Preoperative evaluation before MitraClip®: present and future perspective

Gemma Salerno¹, Frank Patrick Schmidt², Maurizio Cappelli Bigazzi¹, Chiara Sordelli¹, Renato Bianchi¹, Paolo Golino³, Paolo Calabrò¹, Maria Giovanna Russo¹, Raffaele Calabrò¹ & Giuseppe Pacileo*,¹

¹Department of Cardiology, Second University of Naples, Ospedale dei Colli, Naples, Italy
²Department of Medicine II, University Center of Johannes Gutenberg-University Mainz, Mainz, Germany
³Department of Cardiology, AO Sant’Anna e San Sebastiano, Caserta, Italy

*Author for correspondence: Tel.: +39 817 062 674; gpacileo@tin.it

ABSTRACT Mitral regurgitation (MR) is the second most common heart valve disease worldwide. Currently, the management of MR is based on medical therapy (including biventricular pacing), surgery (mitral valve replacement or repair) and percutaneous therapy. However, in spite of guideline recommendations, 50% of individuals assessed in the Euro Heart Survey were not referred to surgical intervention due to comorbidities or real or perceived high risks for cardiac surgery; thus, in recent years, the focus of research has shifted to the development of percutaneous approaches to treat severe MR in order to restore valve function in a minimally invasive fashion. Among these techniques, the percutaneous mitral valve repair procedure using the MitraClip® system (Abbott Vascular, IL, USA) is one of the most promising. Usually, patient selection for MitraClip implantation is based on careful echocardiographic assessment of valve disease; however, although definitive data are lacking, evidence is mounting for a multiparametric approach including the evaluation of the functional status of patients.

Mitral regurgitation (MR) is the second most common valvular heart disease after aortic stenosis. Without surgical intervention, the outcome of patients affected by significant MR is poor because of worsening left ventricular (LV) failure, pulmonary hypertension (PHT), atrial fibrillation and death [1]. The most common causes of MR include ischemic and nonischemic heart diseases and/or valve degeneration. Indeed, structural abnormalities of the valve leaflets and the subvalvular apparatus, including tendinous chord rupture, may provoke degenerative MR (DMR).

In these patients, surgical repair, when feasible, is the therapy of choice because of better perioperative mortality, preservation of postoperative LV function and improved long-term survival compared with valve replacement [2]. However, some patients are at high surgical risk due to advanced age or other comorbidities and thus are not amenable for surgery. On the other hand, both ischemic and nonischemic heart diseases may cause ‘functional’ MR (FMR) through several mechanisms, such as impaired LV wall motion, LV dilatation and papillary muscle displacement and dysfunction.

Contrary to DMR, surgical correction for FMR is controversial, with no consistent data being available in terms of survival and quality of life. In addition, owing to advanced age and multiple comorbidities, in a large percentage of FMR patients, mitral valve (MV) repair or replacement are denied, as shown by the Euro Heart Survey [3]. Various percutaneous techniques have been developed to treat MR with less invasive approaches in order to minimize surgical trauma. Percutaneous repair with the MitraClip® system (Abbott Vascular, IL, USA) is a novel interventional technique developed as an alternative to the surgical approach for the treatment of severe MR. The device

KEYWORDS • cardiopulmonary exercise test • echocardiography • MitraClip® procedure • mitral regurgitation • percutaneous intervention
mimics the surgical ‘edge-to-edge’ Alfieri technique (Figure 1) through mechanical coaptation of the mitral leaflets [4,5]. In the percutaneous procedure, a guide catheter is introduced into the right femoral vein and advanced up the inferior vena cava to the right atrium and then to the left atrium (LA) by a trans-septal approach. A delivery system with a clip (Figure 2) is steered through the MV and positioned under echocardiographic and fluoroscopic control until a successful result, as shown by decreased MR, is obtained (echocardiographic assessment of MR <2+; Figure 3). A second clip can be placed if necessary in order to achieve a satisfactory reduction in MR. The MitraClip has been evaluated in the EVEREST I study, which demonstrated its safety and feasibility [6,7]. The first randomized controlled study, the EVEREST II study, randomized 279 patients with moderately severe or severe (grade 3+ or 4+) MR in a 2:1 ratio to percutaneous treatment with the MitraClip system or surgical repair or replacement (n = 95). At 1 year, the rates of the primary efficacy end point (a composite of freedom from death, surgery for MV dysfunction and grade 3+ or 4+ MR) favored surgery (73 vs 55%; p = 0.007), with need for surgical intervention for MV dysfunction being tenfold lower than in the percutaneous group (2 vs 20%; p < 0.01). However, the percutaneous approach was safer (30-day major adverse cardiac events: 15 vs 48%; p < 0.001) [8]. These results corroborated the advantage of surgery according to the current guidelines, recommending surgery for patients with degenerative MV regurgitation, good LV function and a low operative risk. However, it should also be noted that the interventional cardiologists who performed MitraClip procedures did not have well-established experience before the randomization phase (the average number of previous MitraClip procedures was three). A subgroup analysis carried out on data from EVEREST II found that the Mitraclip was not inferior to cardiac surgery in older patients and patients with functional regurgitation and reduced LV function [8]. Recently, investigators led by Mauri, of Brigham and Women’s Hospital (MA, USA), analyzed the data at a 4-year follow-up. The composite efficacy end point was numerically higher with surgery, but the difference was no longer significant compared with at the 1-year follow-up. Rates of mortality and moderate-to-severe and severe MR were comparable between the groups. However, the need for surgery for MV dysfunction was almost five-times greater after percutaneous therapy [9].

Causes, mechanisms & pathophysiology of MR

The MV apparatus is a complex anatomic structure composed of several elements, each of them playing an important role in the physiological mechanism of closing and therefore are susceptible to being involved in MR. Schematically, we can distinguish the mitral annulus, two distinct leaflets (anterior and posterior) and chordae, which connect both leaflets to the anterolateral and posteromedial LV papillary muscles. Notably, the geometry and function of LA and LV also play important roles in the MV dynamics and function. The posterior leaflet is further separated into three separate, named scallops: P1, P2 and P3 (from lateral to medial). Although the anterior mitral leaflet is typically not anatomically divided, its segments are named A1–A3 in order to reflect the segmentation of the opposing posterior leaflet scallops. The shape of the mitral annulus is comparable with a saddle structure with peaks anteriorly and posteriorly, and nadirs medially and laterally. The anterior aspect of the mitral apparatus is a stiff fibrous band that is common with the aorta (aortomitral fibrosa or curtain), while the remaining medial, lateral and posterior aspects are more susceptible to remodeling and distortion of shape [10].

