patients from referral to surgery altogether. The recent development of less invasive transcatheter repair provides an additional therapeutic option for some nonoperative patients. Detailed patient and valvular pathology assessments are essential for appropriate utilization of medical, surgical, and transcatheter therapies. Given this complexity, current guidelines recommend that patients being considered for surgical or transcatheter therapies undergo consultation with a multidisciplinary heart team within a heart valve center of excellence. In the current review, we summarize the pertinent aspects of patient and valvular assessments used to guide the optimal timing and type of intervention for severe chronic MR.

MR is the most prevalent heart valve disease in the United States. Moderate or severe MR is found in 0% to 1.0% of people aged 18 to 64 years, 6.4% of people aged 65 to 75 years, and a striking 9.3% of people aged ≥ 75 years.¹ The

volume overload of chronic MR results in progressive cardiac remodeling and cyclical worsening of MR severity, which ultimately leads to heart failure and increased mortality. Beyond determining and tracking MR severity, management is dependent on differentiation between primary and secondary mechanisms of regurgitation. Primary (or degenerative) MR results from lesions of ≥ 1 element of the mitral valve apparatus, including the leaflets, chordae tendinae, annulus, and papillary muscles. Secondary (or functional) MR is characterized by a structurally normal valve apparatus and instead develops from abnormal LV function and geometry, such as in ischemic or dilated cardiomyopathy. In primary MR, therapies are generally focused on mechanically correcting the valvular dysfunction. Alternatively, secondary MR management is initially focused on the root problem of LV dysfunction. If significant secondary MR persists after optimized medical therapy for heart failure, revascularization, and resynchronization therapy, then mitral valve repair or replacement of the valve is considered.²

Valvular repair or replacement is a common final management option in both primary and secondary MR, resulting in $\approx 50\,000$ annual mitral valve operations in the United States; however, defining the optimal timing of these interventions can be challenging. Anticipated disease progression must be considered regarding the benefits and risks of surgical and transcatheter-based approaches. With mild MR, the rate of progressive remodeling such as ventricular dilation is low; however, remodeling with systolic dysfunction and the risk of sudden cardiac death increase in older patients and when MR is moderate or worse. Persons aged ≥ 50 years with medically managed primary MR face a 3% annual risk of mortality if the MR is moderate and 6% if severe.³ Furthermore, within 10 years of diagnosis of severe primary MR, nearly 90% of patients experience clinical events resulting in death or surgical therapy.⁴ Similarly, $\approx 50\%$ of patients with secondary MR following a myocardial infarction develop heart failure or death within 5 years, a 3-fold higher risk than post-myocardial infarction patients without MR.⁵ Despite these findings, surgical repair or replacement is often delayed to avoid exposure to procedural risk or postoperative risk of anticoagulation,

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or concerns about durability of repair or bioprosthetic replacement over following decades.

In addition to the fine balance between risk of disease progression and procedural risk, elevated patient risk frequently contributes to the challenge of defining optimal timing for valvular intervention. Among patients who meet the current surgical indications for treatment of MR, almost 50% are not offered this therapy for reasons such as prohibitively high surgical risk from comorbidities, frailty associated with advanced age, lack of clinician familiarity with current guidelines, or a combination of these factors.^{6,7} Such patients are left with few clinical options, resulting in frequent referral to palliative care and hospice programs.

