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Contemporary Status of Percutaneous Transcatheter Edge-to-Edge Repair: Is It a Complement or Replacement to Mitral Surgery?

Hunbo Shim[1], MD, PhD, Edward Percy[1,2], MD, Sameer Hirji[1], MD,MPH, and Tsuyoshi Kaneko[1], MD

Abstract

Transcatheter mitral valve repair devices borrow from the concept of surgical edge-to-edge approximation and are becoming increasingly used in patients with both primary and functional mitral regurgitation. The application of these new devices is expanding globally; however, debates between which patients are amenable to surgery vs. percutaneous approaches are ongoing. As new trials and regulatory approvals have evolved, the indications for transcatheter approaches have expanded, in a way that is complementaty to existing indications for surgical repair. In general, the treatment of mitral regurgitation should be stratified based on underlying pathophysiology and anatomy by a multidisciplinary team including cardiac surgeons and interventional cardiologists. This review aims to provide practical approaches to patient selection and treatment strategies for mitral regurgitation based on historical data and recently published trials, with a focus on the distinction between surgical and transcatheter mitral therapies.

Keywords

MitraClip, mitral valve surgery, mitral regurgitation, transcatheter mitral valve repair

Central Message

Transcatheter mitral repair should be viewed as a compliment to mitral surgery, not a replacement. Treatment strategies for mitral regurgitation should be approached by a multidisciplinary heart team, in which surgeons should be actively involved.

Introduction

Mitral regurgitation (MR) is the most common valve disease in the United States. Its prevalence increases with age, and roughly 10% of individuals aged 75 and older have evidence of at least moderate MR.[1,2] Many clinicians further postulate that this number is expected to nearly double by 2030 given the longevity of the aging population.[1] MR is generally classified as either primary, involving lesions of the valve leaflets or chordae tendinea, or secondary/functional, which can occur in the setting of tethered but intact leaflets, due to either left ventricular dysfunction, dilatation, or remodeling.[2] The pathophysiology of MR is a result of the complex interaction between the left atrium, mitral valve (MV) annulus, leaflet tissue, subvalvular apparatus, and left ventricle. Thus, the successful management of MR requires a thorough and systematic understanding of these underlying interactions.

In terms of correction of MR, surgery remains the gold standard in primary MR, but outcomes for surgery in secondary or functional disease remain suboptimal, with a lack of equipoise between repair or replacement.[3,4] The presence of high-risk comorbidities and advanced age has further complicated the surgical landscape in terms of patient selection.[5] These concerns, in part, have been an impetus for clinicians to explore less invasive options for management of MR, and as a consequence, we have witnessed a remarkable growth and innovation in transcatheter mitral technologies, in particular, the MitraClip system (Abbott Laboratories, Abbott Park, IL, USA). The MitraClip system, which mimics the surgical Alfieri's "edge-to-edge" technique, consists of steerable guide catheter, clip delivery system, and an implantable clip (Fig. 1). Femoral venous access and a transseptal approach allow the clip to be

[1]Division of Cardiac Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
[2]Division of Cardiovascular Surgery, University of British Columbia, Vancouver, Canada

Corresponding Author:
Tsuyoshi Kaneko, Division of Cardiac Surgery, Brigham and Women's Hospital, 15 Francis St., Boston, MA 02115, USA.
Email: tkaneko2@bwh.harvard.edu