Figure 1. Edge-to-edge repair, as described by Alfieri, transforming the mitral valve into a double-orifice mitral valve by coapting the central leaflet scallops.
including the chords. Causes of primary MR include most commonly degenerative disease (Barlow syndrome, fibroelastic degeneration, Marfan syndrome, Ehlers–Danlos syndrome and annular calcification), rheumatic disease and endocarditis [5]. In the functional or secondary forms (i.e., FMR), the valve is structurally normal, denoting abnormal function of normal leaflets in the context of impaired ventricular function resulting from ischemic heart disease or dilated cardiomyopathy. In cases where both mechanisms are present, one of them is usually predominant and will guide the management. Chronic secondary MR is a common complication in patients with systolic heart failure. It results from an imbalance between tethering forces (annular dilatation, apical and outward displacement of one or both papillary muscles and LV sphericity) and closing forces (decreased LV contractility, global LV dyssynchrony and papillary muscle dyssynchrony). Since these factors may alter during the cardiac cycle and with changes in loading conditions, FMR is by nature dynamic. FMR due to nonischemic conditions occurs in the presence of dilated cardiomyopathy or MV annular enlargement secondary to LA dilatation in patients with chronic atrial fibrillation [11]. In most cases, chronic ischemic and nonischemic FMR results from systolic restriction of leaflet motion, and two main patterns of mechanisms can be described. The restrictive motion is most frequent in patients with previous posterior infarction (asymmetric pattern/tethering). In this scenario, the traction on the anterior leaflet by secondary chordae can induce the so-called ‘seagull sign’. By contrast, when both leaflets show a reduced systolic motion leading to incomplete coaptation, the pattern/tethering is symmetric, as in patients with idiopathic cardiomyopathy or with both anterior and inferior infarctions [13].

Carpentier introduced a functional classification of MR based on leaflet movement: type I with normal leaflet movement (e.g., MR caused by annular dilatation or leaflet perforation due to infective endocarditis); type II with exaggerated leaflet movement (e.g., MV prolapse); and type III is subdivided into type IIIa, implying restricted leaflet motion both in diastole and systole due to the shortening of the chordae and/or leaflet thickening, such as in rheumatic disease, and IIIb, with restricted leaflet movement only during systole, such as in ischemic or nonischemic cardiomyopathy [12].

The clinical scenarios of MR can be extremely different if the mechanisms of regurgitation arise acutely or chronically. In acute MR, the atrium is noncompliant, so mechanical energy generated by the LV causes an increase in intra-atrial pressure. By contrast, in chronic MR, the atrium is more compliant, so mechanical energy generated by the ventricle causes volume overload and atrial enlargement. For this reason, chronic MR may be associated with a small regurgitation wave [13]. Patients with chronic MR often remain asymptomatic for many years and the LV progressively dilates to accommodate the increased volume load and maintain cardiac output, finally resulting in heart failure and increased risk of sudden death when the MR becomes decompen-sated and LV contractile dysfunction is manifest.
Figure 3. The clip delivery system. The clip delivery system is advanced through the guide catheter into the LA and positioned so that the clip is orthogonal to the plane of the mitral valve annulus and at the origin of the regurgitant jet. (A & B) 3D transesophageal echocardiography (TEE) images of the steerable guide catheter advanced into the LA after the trans-septal puncture utilizing Flexizoom with the 4D TEE transducer by GE Healthcare’s Vivid E9. The red arrow indicates the hyperechogenic tip. (C) The mitral valve after the grasping of the two leaflets from surgeon’s view utilizing the innovative slice tool, FlexiSlice, with the 4D TEE transducer by GE Healthcare’s Vivid E9. Note the double orifices from the en-face LA view (top left) and the good orientation of the MitraClip®, which is perfectly aligned perpendicular to the line of coaptation (this view mimics the transgastric short-axis view). AML: Anterior mitral leaflet; IAS: Interatrial septum; LA: Left atrium; PML: Posterior mitral leaflet; RA: Right atrium.

Patient selection
An appropriate selection of patients for the MitraClip procedure has to begin from:

- The grading of MR severity;
- The assessment of the mechanism underlying the regurgitation, defining both the anatomic features of the MV (DMR) and the anomalies of LV function (FMR);
- The assessment of the functional status and surgical risk.

Grading of MR severity
MR incidence and clinical importance are largely underestimated partly because physical examination is rather insensitive. When present, secondary MR may exhibit a broad range of severity and conveys a dismal prognosis. The increased mortality risk is related not only to the presence of MR, but also more importantly to the severity of MR. Indeed, the more severe the secondary MR is, the more it worsens the prognosis. Moreover, MR begets MR due to adverse LV remodeling, which is known to independently affect outcomes. This has led to a focus of attention towards the amelioration of the methods used to quantitate the severity of MR. Echocardiography is the best method for the assessment of MR severity and its mechanism, repairability and hemodynamic consequences.
Preoperative evaluation before MitraClip®: present & future perspective

[12,14,16,17,18], 2D transthoracic echocardiography (TTE) is used to assess MR severity, whereas transesophageal echocardiography (TEE) is used to assess valve morphology (VM). TTE may sometimes underestimate the severity of MR. If there is any doubt regarding the severity of MR, TEE should be performed. For the assessment of MR, TEE should be performed without sedation if tolerated by the patient. Furthermore, it is desirable to increasingly include 3D echocardiographical methods into the assessment of MR. Criteria for grading MR severity have been developed by both European and American echocardiographic societies and are summarized in Table 1 [12,15].