Advances in technology have led to the development of less invasive transcatheter techniques for mitral valve repair and provide a new clinical option for these nonoperative patients. The MitraClip system (Abbott Laboratories), based on the surgical Alfieri edge-to-edge repair, allows transcatheter mitral valve repair (TMVR).⁸ To compare the safety and efficacy of MitraClip TMVR versus conventional surgical repair, the EVEREST II trial was conducted after the feasibility of MitraClip TMVR was sufficiently demonstrated in the EVEREST I trial.⁹ The EVEREST II trial was a prospective randomized nonblinded multicenter clinical trial comparing MitraClip TMVR with surgical valvular repair or replacement.¹⁰ At 30 days after the procedure, there were significantly more adverse events in the surgical group compared with the MitraClip group, seen mostly in blood product transfusion (45% versus 13%, $P<0.001$) and prolonged mechanical ventilation following the intervention (4% versus 0%, $P=0.02$). The primary effectiveness composite endpoint of freedom from death, surgery for mitral valve dysfunction, and 3+ to 4+ MR favored surgical management over MitraClip at both the 1- and 4-year follow-up time points.^{10,11} There were no significant differences in mortality or frequency of 3+ or 4+ MR between the 2 groups. Likewise, New York Heart Association functional class and quality of life also improved in both groups through 12 and 48 months of follow-up. However, 20% of patients treated with MitraClip required further surgical management compared with 2% of patients needing redo surgery following initial surgical management ($P=0.007$; 48 month outcome 24.8% versus 5.5%, $P<0.001$). Although surgical management remains the standard of care for severe symptomatic MR, these findings demonstrated that MitraClip TMVR could be a viable alternative for severe MR patients who are not considered surgical candidates. This was further assessed with the REALISM continued-access registry in which patients with high surgical risk were treated with MitraClip TMVR. A group of 127 high-risk patients with severe primary MR were pooled from the EVEREST II and REALISM populations to provide a better understanding of the utility of MitraClip therapy in such patients. Initial results were very

promising, including a 95% procedural success rate and 30-day mortality of 6.3% compared with the Society of Thoracic Surgeons (STS) risk score–predicted mortality of 13.2% for surgical MV replacement. Reflective of significant comorbidities, 1-year mortality was 23.6%; however, 86.9% of surviving patients were in New York Heart Association functional class I or II, and improvements in quality of life and heart failure hospitalization rates as well as LV reverse remodeling were all observed.¹²

These findings contributed to approval by the US Food and Drug Administration in October 2013 for the use of MitraClip in patients with symptomatic 3+ or 4+ primary MR at prohibitive risk of surgery. Under this approval, 564 such patients were treated in the United States through August 31, 2014, and followed through the STS and American College of Cardiology transcatheter valve therapy registry. Early results were similar to the clinical trial experience, including a 91.8% procedural success rate and 30-day mortality of 5.8% compared with STS predicted mortality of 10% for surgical valve replacement.¹³ Parallel to the US experience, international commercial experiences have also established the safety and efficacy of this technique in high-risk patients, including low procedural and postdischarge mortality and improvements in New York Heart Association functional class and quality of life.¹⁴

Although available in Europe and elsewhere for secondary MR, the safety and efficacy of MitraClip TMVR in these nonoperative patients is being studied in the United States and Canada through the multisite clinical trial “Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation” (COAPT; ClinicalTrials.gov identifier NCT01626079).

Additional devices in development for transcatheter and less invasive surgical mitral valve repair and replacement are expected to further complement conventional cardiac surgery as therapeutic options in the next 5 to 10 years. These devices are numerous and exist within the continuum of medical device approval, ranging from preclinical studies and first-in-man use to Conformité Européenne mark granted and investigational device exemption submitted or under way. No transcatheter mitral valve replacement devices are currently approved for use, but many companies have completed first-in-man implants, whereas several others remain in preclinical development. These replacement devices vary in both access site (transfemoral versus transapical and transatrial) and design, including self-expanding, self-conforming, and self-anchoring valve technology. Compared with transcatheter mitral valve replacement, the realm of TMVR has made faster strides toward approval, with at least 3 technologies (not including MitraClip) having gained the Conformité Européenne mark for approved use in Europe. This may be because TMVR is thought to have a higher safety profile than replacement,

even though the clinical effects may not be as durable.¹⁵ The existing and upcoming mitral valve repair technologies are best categorized by functional mechanism, including edge-to-edge repair, chordal repair, indirect or direct annuloplasty, or enhanced coaptation. Detailed reviews of current and developing TMVR and replacement technologies have been reported recently.^{15,16}