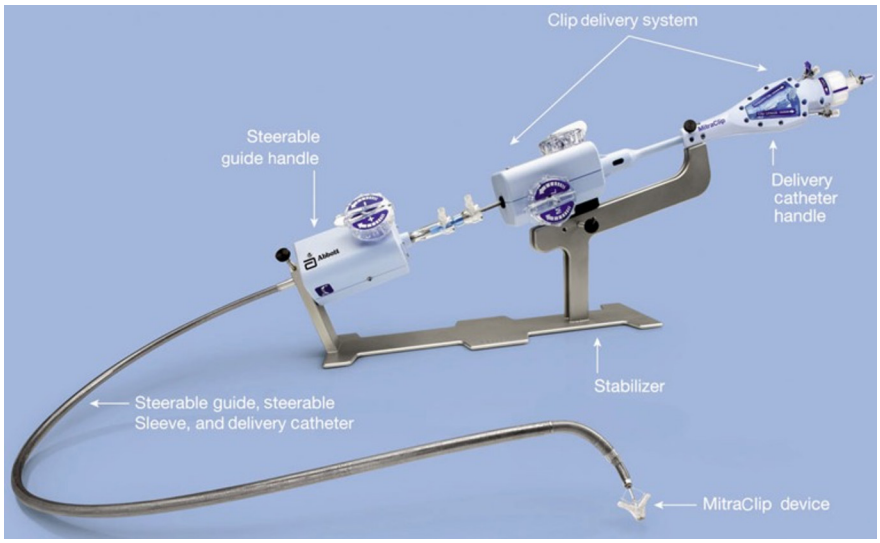

Fig. 1. The MitraClip system consists of the steerable clip delivery system with the clip device affixed to the distal end. Reproduced with permission from Sherif MA, Paranskaya L, Yuecel S, et al. MitraClip step by step; how to simplify the procedure. *Neth Heart J.* 2017;25(2):125–130, under Creative Commons Internation License: http://creativecommons.org/licenses/by/4.0/. No changes were made.

deployed in the line of coaptation at the origin of the regurgitant jet, guided by a combination of both transesophageal echocardiography (TEE) and fluoroscopy (Fig. 2).[6]

The MitraClip system was initially approved by the Food and Drug Administration (FDA) in 2013 for use in high-risk patients with primary MR.[7] More recently in 2019, it was approved in patients with secondary MR following the success of the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial.[8] Since initial introduction, it has been used in over 70,000 patients globally with several multicenter, randomized and registry studies examining its applications.[9–12] Recently, the updated third-generation MitraClip devices (NTR and XTR) were introduced. The NTR clip has the original NT Clip size, but with an improved delivery system. The XTR has been designed with arms that are 3 mm longer, with the intention of improving overall grasp and reach. With the expanded FDA approval and recent innovations in the delivery systems, the number of cases amenable to MitraClip technology is expected to grow significantly. In light of these developments, a contemporary critical appraisal of the MitraClip system for the treatment of both primary and secondary MR is warranted. In particular, as

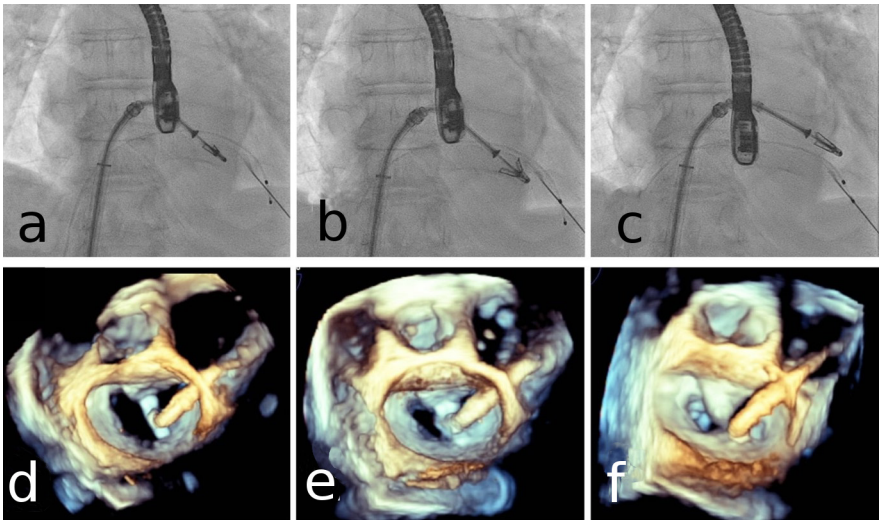

Fig. 2. Fluoroscopy demonstrating MitraClip implantation with clip delivery system across the interatrial septum (a, b, and c) and three-dimensional transesophageal echocardiography of surgeon's view of mitral valve during the procedure (d, e, and f).

seen in transcatheter aortic valve replacement (AVR) surpassing the number of surgical AVR performed in the United States, the question is whether wider patient population should be treated with MitraClip over surgical MV repair. In this review, we will examine the mechanics of the MitraClip system and discuss practical approaches to patient selection and treatment strategies. Most importantly we will discuss the current and the future directions of this technology in relationship to MV surgery.