The EVEREST studies classified MR by TTE into four grades. In order to qualify for the procedure, MR needs to be moderate to severe (3+) or severe (4-/4+). Three criteria needed to be met and, of these criteria, at least one had to be quantitative [6–8]. Therefore, echocardiographic laboratories are encouraged to become proficient in MR quantification in order to measure regurgitant volume as a marker of volume overload and effective regurgitant orifice area (EROA) as a marker of lesion severity. Quantitative assessment defines the progression of MR, which color flow imaging does not detect well [19]. Despite several inherent limitations of the proximal isovelocity surface area (PISA) method, including its lower accuracy in eccentric jets, the changes in PISA radius throughout systole and the often unmet assumption that the proximal flow convergence is hemispheric, the 2D PISA method is currently the recommended approach for MR quantification. Particularly in secondary MR, elliptic and irregular configuration of the effective regurgitant orifice (ERO) may render the ERO calculation inaccurate by the 2D PISA method. Such a complex geometry may contribute to the discrepancy between secondary and primary MR severities in terms of outcome. However, the regurgitation volume also depends on a systolic time run profile of the

<table>
<thead>
<tr>
<th>Table 1. Grading the severity of mitral regurgitation.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
</tr>
<tr>
<td>Qualitative</td>
</tr>
<tr>
<td>Mitral valve morphology</td>
</tr>
<tr>
<td>MR color jet</td>
</tr>
<tr>
<td>Flow convergence†</td>
</tr>
<tr>
<td>CW Doppler signal of MR jet</td>
</tr>
<tr>
<td>Semiquantitative</td>
</tr>
<tr>
<td>Mitral inflow</td>
</tr>
<tr>
<td>LA/LV size</td>
</tr>
<tr>
<td>TVImit/TVIAo</td>
</tr>
<tr>
<td>Quantitative</td>
</tr>
<tr>
<td>RF (%)</td>
</tr>
<tr>
<td>EROA (mm²)**</td>
</tr>
</tbody>
</table>

*At a Nyquist limit of 50–60 cm/s.
†Matching apical four- and two-chamber views.
‡Unless other causes of systolic blunting (atrial fibrillation or elevated LA pressure).
§Without any other reason of elevated LA pressure and of mitral stenosis.
¶Classically, the severity of organic MR is classified as mild, moderate or severe. Furthermore, moderate MR can be subclassified into ‘mild to moderate’ (EROA of 20–29 mm² or a R Vol of 30–44 ml) and ‘moderate to severe’ (EROA of 30–39 mm² or a R Vol of 45–59 ml).
††In functional MR, lower thresholds of severity have been suggested according to their prognostic power (20 mm² for EROA and 30 ml for regurgitant volume) [8,13].
**Continuous-wave; EROA: Effective regurgitant orifice area; LA: Left atrium; LV: Left ventricle; MR: Mitral regurgitation; PM: Papillary muscle; RF: Regurgitant fraction; R Vol: Regurgitant volume; TVIAo: Aortic velocity-time integral; TVImit: Mitral velocity-time integral; VC: Vena contracta.
regurgitation, the size and pressure conditions in the LV and the LA and the geometry and contraction of the LV. An EROA \( \geq 40 \, \text{mm}^2 \) is linked to approximate doubling of the mortality risk and quadrupling of the risk of cardiac events, superseding jet-based measures and indicating a risk of excess mortality compared with expected survival \(^{20}\). On the other hand, an EROA \( \leq 40 \, \text{mm}^2 \) (between 20 and 39 mm\(^2\)) is associated with a slow deterioration of outcome within the first few years, indicating the ‘watchful waiting strategy’ for medical management. The relationship of EROA with subsequent cardiac events was established independently. In secondary MR, an EROA \( \leq 20 \, \text{mm}^2 \) is prognostically in favor of severe MR, while, as previously described, a double cut-off is used to define severe primary MR. 3D echocardiography is an imaging technique that can provide the actual geometry of the flow convergence. Therefore, determination of the resulting surface using a 3D volume lead technique has been included in the current guidelines for 3D echocardiography \(^{21}\). As is well known, one of the first applications of 3D echocardiography has been the assessment of LV volume and function independently of geometric assumptions regarding LV shape. These are landmarks during the evaluation of secondary MR.

Direct measurement of PISA with 3D color Doppler echocardiography does not require the use of geometric assumptions and should reduce the errors in calculating EROA with the 2D method. Using this new tool, an ongoing prospective multicenter study evaluating the prognostic impact of the quantified degree of secondary MR using real-time 3D color TTE in patients with heart failure is being conducted (the POMAR study). Furthermore, cropping of a 3D color Doppler dataset can reveal different vena contracta areas in the principal views and can better define its shape along the commissural line (in an en-face view to the MV). It must be remembered that echocardiographical assessment only provides a snapshot from a single time point, which is affected by multiple factors, including filling status, blood pressure, heart rate and arrhythmia (e.g., atrial fibrillation), as well as, importantly, the use of sedatives, narcotics and catecholamines. Therefore, consideration must always be taken to ensure that the conditions under which the echocardiography is performed remain identical before and after the procedure.

Stress echocardiography is currently an underused technique that can provide additional information on the severity of the regurgitation and functional capacity that is useful for risk stratifying patients and for clinical decision-making in both types of MR. Dobutamine stress echocardiography may be useful in the assessment of FMR in order to determine the extent of the viable myocardium and contractile reserve that might recover with revascularization, medical treatment or possibly resynchronization. It is not as useful in the grading of the severity of MR, as it has a direct influence on loading conditions. On the other hand, exercise stress echocardiography can play an important role into revealing the clinical significance of FMR and can reveal hemodynamically significant MR in patients who have only mild MR at rest. Therefore, it has been established that an exercise-induced increase in ERO of \( \geq 13 \, \text{mm}^2 \) is linked to increased morbidity and mortality \(^{21}\).

In the following three circumstances of FMR, exercise echocardiography has been shown to provide implementable information \(^{22,23,24}\):

- Where there is a mismatch between the degree of exertional dyspnea and the extent of LV dysfunction or degree of regurgitation at rest;
- Where there is pulmonary edema without any clear reason;
- Where there is an indication for surgical revascularization in patients with moderate ischemic MR at rest and the development of severe MR on exercise, which might suggest the implementation of surgery with a MV repair procedure.

In patients with heart failure, exercise-induced increases in MR are related to the dynamic distortion of the MV geometry. It was hypothesized that dynamic MR may also be related to intermittent changes in LV synchronicity during exercise \(^{25}\) and LV asynchronism at rest substantially contributes to the worsening of FMR during dynamic exercise in patients with chronic heart failure due to LV systolic dysfunction \(^{26}\).

In patients with primary MR, current guidelines support the use of exercise echocardiography inpatients with discordant symptoms in order to objectivize the hemodynamic burden of FMR. Similar to secondary MR, primary MR seems to be susceptible to dynamic condition, which is incompletely described at rest. Recent studies show that decreased exercise capacity and
exercise-induced MR development or exercise PHT are linked to the evolution of the symptomatic scenario. Furthermore, according to recent evidence, exercise echocardiography should be performed on a regular basis in asymptomatic patients with severe MR in order to detect the absence of contractile reserve, which reveals subclinical LV dysfunction [27]. The lack of contractile reserve, initially defined as an increase in the LV ejection fraction at exercise of ≤4%, predicts poor postoperative prognosis in minimally symptomatic severe MR patients undergoing to surgery [28]. Otherwise, contractile reserve can be assessed by 2D speckle tracking, whereby a <1.9% increase in global longitudinal strain at peak exercise predicts postoperative LV deterioration in asymptomatic patients [24].

