MitraClip patient selection: inclusion and exclusion criteria for optimal outcomes

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Edge-to-edge repair with the percutaneous MitraClip technology has changed the landscape for patients with symptomatic, severe degenerative mitral valve regurgitation who are at prohibitive surgical risk. While the results of randomized controlled trials of MitraClip therapy in patients with functional mitral valve regurgitation are still pending, single center experiences as well as registry data generally support the real-world application of the MitraClip therapy. In the majority of individuals treated with MitraClip, complete or near-complete relief of mitral regurgitation occurs, with results approaching the effectiveness of open surgery. This perspective summarizes the data, with a focus on current selection criteria of percutaneous MitraClip edge-to-edge repair that can optimize clinical outcomes.

Keywords: MitraClip; functional mitral valve regurgitation (FMR); degenerative mitral valve regurgitation (DMR); inclusion exclusion criteria

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(RESHAPE) and the Multicenter Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation [MITRA-FR, NCT01920698 (3)] randomized trials. These trials compare the percutaneous edge-to-edge repair with optimal medical therapy (COAPT, RESHAPE, MITRA-FR) or surgery (MATTERHORN) in FMR patients and should help to clarify the role and indication of percutaneous MitraClip edge-to-edge repair in these patients.

Single center reports have evaluated outcomes of patients with versus without “EVEREST criteria” (Table 2), which had been used to enroll patients into the pre-clinical studies. Overall, these studies have shown comparable outcomes, but higher rates of recurrent symptomatic MR and need for more re-interventions, mainly because of functional etiology or complex valve pathology (5). Few prospective observational registries have reported direct outcome comparisons between FMR and DMR patients treated with MitraClip (2,6-11). In a recent meta-analysis of these studies, Chiarito et al. showed that mitral valve re-intervention at 1 year was at a significantly lower rate in patients with FMR compared with those with DMR (4% vs. 10%, FMR vs. DMR, respectively; RR 0.60; 95% CI: 0.38 to 0.97; P=0.04) without a significant difference in mortality between the two groups (18% vs. 14%, FMR vs. DMR, respectively; RR 1.26; 95% CI: 0.90 to 1.77; P=0.18). Both, DMR and FMR patients showed an acceptable 15% recurrence of ≥2+ MR. While incomplete, these data should be considered successful in the context of historically high surgical failure rates after surgical valve repair for FMR patients (between 14–66%) (12-14). Notably, FMR patients presented more frequently in severe heart failure (i.e., NYHA III/IV) and were re-hospitalized for heart failure more often at 1-year follow-up, despite no significant difference in the recurrence of MR ≥2+ between the two groups (15). These results underscore the clinical dilemma of treating patients with severe functional MR, without directly addressing the underlying valvular cardiomyopathy.

**Does the degree of MR matter?**

The degree of MR going into the procedure can affect the short- and long-term outcome after the implantation. The Transcatheter Valve Therapy (TVT) registry data demonstrated that baseline MR degree grade impacts the success as defined by post-procedural MR ≤2 (OR per increasing grade: 0.66; 95% CI: 0.47 to 0.93; P=0.02). In addition, the presence of multiple jets of MR can negatively impact short- and long-term outcomes of MitraClip due to the high likelihood of requiring multiple clips to achieve an adequate reduction of MR (16). On the other hand, there are reports cautioning against a single clip strategy, suggesting increased risk of residual and recurrent MR (17).

**Ejection fraction—how low is too low?**

Data from the German transcatheter mitral valve interventions registry (TRAMI, >800 patients) show that an ejection fraction of <30% is an independent predictor of 1-year mortality (18). Similarly, Giannini et al. have
Table 2 Everest criteria (4)

<table>
<thead>
<tr>
<th>Major inclusion criteria</th>
<th>Major exclusion criteria</th>
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<tbody>
<tr>
<td>Moderate-severe (3+) or severe (4+) chronic MR and Symptomatic with &gt;25% left ventricular ejection fraction and left ventricular end-systolic diameter ≤55 mm or</td>
<td>Acute myocardial infarction in the prior 12 weeks of the intended treatment</td>
</tr>
<tr>
<td></td>
<td>The need for any other cardiac surgery</td>
</tr>
<tr>
<td>Asymptomatic with one or more of the following:</td>
<td>Any endovascular therapeutic interventional or surgical procedure performed within 30 days prior</td>
</tr>
<tr>
<td>(I) LVEF 25% to 60%</td>
<td>Ejection fraction ≤25%, and/or end-systolic dimension &gt;55 mm</td>
</tr>
<tr>
<td>(II) LVESD ≥40 mm</td>
<td>MV orifice area &lt;4.0 cm²</td>
</tr>
<tr>
<td>(III) New onset of atrial fibrillation</td>
<td>If leaflet flail is present, width of the flail segment ≥15 mm, or flail gap ≥10 mm</td>
</tr>
<tr>
<td>(IV) Pulmonary hypertension defined as pulmonary artery systolic pressure &gt;50 mm Hg at rest or &gt;60 mmHg with exercise</td>
<td>Severe mitral annular calcification</td>
</tr>
<tr>
<td>Candidate for MV repair or replacement surgery, including cardiopulmonary bypass</td>
<td>If leaflet tethering is present, coaptation depth &gt;11 mm, or vertical coaptation length is &lt;2 mm</td>
</tr>
<tr>
<td>The primary regurgitant jet originates from malcoaptation of the A2 and P2 scallops of the MV. If a secondary jet exists, it must be considered clinically insignificant</td>
<td>Leaflet anatomy that may preclude clip implantation, proper clip positioning on the leaflets, or sufficient reduction in MR. This may include the following: Evidence of calcification in the grasping area of the A2 and/or P2 scallops Presence of a significant cleft of A2 or P2 scallops More than 1 anatomic criteria dimensionally near the exclusion limits Bileaflet flail or severe bileaflet prolapse Lack of both primary and secondary chordal support Prior MV surgery or valvuloplasty or any currently implanted mechanical prosthetic valve or currently implanted ventricular assist device Echocardiographic evidence of intracardiac mass, thrombus, or vegetation History of or active endocarditis or rheumatic heart disease History of atrial septal defect or patent foramen ovale associated with clinical symptoms</td>
</tr>
</tbody>
</table>