Approaches to Patient Selection

Since overall outcomes vary greatly depending on the etiology and mechanism of MR, appropriate patient selection is paramount. The first step involves making the correct distinction between primary and secondary MR through careful assessment of MV leaflet, annular and subvalvular morphology, leaflet motion, and annular dynamics. Transthoracic echocardiography is most commonly utilized, but if image acquisition is poor and the clippability is uncertain, TEE may be utilized to precisely define anatomy and MV function. Unlike secondary MR, the diagnosis of primary MR is often easier to discern because it is generally based on morphological abnormalities of the mitral leaflets or chordae.

Treatment Strategies for Primary MR

1. The Role of Surgery

For all patients with primary MR, surgery remains the principal treatment modality. This is because the annual risk of sudden death in primary disease is high—ranging from 0.8% in asymptomatic patients with normal ejection fraction and sinus rhythm, to 12% in symptomatic patients with New York Heart Association (NYHA) functional classification III/IV.[2,13,14] According to current guidelines,[15,16] MV surgery is indicated in patients with severe MR and left ventricular ejection fraction (LVEF) >30% who are symptomatic (Stage D) or asymptomatic but with LVEF 30% to 60% or LV end-systolic dimension (LVESD) ≥40 mm (Stage C2) and new onset of atrial fibrillation, or systolic pulmonary arterial pressure above 50 mmHg.[17] Since MV repair mitigates the hemodynamic burden and maintains LV function by restoring the competence of the MV, it is strongly preferred over replacement, despite the lack of randomized trials comparing outcomes after MV repair vs. replacement for primary disease.[18] Factors associated with successful repair are largely attributable to anatomy, technical feasibility, surgeon volume, and expertise.[19,20] MV repair also has benefits over replacement in terms of mortality, preservation of LV function, improved durability, and restoration of life expectancy to that of the age- and sex-matched US population.[21–27]

2. The Role of the MitraClip System

Early experiences with the MitraClip device showed promising results with high rates of MR reduction and low procedural mortality.[28,29] For instance, among 564 high-risk surgical patients (median Society of Thoracic Surgeons (STS) predicted mortality score of 7.9%), Sorajja et al. reported a procedural success rate of 90.6% with a 2.3% in-hospital mortality.[29]

Despite the favorable short-term outcomes, longer-term outcomes following MitraClip in primary MR have not been so successful. This was observed in the EVEREST II (Endovascular Valve Edge-to-Edge Repair Study) trial, the first prospective multicenter, randomized control study that compared the safety and effectiveness of the MitraClip System with MV surgery in the treatment of severe MR.[30] The study included symptomatic patients with LVEF >25% and LVESD ≤55 mm, or asymptomatic patients with LVEF 25% to 60%, LVESD ≥40 mm, new atrial fibrillation, and pulmonary hypertension. Seventy-three percent of those included had primary MR.[30] Although the rate of major adverse events was statistically lower in the MitraClip group compared to surgery at 30 days—this was primarily driven by reductions in blood transfusions—the rates of the primary composite end-point (freedom from death, reintervention, and grade ≥3+ MR) were more favorable for surgery (73% vs. 55%; $P = 0.007$) at 1 year. Beyond 1 year, however, the mortality rate, NYHA functional class, and freedom from reoperation were similar between the groups.[30]

While these results have informed current use of MitraClip, there were several notable limitations of the EVEREST II trial. First, the overall study population was a heterogeneous mix of patients with primary and functional MR. Second, the inclusion criteria in the trial were different from current or previous guidelines for MV surgery, which introduced selection bias. Third, significant differences in patient compliance between the MitraClip and surgery groups have led to difficulty in evaluating overall effectiveness and, finally, the fact that the surgical group included both repair and replacement was also a major confounder.[31]