The management of patients with asymptomatic severe primary MR with preserved LV systolic function remains controversial, opposing early elective surgery [20] for the ‘watchful waiting’ strategy instead [29]. Current American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend MV repair for patients with either PHT or exercise PHT (pulmonary artery systolic pressure [SPAP] >60 mmHg), even in the absence of LV dysfunction or dilatation or symptoms (class IIa) [17].

According to the 2012 version of European Society of Cardiology (ESC) guidelines, surgery should be considered in asymptomatic patients with preserved LV function and a new onset of atrial fibrillation or PHT (systolic pulmonary pressure at rest >50 mmHg; class IIa) or PHT on exercise (SPAP ≥60 mmHg at exercise; class IIb) [30].

Enhancing echocardiography assessment of asymptomatic, severe DMR with an exercise test allows for a more precise identification of patients who require a closer follow-up and who might derive benefits from early referral for surgery. Watchful waiting seems to be more indicated in patients without the aforementioned risk factors or when MV repair is improbable.

### Assessment of MV anatomy & mechanisms underlying MR

As with surgical mitral repair, the echocardiographic assessment of mitral functional anatomy and the determination of the mechanism of MR are mandatory in order to select patients who can benefit from percutaneous intervention and to tailor the repair strategy. The MitraClip system is effective in selecting patients with both DMR and FMR. In DMR, the percutaneous clip anchors the flail and/or prolapsed leaflet, whereas in patients with FMR, it helps with the physiological closing forces by decreasing the time and the force required to close the valve, thereby improving the coaptation of the tethered leaflet(s).

In addition, the clip creates a tissue bridge between the two mitral leaflets, thus limiting annular dilatation and supporting the durability of the repair. Finally, the clip restrains the LV wall by restricting LV dilatation and induces reverse LV remodeling, which, in patients with functional/ischemic MR, may further reduce tethering and the resultant regurgitation.

Because percutaneous edge-to-edge repair by an implantable MitraClip approximates the middle scallops of the MV, creating a double-orifice MV, the central mitral scallops – A2 and P2 – have to be principally involved in the predominant mechanism of MR. The guidelines for the selection of patients for MitraClip reflect the selection criteria used in the two EVEREST trials. Patients with DMR (Carpentier type II dysfunction) with either prolapse or flail of the A2 and/or P2 scallops are candidates for the MitraClip, and in EVEREST II, such patients represented approximately two-thirds of those evaluated. Similarly, patients with FMR, either due to dilated cardiomyopathy or ischemic LV remodeling, are also candidates if the dominant MR jet rises from A2 to P2. In EVEREST II, these patients accounted for a third of those enrolled. In EVEREST II, patients with significant MR originating from the medial or lateral aspects of the valve were excluded, as were those with rheumatic disease, endocarditis and a MV area of <4 cm². Relative contraindications also include abnormal thicknesses of the leaflets or calcification that would hamper grasping by the device arms. Further functional anatomic features can exclude percutaneous MitraClip repair. In patients with FMR, a coapting surface length of <2 mm and/or a coaptation depth of >11 mm are considered to be contraindications for this kind of approach. In patients with DMR, those with a flail height (gap) of >10 mm and a flail width of <15 mm are excluded (Figures 4 & 5). For the MitraClip procedure, patients need to have moderate-to-severe or severe MR (>3 to 4), as previously described, and the appropriate MV morphology that is summarized in Box 1 [10].

During the feasibility planning of MitraClip
therapy, it is also important to rule out a coexisting relative MV stenosis with a mean gradient of ≥5 mmHg, as well as a rheumatic or a calcified restrictive leaflet morphology, either of which leads to a clear rise in the mean MV gradient after MitraClip implantation or can prevent secure attachment of the MitraClip. Caution is recommended as the safety and effectiveness of the MitraClip delivery system has not been established in the specific patient populations described in Boxes 2 & 3.

The morphological suitability criteria for MitraClip intervention have recently been modified (Table 2) according to the EVEREST criteria and the Crossroads training experiences on patient selection in:

- ‘Optimal VM’, which is well-suited for implantation;
- ‘Conditionally suitable VM’, which should be preferably treated in experienced centers, and
- ‘unsuitable VM’, which is contraindicated for therapy [31].

2D TEE MV anatomic assessment is performed using a systematic approach based on the description by Foster et al. in 1998 [32]. Some of the key views that may help with characterizing the valve pathology are summarized in Table 3.

A more detailed understanding of MR mechanisms and an accurate definition of the anatomy for distinguishing between simple and complex lesions have been facilitated by the use of real-time 3D TEE (RT3D-TEE) and will be necessary for improving percutaneous valvular interventions. RT3D-TEE has more or less become the standard imaging technique for the procedural guidance of MitraClip implantations [33] and its use is recommended by recent guidelines [21]. Since the normal MV is a complex, nonplanar, saddle-shaped structure, it cannot be examined in a single 2D ultrasound plane. Recent studies have demonstrated that RT3D-TEE is suitable for both the static and dynamic quantification of MV morphology under normal and pathological conditions. Precise knowledge of the MV anatomy during the cardiac cycle, including mitral annulus changes and mitral leaflet curvature and stress, is necessary in order to allow accurate characterization of the etiology of MV prolapse and therefore to further enhance MV repair surgery or MitraClip therapy and to define objective criteria for assessing postsurgery/procedure follow-up [34]. The measurement of the mitral annulus area by 3D echocardiography is accepted as an accurate method and a comparator for other methods [35]. Schmidt et al. have recently demonstrated that, in FMR, percutaneous treatment with the MitraClip device can produce immediate reductions both in mitral annulus size (anterior–posterior MV diameter) and tenting [36]. By contrast, these effects on mitral geometry cannot be demonstrated in DMR. Knowledge of this difference between the two types of MR may be important for improving procedural strategies (Figure 6) [36].