Demonstrated that reverse left ventricular (LV) remodeling after percutaneous edge-to-edge repair can more likely be expected in patients without advanced congestive heart failure (i.e., left ventricular ejection fraction >30%) and without severe left ventricular dilation (left ventricular end-diastolic diameter <70 mm, left ventricular end-diastolic volume <200 mL) (19). Moreover, it is well known that left ventricular dysfunction, as assessed by echocardiography prior to repair or replacement, is often underestimated in patients with severe MR because of a systolic unloading resulting from low-resistance ejection to the left atrium (20). Current clinical trials have excluded most patients with ejection fraction <30%, and practice guidelines also caution against open surgery for patients with such severe dysfunction. While MitraClip can palliate symptoms in patients with severe dysfunction and even salvage those in cardiogenic shock, the long-term survival effect of such treatment needs further study.

Does the valve area and calcification matter?

The TVT registry data did not show any significant association of pre-procedural mitral valve area <4 cm², mitral annular calcification, or mitral valve gradient...
>4 mmHg with procedural success (1), even though these findings were evident in ~20% of patients. In carefully selected patients with these abnormalities, MitraClip can be performed successfully. Notably, the greatest reduction in mitral valve area with MitraClip occurs when clip placement is performed in the center of the valve (i.e., A2-P2), as this position leads to the greatest reduction in the septal-lateral dimension of the mitral valve (i.e., up to 50% reduction in area). When MR treatment occurs away from this area (i.e., A1-P1 or A3-P3), treatment may be successful but other studies have shown that optimal results are less likely in patients with even borderline elevated mitral gradient pre-procedure and mitral annular calcification (16). In our experience, we have not found value in the use of MitraClip in patients with either rheumatic or radiation-induced heart disease and overall support the best practice of MitraClip therapy for patients with a mitral valve area ≥4 cm².

**Other applications**

MitraClip therapy has also successfully been applied in other applications, such as hypertrophic obstructive cardiomyopathy (HOCM) (21), as well as in the treatment of recurrent mitral valve regurgitation after mitral valve ring repair (22). For HOCM, MitraClip limits the systolic anterior motion of the anterior mitral valve leaflet, thereby reducing left ventricular outflow obstruction, while also addressing the dynamic mitral regurgitation. Early experience has been positive, though caution must be used in these patients due to their relatively small mitral annuli. Similarly, relatively small mitral annuli are also a concern in patients with prior surgery, due to the frequent use of down-sized annuloplasty bands or rings. MitraClip in post-surgical patients is possible, provided there is suitable tissue for anchoring—a challenge when leaflet resection has been undertaken. Although the DFU for MitraClip excludes its use in patients with femoral or caval thrombi, a case report by Barbin et al. shows that it can be done if absolutely necessary and in the context of lack of alternative treatment options (23).

**Importance of a multidisciplinary heart team approach**

MITRA-FR (3), RESHAPE and COAPT will clarify the role of MitraClip vs. optimal guideline-directed medical therapy alone in patients with functional mitral valve regurgitation. While we await the results of these important trials, we consider the addition of an advanced heart failure specialist to the heart team essential. In concert with a cardiovascular surgeon and an implanting interventional cardiologist, this team can ascertain that the patient with functional mitral valve regurgitation receives the optimal therapy for the primary left ventricular pathophysiology. The heart team should therefore always carefully weigh risks and benefits as well as the likelihood of adequate repair success between MitraClip and surgical repair. Some may advocate a ‘give MitraClip a try first’ strategy, but this approach must be tempered greatly when the patient is operable and the chance of complete MR relief with repair-surgery is high. Indeed, most of the patients with failed MitraClip implantation will require a mitral valve replacement (24).

**Conclusions**

MitraClip presents an excellent therapeutic option for patients with mitral valve regurgitation who are at prohibitive risk for a surgical repair or replacement. Ongoing randomized controlled trials in patients with functional mitral valve regurgitation will provide further insight into the role of this therapy in comparison to medical therapy or surgery. It remains crucial to select the best-suited patients for this therapy through an advanced heart team decision-making process. Current inclusion and exclusion criteria have consistently been shown to be key in short- and long-term procedural success.

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**Footnote**

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

**References**