In a subset of older patients with the complex primary disease and high comorbidity burden, however, the benefits of surgical repair may be diminished, paving the way for use of the MitraClip system. For instance, Gillinov et al. have previously demonstrated that repair is not associated with survival benefit in these individuals, where long-term survival is likely to be governed more by the patient's comorbidities than the operation itself.[23] Furthermore, among the patients enrolled in the EVEREST II trial, 127 were retrospectively identified as having a prohibitive surgical risk with mean STS score of 13.2%. Among the surviving patients who underwent treatment with MitraClip systems, outcomes appeared to be favorable: 82.9% maintained a regurgitation grade of ≤2 + at 1 year, and 86.9% had NYHA class I/II. Heart failure-related hospitalizations and Short Form 36 quality-of-life scores were also reduced in these patients.[30]

Likewise, the High and Intermediate Risk Degenerative Mitral Regurgitation Treatment (HiRiDe) trial was designed to randomize high- and intermediate-risk patients between MitraClip and surgery. Unfortunately, this study was prematurely terminated due to enrollment difficulties. For low- or

intermediate-risk elderly patients with primary MR, MitraClip has been associated with a lower incidence of acute postoperative complications and increased survival within 1 year compared to surgery, but at the expense of greater rates of MR recurrence and reduced survival beyond the 1-year period.[32,33]

In light of the above results, the MitraClip system is currently restricted to the management of symptomatic (NYHA functional class III or IV) patients with severe primary MR, who have a reasonable life expectancy, and prohibitive surgical risk due to their underlying comorbidities.[15,20] In these patients, MitraClip has been associated with improved functional status, favorable ventricular remodeling, and decreased rehospitalization at 1 year.[34] This is reflected by a Class IIb recommendation in the 2014 guidelines on the management of valvular heart disease.[16] Additionally, the following anatomical morphological considerations should be taken into account: a coaptation depth <11 mm, flail width <15 mm, fail gap <10 mm, and minimal calcification in the grasping area. To avoid postprocedural stenosis, MV area should be more than 4.0 cm^2. Despite these recommendations, however, it must be noted that there have been no good quality studies directly comparing the use of MitraClip vs. surgery in primary MR.

Treatment Strategies for Functional MR

1. The Role of Surgery

The pathophysiology of functional MR is complex and typically results from distorted geometry of a dysfunctional LV. This eventually leads to papillary muscle displacement, annular dilatation, and/or reduced closing forces in an otherwise intact MV. Since there is no organic cause for MR, the role of surgery in patients with functional MR is limited. Currently, there is also no evidence for a survival benefit of surgery in severe functional MR although recent observations have demonstrated a higher MR recurrence rate following MV repair[35] and higher mortality in MV replacement.[36] Wu et al. compared results of MV repair to medical management in 419 patients with EF ≤30% and moderate-to-severe MR. The study found no difference in mortality, rates of ventricular-assisted device insertion, and transplantation between 2 groups.[35]

For patients with functional MR who undergo surgical revascularization, the effect of concomitant MV surgery is suboptimal. A randomized trial from the Cardiothoracic Surgical Trials Network (CTSN) showed no difference in LV reverse remodeling at 2 years between coronary artery bypass surgery (CABG) alone and CABG with concomitant MV repair among the 301 patients with moderate ischemic MR. Although MV repair demonstrated reductions in MR, the rates of neurological events and arrhythmias were significantly higher.[37] In light of these observations, current guidelines weakly recommend combined MV repair in patients with chronic, severe functional MR who are undergoing either coronary artery bypass or aortic valve replacement (Class IIb).[38] It should be noted that these concomitant cases may demonstrate improvements in symptoms and exercise tolerance, but not in overall survival rate.[39–42] Likewise, for severe symptomatic patients with severe ischemic MR, chordal sparing MV replacement may be reasonable over downsized annuloplasty repair. This is based on findings of another CTSN trial, which compared MV repair vs. replacement in 251 patients with severe ischemic MR, and showed that MV repair patients experienced a significantly higher rate of recurrent moderate or severe MR with more cardiovascular readmissions in follow-up.[43] In symptomatic patients with NYHA III or IV, MV surgery is considered only if guideline-directed medical therapy (GDMT) is unsuccessful at relieving symptoms but the recommendation level is low (Class IIb).