RT3D-TEE imaging has a higher resolution than 2D imaging for identifying specific mitral scallops (A1, A3, P1 and P3) and commissures. Furthermore, 3D offline reconstruction of the MV allows for a more detailed assessment of the shape and diameters of the mitral annulus compared with 2D TEE, as previously described. Both approaches provide almost similar values for the tenting area and the coaptation depth in FMR [37]. The implementation of echocardiography studies with 3D approaches improves the direct calculation of the leaflet angles, tenting volume and surface of the leaflets. 3D TEE imaging provides valuable and complementary information to multiplane 2D TEE or the assessment of patients with MR and may facilitate clinical decisions regarding the timing (early vs delayed surgery) and the correct approach to each case (surgery vs MitraClip procedure), thereby informing the patient of the probability of a percutaneous versus a surgical indication. Finally, echocardiographic evaluation has to include an accurate assessment of both LV and right ventricular (RV) chamber size and function (by both 2D and 3D approaches), as well as tricuspid regurgitation (TR) and pulmonary artery pressure (PAP). More than 30% of patients with DMR and FMR have concomitant TR ≥2 at the time of mitral surgery. The presence of severe TR is an independent predictor of poor outcome and lower quality of life after MV surgery [38,39]. On this basis, Taramasso et al. have assessed the impact of preprocedural TR ≥3 on the outcomes at mid-term follow-up after MitraClip treatment [40]. Their preliminary data show that TR is associated with an impaired quality of life in MitraClip candidates and, moreover, in patients with significant TR, in spite of similar echocardiographic profiles, the recurrence of MR ≥3, the incidence of death and rehospitalization for heart failure were higher at mid-term follow-up [40]. Tricuspid annular plane systolic excursion (TAPSE) <15 mm as a marker
Figure 4. Morphological characterization for MitraClip® eligibility. 2D transesophageal echocardiography (TEE) showing the measurement of (A) the coaptation depth and (B) coaptation length. Unsuitable morphologies for a MitraClip® implantation: (C) 2D TEE Image of an A2–P2 scallop prolapse, showing the measurement of the flail gap (>10 mm) resulting in severe mitral regurgitation; (D) a 3D reconstruction using Flexizoom with the 4D TEE transducer by GE Healthcare’s Vivid E9 confirmed a huge flail gap in the midportion.

LA: Left atrium; LV: Left ventricle.

Assessment of functional status & surgical risk
In addition to the MV anatomy and MR mechanism, the assessment of clinical status and functional impairment plays an important role in determining whether patients will derive benefits from the MitraClip procedure in terms of outcomes and improvements of functional status. Data published by Ussia et al. showed an improvement in New York Heart Association (NYHA) functional class (FC) after the procedure [5]. MR reduction after MitraClip implantation causes a reduction of LV volume overload and LV wall stress, improving the LV efficiency and pulmonary hemodynamics and leading to a clinical benefit and an improvement in NYHA FC [5]. In addition, the patients’ clinical
status may be defined by the 6-min walk test (6MWT) distances, the Minnesota Living with Heart Failure questionnaire (MLHFQ) score and the N-terminal pro-brain natriuretic peptide (NT-proBNP) plasma level. Franzen et al. showed that MitraClip therapy is feasible and effective in patients with end-stage heart failure and severely depressed LV ejection fraction, and at a median follow-up of 6 months, caused an improvements in NYHA FC in most patients, in 6MWT distances, in MLHFQ scores and NT-proBNP plasma levels, as well as LV ejection fraction and LV end-diastolic and end-systolic volumes \([3]\). Notably, more recently, an improvement in 6MWT distance and NYHA FC associated with significant cardiac reverse remodeling were even observed in patients with severely reduced LV ejection fraction at a follow-up of 1 year after MV repair \([42]\) and in approximately three-quarters of critically ill, elderly patients with moderate-to-severe MR not amenable to surgery \([43]\).

Our preoperative protocol includes echocardiogram (as previously described by TTE/TEE with the implementation of 3DRT-TEE) and evaluation of the surgical risk and the functional status. The functional status is usually assessed, as previously described, by the presence of heart failure symptoms (NYHA class) and 6MWT distance, according to the data available in literature, while quality of life can be evaluated by MLHFQ and Short Form-36 questionnaires. However, in patients with chronic MR, symptoms may appear only in the later stages of the disease and sometimes coincide with irreversible myocardial damage. The management of patients with MR is based in great part on functional limitations occurring with activity. In asymptomatic patients, no limitation is clinically detected, but this subjective assessment of FC does not account for the physical activity level of patients who are often sedentary and may be influenced in several situations or by comorbidities such as respiratory diseases. As a consequence, defining FC determinants in MR is a vexing problem. Although some patients with severe MR complain of no functional limitations, others with similar MR develop severe

<table>
<thead>
<tr>
<th>Box 1. Recommended mitral valvemorphological criteria.</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Moderate to severe mitral regurgitation (grade 3 or more out of four grades)</td>
</tr>
<tr>
<td>• Pathology in A2-P2 area</td>
</tr>
<tr>
<td>• Coaptation length &gt;2 mm (depending on leaflet mobility)</td>
</tr>
<tr>
<td>• Coaptation depth &lt;11 mm</td>
</tr>
<tr>
<td>• Flail gap &lt;10 mm</td>
</tr>
<tr>
<td>• Flail width &lt;15 mm</td>
</tr>
<tr>
<td>• Mitral valve orifice area &gt;4 cm(^2) (depending on leaflet mobility)</td>
</tr>
<tr>
<td>• Mobile leaflet length &gt;1 cm</td>
</tr>
</tbody>
</table>

\(^{†}\)The current patient considerations are based on the EVEREST II study and commercial European experience to date. The MitraClip Patient Selection Considerations document has been endorsed by the Crossroads faculty.

<table>
<thead>
<tr>
<th>Box 2. Disease-related criteria.</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Rheumatic heart disease</td>
</tr>
<tr>
<td>• Drug-induced mitral regurgitation (serotonergic properties, such as fenfluramine-derived amphetamines, including benfluorex; rye ergot derivatives, including dopamine agonists, such as asbromocriptine, lisuride, pergolide and cabergoline; migraine treatments, such as methysergide, ergotamine and dihydroergotamine; and drugs used for cognitive and neurosensory deficits, such as nicergoline and dihydroergocryptine, among others) currently underestimated</td>
</tr>
<tr>
<td>• Restrictive mitral regurgitation due to prolonged following mediastinal irradiation</td>
</tr>
<tr>
<td>• Mitral valve reconstruction leaflet surgery or annuloplasty ring (may perturb echocardiography visualization)</td>
</tr>
<tr>
<td>• Barlow’s disease or myxomatous leaflets (thickness &gt;5mm)</td>
</tr>
<tr>
<td>• Endocarditis</td>
</tr>
<tr>
<td>• Severe calcification (papillary muscles, leaflets and annulus)</td>
</tr>
<tr>
<td>• Intracardiac thrombus/mass</td>
</tr>
<tr>
<td>• Leaflet perforations</td>
</tr>
<tr>
<td>• Systemic disease (may influence leaflet quality)</td>
</tr>
</tbody>
</table>
Box 3. Procedural-related criteria†.