Parallel to the current and numerous developing therapeutic options, the variety of patient characteristics and MR mechanisms result in a complex decision tree directing patient evaluation as well as timing and appropriateness of therapy. As such, current guidelines recommend that patients being considered for surgical or transcatheter therapies undergo consultation with a multidisciplinary heart team within a heart valve center of excellence.² This includes focused evaluations by physicians and advanced practitioners with expertise in heart failure, echocardiography, interventional cardiology, and cardiac surgery. Care by heart failure specialists promotes achievement of optimized guideline-directed medical therapy in secondary MR patients, such that MR severity improves in many cases. Likewise, use of beta blockers, angiotensin-converting enzyme inhibitors, and aldosterone antagonists can be maximized in primary MR patients who have developed LV dysfunction. Similarly, simultaneous patient assessment by cardiac surgeons and cardiologists with expertise in echocardiography and interventional therapies facilitates evaluation for candidacy of surgical or transcatheter therapies. Evaluation by multiple clinicians in the same setting enables real-time discussion and planning with the patient and enhances communication with referring providers.

The Continuum of Chronic Primary MR

The natural history of chronic primary MR is a cyclical progression driven by chronic left atrial and LV volume overload, whereby the addition of regurgitant volume to pulmonary venous filling results in increased left atrial volume and pressure. Increased left atrial diastolic pressure produces increased LV diastolic filling, which in turn feeds more MR volume in the subsequent LV systolic event. Primary MR may progress suddenly due to chordal rupture with flail leaflet with resultant increase in the regurgitant volume and orifice area, often to the severe range; however, less immediate and significant MR volume, as typically seen with myxomatous degeneration and MV prolapse, produces more modest volume and pressure alterations. These changes are accommodated by atrial dilation, minimizing increased chamber pressure. With these adaptive physiological responses, there is considerable individual variation of progression from mild to moderate primary MR, but overall risk of developing LV

dilation or systolic dysfunction is low.¹⁷ In the absence of symptoms, serial echocardiographic evaluation in patients with mild primary MR should be completed every 3 to 5 years.² A transition to moderate or severe MR indicates disease progression but may or may not be associated with onset of noticeable symptoms, even if this results in LV dilation and dysfunction. Asymptomatic patients with moderate MR should have repeated echocardiographic evaluations every 1 to 2 years, and severe MR should be reassessed every 6 to 12 months.²

Once symptoms of severe MR develop, the lack of repair or replacement is associated with high annual mortality from heart failure and sudden cardiac death, with only one-third of patients surviving to 8 years.¹⁸ Furthermore, valvular repair or replacement completed after development of heart failure symptoms or LV dysfunction improves but does not normalize prognosis relative to the age-matched population.^{19–26} Serial assessment is essential because, ideally, surgery for primary MR is completed before development of heart failure symptoms or LV dysfunction. Additional clinical sequelae of chronic MR that may develop prior to heart failure symptoms and LV dysfunction include atrial fibrillation and pulmonary hypertension. These comorbidities herald a transition from a compensated stage of chronic primary MR to a decompensated stage characterized by the development of symptoms and LV dysfunction.³ Because pulmonary hypertension and atrial fibrillation may reverse following valvular intervention, these findings pinpoint an opportunity to proceed with surgery prior to permanent damage and increased mortality.

Another consideration is that hemodynamic changes with exercise can result in increases of MR volume and pulmonary hypertension. These dynamic changes can result in exercise intolerance as an early symptom of MR that can be difficult to perceive. Serial exercise stress tests can demonstrate progression of subtle symptoms. Similarly, exercise tests coupled with hemodynamic assessment by echocardiography or invasively during cardiac catheterization can demonstrate such inducible worsening of MR, which is associated with increased progression to frank symptoms.^{27–29} In this context, development of an indication for valvular intervention is frequent in asymptomatic patients with severe MR, occurring at a rate of 8% per year (Table 1).³⁰

The Continuum of Secondary MR

Secondary MR, resulting from leaflet malcoaptation driven by remodeling of the left ventricle in ischemic and dilated cardiomyopathies, is associated with increased mortality. Posterior leaflet restriction can follow lateral myocardial infarction. In addition, geometric changes in dilated cardiomyopathy include mitral annular dilation, which displaces leaflets