2. The Role of the MitraClip System

The utility of MitraClip for treatment of functional MR is gaining momentum given the lack of survival benefit from surgery in this population. A recent meta-analysis of MitraClip in patients with functional MR included 23 studies and found that MitraClip was associated with improvements in symptoms, a decline in heart failure hospitalization, and reductions in cardiovascular mortality. A total of 3,253 patients with a mean follow-up of 11.7 years were included in the study. The mortality rate at 1 year was 18.5%, and 83.4% of patients maintained an MR grade ≤2+ . At 1 year, 76.6% of the patients remained in NYHA functional class I or II.[44]

Likewise, in a subset analysis of 616 patients with functional MR from the EVEREST II trial, MitraClip was associated with acceptable safety, reductions in MR severity, improvement in symptoms, and positive ventricular remodeling.[45] When stratified by non-high surgical risk vs. high surgical risk status (defined as STS risk of mortality ≥12% or predefined risk factors), both groups achieved comparable MR reductions at 1 year and improvements in LV end-diastolic volume. In the high-risk cohort, the annualized rate of heart failure hospitalizations decreased from 0.68 to 0.46 in the 12 months before to 12 months after the procedure ($P < 0.001$). This large subgroup analysis showed that highly selected patients with functional MR can attain significant benefits from the MitraClip system.

The durability of MitraClip in functional MR without annular intervention remains a concern in the long run. Surgically, restrictive annuloplasty is the most preferred procedure to restore valve competence especially in the setting of annular dilation.[46] Furthermore, the addition of annuloplasty to the surgical edge-to-edge procedure has shown improved outcomes previously.[47] In fact, De Bonis et al. reported lower durability of MitraClip compared with the surgical edge-to-edge technique combined with annuloplasty at 4 years. In these MitraClip patients, freedom from MR ≥3+ at 4 years was only 75%, compared to 94% in the surgical group ($P = 0.04$). The use of MitraClip was also a significant predictor of MR recurrence, although there was no difference between the 2 groups in terms of late mortality or reoperation.[47] In contrast, 5-year results

from the EVEREST II trial showed comparably low rate of reintervention for mitral valve dysfunction with either MitraClip or surgical therapy. Between 6 months and 5 years, there was no difference in freedom from reintervention for MV dysfunction (77.7% with MitraClip repair vs. 76.2% with surgery; $P = 0.77$).[48] Given these conflicting results and a paucity of high-quality data in this area, the role of the annuloplasty in addition to transcatheter edge-to-edge repair for functional MR remains in question although we surgeons believe that it is an integral aspect of MV surgery.

MitraClip Versus Medical Therapy in Functional MR: The Debate Between COAPT and MITRA-FR

As we seek to further understand the role of MitraClip in patients with functional MR, it is important to dissect and understand the results of 2 recent landmark randomized controlled trials comparing MitraClip with guideline-directed medical treatment patients with severe functional MR and symptomatic heart failure.[10,11] Interestingly, despite overall similarities in study design, the 2 study findings were dramatically different and controversy-provoking. The trials themselves can be summarized as follows:

1. Trial Study Design and Key Outcomes

a.The COAPT trial[10]. A total of 614 patients with grade 3 to 4+ functional MR despite the maximal GDMT were randomized to MitraClip and GDMT (**n** = 302) vs. GDMT alone (**n** = 312). The objective of the trial was to assess the safety and efficacy of the MitraClip in this population. All patients had LVEF 20%-50% and LVESD <70 mm. The trial showed that MitraClip plus GDMT was superior to GDMT alone in reducing 2-year HF hospitalization (35.8% vs. 67.9%, hazard ratio (HR) 0.53; 95% CI:0.40 to 0.70; **P** < 0.001) and mortality (29.1 vs. 46.1%; HR 0.62; 95% CI 0.46 to 0.82; **P** < 0.001). Significant improvements were also noted in quality of life, as indicated by NYHA functional class I or II (72.2% vs. 49.6%) and change in the mean Kansas City Cardiomyopathy Questionnaire Score (KCCQS) (+12.5 vs. −3.6 points). The MitraClip-induced left ventricular reverse remodeling at 12 months showed reduced LVEDV. MitraClip also showed an excellent safety profile, with a complication rate of only 3.4% at 12 months (composite of single leaflet attachment, device embolization, endocarditis or mitral stenosis needing surgery, left ventricular assist device implantation, cardiac transplantation, and device complication requiring non-elective cardiovascular surgery).