- Jet origin involvement in the A1–P1 or A3–P3 areas
- Short posterior leaflet (<8 mm)
- Restricted posterior leaflet in combination with mobile anterior leaflet
- Prolapse/flail width >15 mm
- Calcification in the grasping area near the jet
- Severe annular calcification
- Cleft
- Insufficient echocardiography window for procedural guidance
- Asymmetric thickness of anterior and posterior leaflets
- Reduced and enlarged dimensions of the left atrium
- Shifted heart axis (e.g., dextrocardia and pneumectomy)
- Any intracardiac device that may impact trans-septal access

†The current patient considerations are based on the EVEREST II study and commercial European experience to date. The MitraClip Patient Selection Considerations document has been endorsed by the Crossroads Faculty.

Preoperative evaluation before MitraClip®: present & future perspective

Functional limitations. The cardiopulmonary exercise test (CPET) with the determination of gas exchange more objectively assesses the capacity to exercise, minimizing the subjective aspects of obtaining the medical history and, according to our opinion, this should be integrated (where feasible and available) in the screening approach. In addition to the exercise test and the commonly used 6MWT, CPET provides a quantitative, objective and noninvasive evaluation of O₂ consumption and ventilatory parameters that are useful for risk stratification in patients with congestive heart failure. Recent outcome studies reported notable risks incurred by subsets of asymptomatic patients with MR [19,20], and guidelines highlight the importance of “a well-established estimation of exercise tolerance” and recommend exercise testing in order to objectively assess exercise tolerance [17]. In asymptomatic organic MR, FC quantitatively assessed by CPET is unexpectedly markedly reduced in one out of every four to five patients, with exercise levels that may be only half of those expected for their age. Reduced FC is an independent prognostic risk factor that is not related to the severity of MR. Markedly decreased FC (peak VO₂ ≤84% of expected) should suggest prompt MV surgery or percutaneous edge-to-edge repair because of the higher rate of events under medical management. Therefore, CPET frequently reveals subclinical functional limitations and is an important tool in managing patients with organic MR [44].

In patients with severe organic MR and mild or no symptoms, cardiopulmonary performance improves after successful minimally invasive video-assisted MV repair. Improvement is directly related to preoperative LV function and contractile reserve [45]; therefore, these data should lead to a greater use of CPET in MR in order to detect objective FC limitation before patients develop heart failure, which is associated with poor postoperative outcomes. However, CPET remains poorly understood and underutilized in current clinical practice. This is mainly due to the costs related to the collection and analysis of expired gases and the lack of trained personnel for the application and interpretation of the test results. Improvement of peak VO₂ after successful surgery remains uncertain and hotly debated, warranting future large prospective studies. At this time, little is known about the effect of the MitraClip procedure on CPET variables, although some studies are currently ongoing and our group is also working on this issue. As an example, we describe the reports of two CPETs performed by the same patient before (Figure 7) and 6 months after (Figure 8) a successful MitraClip procedure (echocardiography results of MR <2+) for severe FMR. At the time of the intervention, the patient was in a poor FC (NYHA class III/IV), affected by ischemic dilated cardiomyopathy, was a cardiac resynchronization therapy defibrillator nonresponder, was in optimal medical therapy and was not eligible for cardiac transplantation due to comorbidities. As can be seen, the exercise time, work load (expressed by maximal watts performed and the percentage of predicted value), peak O₂ uptake, maximum VO₂ (either as an absolute value or as a percentage of the predicted value) and peak O₂ pulse (maximum VO₂/heart rate, an indirect expression of cardiac output) are significantly increased (62 vs 98 watts, 42 vs
69%, 8.3 vs 12.1 ml/kg/min, 39 vs 54% and 8 vs 13 ml/kg/min, respectively). The minute ventilation/carbon dioxide production slope also improved, decreasing from a value of 35 to 30, indicating a better ventilator response. Our patient was able to perform a maximal effort at both times according to a ramp incremental protocol.

We apply this kind of protocol because of its better feasibility and its mirroring of a more physiological effort in such a fragile subset of patients. This is only an example of a patient in which a successful MitraClip procedure determines an improvement of subjective NYHA class (from III/IV to II), which also corresponds to better exercise capacity and CPET parameters.

Neurohormonal activation may play an important role in the impairment of exercise performance in patients with heart failure by limiting exercise-induced vasodilatation or by mismatching peripheral blood flow. As Nakamura et al. have demonstrated, the improvement in exercise capacity was related to an important decrease in plasma atrial natriuretic peptide levels (167 to 41 pg/ml, with a normal range of 5–45 pg/ml) [46]. LV dysfunction is the principle determinant of neurohormonal activation. As a consequence of this, Starling’s unpublished data on MR demonstrated a strong inverse correlation between plasma norepinephrine levels and LV contractility (r = -0.91) in a paper by Le Tourneau et al.; despite an improvement in symptomatic status, the persistent neurohormonal activation even after MV surgery probably reflects an incomplete recovery of LV contractility 7 months after surgery [47]. NT-proBNP plasma levels are strong independent factors in patients undergoing MitraClip procedures and, according to our opinion, should routinely be measured either to guide the selection of patients or during follow-up in order to assess whether there is a real improvement in FC. Furthermore, NT-proBNP levels >10,000 pg/ml in the presence of others negative prognostic factors (e.g., aged >80 years or TAPSE <15 mm as a sign of reduced RV function) suggest that the indication for MitraClip should be reconsidered [39]. The definition of ‘high operative risk’ and ‘very high age’ should also be a heart team decision based on the clinical presentation of the individual patient, their functional status (valuated by 6MWT, CPET, biomarkers as NT-proBNP plasma levels), assessment of risk scores (EuroSCORE II and Society of Thoracic Surgeons [STS] mortality risk calculation scores), LV ejection fraction and the morphology of the MV.