Table 1. Guideline Directives for Mechanical Intervention of Primary Severe MR²

Recommendations	Class
Recommendations for surgical MV repair or replacement	
Symptomatic patients	
LVEF >30%	I
LVEF ≤30%	IIb
Asymptomatic patients	
LV systolic dysfunction (LVEF ≤60% or LVESD ≥40 mm)	I
Normal LV systolic function (LVEF >60% and LVEF <40 mm)	IIa
>95% likelihood of durable repair without residual MR	
<1% mortality risk	
Performed at a Heart Valve Center of Excellence	
And either	
Pulmonary hypertension (PASP >50 mm Hg)	
New onset of atrial fibrillation	
Mitral valve repair is recommended in preference to MV replacement	
Recommendation for transcatheter mitral valve repair	
Symptomatic	IIb
NYHA class III or IV symptoms	
Prohibitive risk of MV surgery	
Reasonable life expectancy	
Optimal GDMT for heart failure	

GDMT indicates guideline-directed medical therapy; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; MR, mitral regurgitation; MV, mitral valve; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure.

sufficiently to decrease the surface of coaptation.^{31,32} In patients with ischemic MR, 5-year cardiac mortality is significantly higher compared with matched patients without regurgitation, independent of age and ejection fraction. Importantly, the adjusted relative risk for mortality is doubled at a regurgitant volume and effective orifice area that would be considered moderate for primary MR.³¹ In patients with both ischemic and nonischemic cardiomyopathies (LV ejection fraction <40%) and heart failure, MR independently predicts worsened survival, whereby survival is related directly to the degree of regurgitation.³³

Surgery for secondary MR has not been evaluated in a randomized clinical trial. Although retrospective assessments have shown surgical mitral valve repair or replacement to be associated with reverse LV remodeling and improvements in heart failure symptoms and quality of life in patients with secondary MR, no clear mortality benefit has been shown.^{34,35} Surgical management is ideally pursued for persistent secondary MR only once medical, revascularization,

and resynchronization therapies have been optimized.² The safety and efficacy of the MitraClip system in patients with secondary MR and the prohibitive risk of surgery is being studied in North America through the COAPT clinical trial (ClinicalTrials.gov identifier NCT01626079).

Assessing Procedural and Patient Risk

Once a patient has developed an indication for valvular intervention, consideration is next focused on the balance of procedural risks and anticipated benefits. Surgical repair of degenerative MR, as an isolated procedure, is a low-risk operation.³⁶ Furthermore, given both lower operative mortality and better preservation of LV function, valve repair is preferred over valve replacement.² Operative risk is also associated with procedural volume, and improved outcomes are observed in high-volume surgical programs.³⁶ This low risk is coupled with increasing evidence of a mortality benefit for early intervention in asymptomatic patients with flail leaflet and preserved ventricular function.³⁷ In so-called heart valve centers of excellence, for which operative mortality is consistently <1%, surgical valve repair is recommended prior to the onset of heart failure symptoms or LV dysfunction if a successful, durable repair is predicted.^{2,36}

The low procedural risk profile of mitral valve surgery can be attributed to a combination of minimally invasive approaches, evolving repair techniques, and experienced clinical centers. Despite this low procedural risk profile, there continues to be a broad spectrum of risk based on individual patient characteristics. Consequently, many patients who are considered to be of prohibitive risk for surgery are not offered this otherwise-indicated care.^{6,7} The determination of the risk–benefit balance is complex, requiring in-depth assessment on a case-by-case basis, and includes frank open discussion of risks and benefits with the patient.