<table>
<thead>
<tr>
<th>Optimal valve morphology</th>
<th>Conditionally suitable valve anatomy</th>
<th>Unsuitable valve morphology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central pathology in segment 2</td>
<td>Pathology in segment 1 or 3</td>
<td>Perforated MV in segment 2 leaflet or cleft</td>
</tr>
<tr>
<td>No leaflet calcification</td>
<td>Mild calcification outside of the grip zone of the clip system, ring calcification, postannuloplasty</td>
<td>Severe calcification in the grip zone</td>
</tr>
<tr>
<td>Mitral valve opening area &gt;4 cm²</td>
<td>Mitral valve opening area &gt;3 cm² with good residual mobility</td>
<td>Hemodynamically significant mitral stenosis (valve opening area &lt;3 cm², MPG ≥5 mmHg)</td>
</tr>
<tr>
<td>Mobile length of the posterior leaflet ≥10 mm and posterior leaflet &lt;7 mm</td>
<td>Mobile length of the posterior leaflet 7--&lt;10 mm</td>
<td>Mobile length of the posterior leaflet &lt;7 mm</td>
</tr>
<tr>
<td>Coaption depth &lt;11 mm</td>
<td>Coaption depth ≥11 mm</td>
<td>--</td>
</tr>
<tr>
<td>Normal leaflet strength and mobility</td>
<td>Leaflet restriction in systole (Carpentier type IIIb)</td>
<td>Rheumatic leaflet thickening and restriction in systole and diastole (Carpentier type IIIa), radiation-associated restrictive MR, drug-related MR</td>
</tr>
<tr>
<td>Flail width &lt;15 mm</td>
<td>Flail width &gt;15 mm only mean pressure gradient with a large ring width and the option for multiple clips</td>
<td>Barlow’s syndrome with multiscallop flail</td>
</tr>
<tr>
<td>Flail Gap &lt;10 mm</td>
<td>Option for multiple clips</td>
<td>--</td>
</tr>
</tbody>
</table>

MPG: Mean pressure gradient; MR: Mitral regurgitation; MV: Mitral valve.
Surgical risk is usually based on either the EuroSCORE [48–50] or the STS mortality risk calculation [51] (a logistic EuroSCORE >20% or an STS mortality risk calculation score >12 is considered to be ‘high risk’) or by the presence of specific surgical risk factors that are not covered in the EuroSCORE. The interdisciplinary team must also assess the valve anatomy and the suitability for MitraClip treatment. As is the case with transcatheter aortic valve implantation, the complexity of the interventional treatment of MR and the high proportion of patients with comorbidities make the creation of a defined treatment team important. A MV team (‘heart team’) should ideally consist [31,52] of:

- An interventional cardiologist with experience in invasive and noninvasive diagnostics and the treatment of valve disease (a minimum experience of 25 interventional MV procedures per year should be aimed for, as well as expertise in trans-septal puncture);
- An echocardiographer with experience in transthoracic and, in particular, TEE diagnosis of valve disease, including the application of 3D approaches;
- A cardiologist with experience in heart failure management and therapy, as well as a geriatrician, should be included in the decision-making process because of the nature of aging patients;
- A cardiothoracic surgeon with expertise in reconstructive operative methods;
- An anesthesiologist with experience in cardiac anesthesics.

A joint decision from the cardiologists and cardiac surgeons in the heart team is necessary and should be documented. In contrast to transcatheter aortic valve implantation [31], the presence or immediate availability of a cardiac surgeon is, however, not required due to the low risk of the MitraClip procedure.

### Hemodynamic assessment: what role does it have in the selection of patients?

Coronary angiography, where clinically indicated, is also recommended in order to rule out any significant coronary artery disease or to treat significant coronary stenoses before performing catheter-assisted valve reconstruction. Both LV angiography and hemodynamic measurements using right heart catheterization can provide additional relevant information for the assessment of the severity of the valve disease and clinical decision-making. EVEREST II demonstrated that percutaneous MV repair was less effective at reducing MR than surgery; however, the procedure was safer and associated with a favorable hemodynamic response, while also providing a similar improvement in clinical outcomes [8]. The hemodynamic changes are reflected by an increase in forward stroke volume and cardiac index (CI) and a decrease in LV end-diastolic pressure. In addition, clip implantation results in a reduction in pulmonary capillary wedge pressure (PCWP) and PAP. As previously described by Siegel et al. [53] and then also by Biner et al. [54], in patients with elevated filling pressures and elevated systolic PAP (≥240 mmHg), there was a significant decrease in filling pressures after successful MitraClip therapy. Moreover, the decrease in systolic PAP correlated with a drop in the mean PCWP and the PCWP V wave. Severe MR is generally associated with volume overload and eccentric LV remodeling. Initially, changes in cardiac geometry allow for the accommodation of the regurgitant volume at low filling pressures. In
the compensatory phase, an increased preload and low afterload facilitate LV ejection, leading to an increased total CI and the maintenance of a normal CI. Chronic volume overload eventually induces LV systolic dysfunction. At this stage, normal CI is maintained at the expense of elevated left-sided filling pressures. If the MR is left uncorrected, there may be impairment of the forward CI and additional elevation of the PCWP and PAP. In patients with MR and hemodynamic decompensation, percutaneous MR reduction results in immediate hemodynamic improvement by increasing the forward CI and unloading the LV and LA without increasing the risk of periprocedural deterioration [54]. The potential increase in LV afterload following the eradication of the low-impedance regurgitant flow into the LA is one of the main issues with the surgical correction of MR. Furthermore, an increase in the afterload associated with the correction of MR could impair LV systolic performance and may result in an acute postoperative low cardiac output state [55–59]. The burden of this phenomenon in patients with surgically corrected MR by valve replacement or repair is not clearly defined because of the presence of several confounding factors linked to the nature of open heart surgery and the effects of cardiopulmonary bypass and cardioplegic arrest. By contrast, the MitraClip procedure represents a unique chance to assess the acute hemodynamic changes that are exclusively attributable to the reduction of MR, not requiring cardiopulmonary bypass. More recently, in addition to LV and LA reverse remodeling and to hemodynamic changes, MitraClip implantation has been demonstrated to be able to induce an improvement in the longitudinal systolic RV function, as evidenced both by the significant increase in TAPSE and by the RV Sm wave [60].