Operative risk is classically defined as the likelihood of mortality or development of significant morbidity during and 30 days following surgery. The STS maintains an audited registry database that collects clinical, demographic, procedural, and outcome data for valve and coronary bypass operations. Using these data, risk models have been developed and validated for heart valve operations, and online risk calculators are available for predicting a patient's operative risks based on individual clinical and demographic data (Online STS Adult Cardiac Surgery Risk Calculator, <http://riskcalc.sts.org>; European System for Cardiac Operative Risk Evaluation, <http://www.euroscore.org/>). Patients can be categorized into 4 different groups of risk based on their predicted risk of mortality within 30 days of surgery: low risk (0–4%), intermediate risk (4–8%), high risk (8–12%), and extreme risk (≥12%).^{38,39} Contemporary risk profiles of

patients undergoing isolated surgical mitral valve repair operations reported in the STS database skew toward low predicted operative risks: 67% of patients had a predicted operative mortality risk <1%, 92% had a predicted risk <4%, and only 1% had a predicted risk of $\geq 12\%$.³⁸

Additional risk factors not captured in the traditional operative risk estimators include frailty, ascending aortic disease, pulmonary hypertension, hostile chest, major organ system compromise, and procedure-specific impediments (Table 2). Of note, frailty is an increasingly recognized risk factor, incorporating issues of weakness, malnutrition, wasting, slowness, and inactivity.⁴⁰ Although some patients may tolerate a surgical procedure, they may not achieve a meaningful functional recovery if they demonstrate marked frailty prior to the intervention. Several objective measures

Table 2. Factors Contributing to Prohibitive Risk for Mitral Valve Surgery

High 30-day predicted operative mortality risk
Online STS Adult Cardiac Surgery Risk Calculator, http://riskcalc.sts.org/
European System for Cardiac Operative Risk Evaluation, http://www.euroscore.org/
Cardiopulmonary comorbidities
High risk of internal mammary artery injury in reoperative surgery
Right ventricular dysfunction with severe tricuspid regurgitation
Severe pulmonary hypertension ($>2/3$ systemic pressure)
Ascending aortic disease
Extensive calcification (porcelain aorta)
Mobile atheroma
“Hostile” chest
Prior mediastinitis
Postradiation mediastinum
Two or more prior cardiac operations
Aorta adherent to posterior sternal table
Other comorbidities
Severe liver disease or cirrhosis (Child-Pugh class B or C)
Major bleeding diathesis
High risk of aspiration
Chemotherapy for malignancy
Severe renal dysfunction (creatinine >2.5 mg/dL)
Major organ system compromise
Frailty
Cognitive impairment
Slow gait or poor ambulation
Needing assistance with activities of daily living

and scoring systems have been developed to categorize the severity of frailty. Typical components include a timed walking test, a grip-strength test, an albumin assessment, and an evaluation of the patient’s activities of daily living.⁴⁰ One single-center experience of all cardiac operations demonstrated frailty to be an independent predictor of in-hospital mortality, institutional discharge, and reduced midterm survival.⁴¹ Many of these indices, regardless of specific components measured, demonstrate prognostic information in addition to the traditional risk calculators.⁴⁰ The modified Rankin Scale is a simple and reliable tool available to provide a measure of a person’s ability to live independently, ranging from no symptoms (score 0) to death (score 6).⁴² Patients with a moderate to severe degree of frailty (i.e., require assistance to ambulate or attend to their own bodily needs, modified Rankin score 4) are generally considered high risk for valvular surgery.² Many of these patients, however, tolerate MitraClip TMVR and are able to recover from the femoral venotomy and general anesthesia required for this procedure. Although in need of prospective assessment, patients with severe frailty who are bedridden and/or require constant nursing care (modified Rankin score 5) may be too disabled to achieve a meaningful benefit from MitraClip TMVR (Table 3).

A final important aspect of risk assessment and pre-procedural planning is consideration of candidacy for salvage surgery in the rare instance of catastrophic complications during the MitraClip procedure. Of the initial 564 commercial US cases of MitraClip TMVR for primary MR, cardiac surgery was required 0.5% of the time, contributing to the 5.8% rate of 30-day mortality in this cohort.¹³ This planning decision is included in the informed consent discussions with patients concerning the risks of MitraClip TMVR. Additional notable procedural risks of TMVR include blood transfusion (12.6%), major vascular complications (5.4%), new atrial fibrillation (3.9%), stroke (3.4%), prolonged ventilation (3.1%), noncere-

Table 3. Contraindications for MitraClip Transcatheter Mitral Valve Repair

Rheumatic mitral valve disease or mitral stenosis
Mitral valve area <4 cm ²
Transmitral gradient >5 mm Hg
Femoral venous, inferior vena cava, or intracardiac thrombus
Active mitral valve endocarditis
Intolerance of procedural anticoagulation
Intolerance of postprocedural antiplatelet therapy
Life expectancy <1 year
Severe frailty or modified Rankin scale 5 (relative contraindication)

bral thromboembolism (1.6%), and residual atrial septal defect (1.6%).¹²

These risks are balanced against the expected benefits of successful TMVR, including decreased hospitalization rates for decompensated heart failure, favorable cardiac reverse remodeling, and improved quality of life. Improvement of MR to a moderate degree or better was reported in >90% of commercial US cases for primary MR.¹³ Retrospective analyses of pooled primary and secondary MR cases in Europe demonstrated similar improvement in mortality among real-world TMVR patients and high-risk patients treated surgically. Furthermore, 1-year survival in patients treated with surgery (85%) or TMVR (85%) was significantly better than patients treated conservatively (68%, $P=0.006$).⁴³ Improvements in quality of life and New York Heart Association functional class also significantly improved relative to baseline assessment.⁴⁴

Assessment of the Mitral Valve

In parallel with the establishment of appropriateness and patient desire to pursue mechanical intervention, detailed assessment of the valvular anatomy and differentiation of primary versus secondary MR is essential to the appropriate use of medical, surgical, and transcatheter therapies. This is accomplished through review of clinical history and visualization of valvular pathology with transthoracic and transesophageal echocardiography.

In considering candidacy for surgical repair or replacement, or for TMVR in nonoperative patients, detailed anatomical assessment of the valve leaflets is critical. The width of a flail segment and the depth that the flail leaflet extends beyond the normal leaflet are important measures because very large dimensions make successful MitraClip implantation difficult. Patients with a flail width ≥ 15 mm or flail gap ≥ 10 mm are generally excluded from candidacy for this therapy.⁴⁵ Similarly, the leaflet tip is important to assess because either significant calcification or short leaflet length may preclude sufficient leaflet grasp with the device. In addition, localization of the major regurgitant jet via echocardiographic assessment is essential because central jets involving the A2 and P2 scallops are ideally suited for MitraClip placement. Lateral or medial pathology is more challenging because there is a higher risk of damaging the valve apparatus, given the likely interaction of the MitraClip device with chordae tendineae associated with the A1/P1 and A3/P3 scallops.

Finally, careful assessment of mitral valve area and transmitral gradients are essential in the evaluation for TMVR. Approximating the anterior and posterior leaflets with the MitraClip transforms the mitral valve into a double orifice system and can lead to iatrogenic mitral stenosis. Preproce-

dural mitral valve area < 4 cm² and transmitral gradients > 5 mm Hg are predictive of postprocedural mitral stenosis and generally are contraindications to MitraClip therapy. To reliably capture all of this information, sonographers and physicians who have received specialized training in the detail necessary for these echocardiographic assessments commonly use specific mitral valve echocardiography protocols.

Conclusion

As the US population continues to age, the prevalence of significant MR is expected to further increase. In high-volume centers of excellence, the operative mortality for mitral intervention is $< 1\%$, and successful surgical repair improves long-term survival enough to equate to an age-matched population with 95% freedom from repeat surgery and $> 80\%$ freedom from moderate to severe or severe MR at 20 years after surgery.³⁶ Nevertheless, almost 50% of patients who meet current indications for mitral valve surgery are not offered this therapy because of elevated surgical risk⁶ from decreased LV ejection fraction, advanced age, and other comorbidities such as advanced chronic obstructive pulmonary disease. TMVR is an exciting new technology that offers a treatment option for many of these patients who, until recently, had limited options outside of palliative care and hospice. The superiority of MV surgery and the complexity of MitraClip TMVR demand detailed clinical assessment to ensure delivery of the appropriate therapy at the appropriate time point to these patients. A multidisciplinary team approach is optimal for the evaluation of these patients and provides multifaceted expertise for a successful mitral valve program.

Disclosures

None.

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