**Figure 6. Measurement of mitral annulus diameters and areas from 3D data.** For the measurements, an end-systolic volume was chosen, image settings (gain and so on) were adjusted and image plains were aligned optimally. Measurements included tenting height (D4), tenting area (A1), anterior posterior diameter (D1), lateral medial diameter (D2) and mitral annulus area (A2).
Conclusion

For patients with symptomatic, operable, severe MR, surgical intervention remains the gold standard treatment. The indication for interventional treatment of MR should always be determined on an individual basis, as there are currently no established guidelines for this therapy. During this decision-making process, a multiparametric approach is suggested and the following factors should be considered:

- The recommendations of the current guidelines from American, European and German societies for cardiology on the treatment of cardiac valve disease [17,30,31,52];
- The morphology of the MV;
- The cause and the severity of the MR;
- The LV and RV function;
- The functional status of the patient;
- The operative risk.

Given the results of the EVEREST II study, it is currently not possible to recommend MitraClip therapy for those patients who are in a highly recommended group for surgical treatment, based on the guidelines of the ESC for the treatment of cardiac valve disease (class I or IIa indication). Mainly patients with DMR or with chronic–ischemic FMR – for whom (operative) revascularization is pursued – are grouped into those classes. However, the grade of evidence for most of the class I or class IIa indications for operation consists of ‘expert- consensus’-level evidence only (evidence grade C) [17,30].

In the case of FMR without an option for simultaneous revascularization, there is little evidence of a benefit of surgery. According to the guidelines for such cases, the emphasis is on optimization of the medical therapy and, in appropriate cases, on biventricular pacing. In
Figure 8. Example of a cardiopulmonary exercise test performed by the same patient with the same protocol 6 months after a successful MitraClip® procedure. The reader should compare the underlined parameters with those in Figure 7. A discussion of these parameters is provided in the main text.

patients without a cardiac resynchronization therapy indication or in patients with persistent severe MR despite CRT, MitraClip implantation can be performed, if anatomically feasible.

According to Boekstegers et al., for certain patient groups, the MitraClip can be considered as a new treatment option [31]. In particular, these groups include:

- Patients with DMR, severe LV failure (LV ejection fraction <30%) and relevant comorbidities;
- Symptomatic patients with severe FMR, severe LV failure (LV ejection fraction <30%) and no option for revascularization;
- Symptomatic patients with severe FMR, mild-to-moderate LV failure (LV ejection fraction from 30 to 50%), no options for revascularization and relevant comorbidities.

Indeed, in these patient groups, who often also have a high operative risk or are inoperable, the MitraClip therapy has turned out to be a safe treatment option with a low 30-day mortality (ACCESS, TRAMI-Register) [61,62].

On the other hand, as suggested by Neuss et al., in the case of an NT-proBNP level of 10,000 pg/ml, patients aged >80 years or TAPSE of 15 mm as a sign of reduced RV function, the indication for MitraClip should be reconsidered [41]. Conservative medical therapy may be an adequate therapeutic option in these end-stage heart failure patients. Therefore, it is still hotly debated as to whether there is a real benefit of MitraClip...
intervention in patients who are affected by severe MR and end-stage heart failure with poor FC.

**Future perspective**

As the first of the interventional approaches to treat MR, the MitraClip procedure has the potential to effectively treat high-risk patients with FMR and significantly reduced LV function, who, in the past, would otherwise have frequently been refused conventional surgical approaches. Moreover, patients with DMR and a high operative risk or of a very high age can be provided with, at least in the mid term, a clinically sensible treatment. It must be stated that the MitraClip therapeutic approach is currently in an early stage of its clinical development. Most available results, including the published data of the EVEREST trials, are based on interventions performed during the early learning curve of the respective interventionalist. With increasing establishment of the method and continued self-critical use, further improvements in treatment results can be expected. On the basis of the most recent data in the literature, we should aim to obtain a better estimation of the clinical value of the MitraClip therapy before indicating patients for intervention enhancing functional assessment and MR grading by different available tools behind imaging. Due to current lack of long-term data, the decisions regarding therapy should be made by the interdisciplinary heart team, as previously described.

**Financial & competing interests disclosure**

FP Schmidt has received honoraria for lectures from Abbott Vascular. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

**References**

Papers of special note have been highlighted as: • of interest; •• of considerable interest


•• Cohort study demonstrating that mitral valve repair using the MitraClip® system in 51 patients at high surgical risk with severe left ventricular dysfunction (34% of patients had left ventricular ejection fraction <20%) is feasible with promising results.

Introduces the MitraClip system as a new technique of percutaneous mitral valve repair for mitral regurgitation. Data from the EVEREST studies suggest that valve repair with the MitraClip system is feasible, safe and associated with inferior clinical efficacy, but with similar improvements to surgical treatment in terms of clinical outcomes.

Introduces the MitraClip system as a new technique of percutaneous mitral valve repair for mitral regurgitation. Data from the EVEREST studies suggest that valve repair with the MitraClip system is feasible, safe and associated with inferior clinical efficacy, but with similar improvements to surgical treatment in terms of clinical outcomes.

The latest edition of American College of Cardiology/American Heart Association guidelines on the management of mitral regurgitation.


Clearly describes the role of echocardiography before, during and after the procedure of MitraClip implantation.

Reference paper on the echocardiographic assessment of mitral regurgitation.


Preoperative evaluation before MitraClip®: present & future perspective

- From the huge clinical experience with the MitraClip procedure in some German cardiovascular centers, this article summarizes their recommendations regarding the current indications and procedural steps of MitraClip treatment and may present a basis for the future development of official European guidelines.

- Demonstrates that percutaneous mitral valve repair using MitraClip is a safe technique in high-risk surgical patients, causing significant 1-year reductions of mitral regurgitation, which results in structural cardiac reverse remodeling and an increased left ventricular ejection fraction. The present data encourage percutaneous mitral valve repair in heart failure patients.

- Emphasizes the favorable hemodynamic effects of MitraClip therapy.

- Emphasizes the favorable hemodynamic effects of MitraClip therapy.

- Emphasizes the favorable hemodynamic effects of MitraClip therapy.

- Emphasizes the favorable hemodynamic effects of MitraClip therapy.

- Emphasizes the favorable hemodynamic effects of MitraClip therapy.

- Emphasizes the favorable hemodynamic effects of MitraClip therapy.

- Emphasizes the favorable hemodynamic effects of MitraClip therapy.

- Emphasizes the favorable hemodynamic effects of MitraClip therapy.

- Emphasizes the favorable hemodynamic effects of MitraClip therapy.

- Emphasizes the favorable hemodynamic effects of MitraClip therapy.

- Emphasizes the favorable hemodynamic effects of MitraClip therapy.