Recently, 3-year follow-up data of the COAPT trial was presented at the 2019 Transcatheter Cardiovascular Therapeutics meeting. This presentation revealed durable results in the MitraClip plus GDMT arm, who again experienced fewer HF hospitalization and deaths than GDMT alone (58.8% vs. 88.1%; HR 0.48; 95% CI 0.39 to 0.59; $P < 0.001$). Interestingly, this data also revealed that the MitraClip provided benefits even when applied after a 2-year delay. Since crossovers were permitted after the 2-year mark in COAPT, 18.6% (58/312) of patients in GDMT-alone group had crossed over to recieve MitraClip. In these patients, first HF hospitalization at 1 year was lower than for those who remained in the GDMT alone g890602890602890602ginally assigned to MitraClip.

b. The MITRA-FR trial[11]. In the MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) trial, 304 patients with severe functional MR and LV dysfunction (LVEF 15% to 40%) were randomized into either the MitraClip and GDMT (**n** = 152) or GDMT alone (**n** = 152). This trial failed to show the superiority of the MitraClip over medical therapy alone in reducing adverse events. The primary composite of mortality and heart failure hospitalization at 12 months was similar between groups (54.6% vs. 51.3%; odds ratio 1.16; 95% CI 0.73 to 1.84). The quality of life, improvement in NYHA functional class, and reverse remodeling at 12 months were also similar with a 14.6% complication rate in the intervention group (composite of device implantation failure, significant hemorrhage or vascular event, atrial septal lesion, cardiogenic shock requiring inotropes, cardiac embolism, tamponade, and urgent conversion to cardiac surgery).

2. Trial Differences and Reconcilliation

Despite similarities in study designs, the 2 trials had disparate findings. The most likely explanation for this discrepancy is most likely due to differences in the characteristics of patients enrolled.

a. Definitions of functional MR. The criteria used for defining the severity of MR were different between the 2 studies. Severe MR in MITRA-FR was defined as an effective regurgitant orifice area (EROA) of more than 20 mm^2, per ESC valvular guidelines[49] while it was more than 40 mm^2 in COAPT, in accordance with the 2014 ACC/AHA guidelines.[17] As a result, MITRA-FR included more modest degrees of MR.

b. Degrees of left ventricular dysfunction. The inclusion criteria for LVEF varied between the trials (20% to 50% in COAPT vs. 15% to 40% in MITRA-FR). Furthermore, patients in MITRA-FR had larger indexed LVEDV (135 ± 35 mL/m^2), compared to COAPT (101 ± 34 mL/m^2). In fact, the COAPT trial excluded patients with LVESD >70 mm. This difference suggests that the patients with more advanced stages of LV dysfunction were included in the MITRA-FR trial, and, therefore, MitraClip may not provide as much benefit in these patients.

c. Differences in guideline-directed medical therapy. Although both studies included GDMT, there was a clinically meaningful difference in these inclusion criteria. In the MITRA-FR trial, GDMT both at baseline and during follow-up was determined locally, was not monitored centrally, and did not require adjudication. The COAPT trial used more strict criteria

for GDMT prior to patient enrollment. Thus, patients in the COAPT trial were clinically optimized prior to enrollment by central enforcement of maximal GDMT. Considering that the management of functional MR is so dependent on the medical restoration of LV function, rather than the pure mechanical leaflet correction, the extent of medical optimization likely contributed to the observed overall results.

d. Differences in proportionate and disproportionate MR. Recently, Grayburn et al. proposed that patients with functional MR represent a heterogeneous group, which can be subdivided further based on whether the estimated EROA is expected or proportionate to the LVEDV based on the "Gorlin hydraulic orifice equation."[50] In MITRA-FR, baseline mean LVEDV was 252 mL and the mean EROA was 31 mm^2. These features are consistent with a degree of MR that is severe, but proportional to the degree of LV dilatation. In contrast, in the COAPT trial, baseline mean LVEDV was 192 mL and the mean EROA was 41 mm^2. Therefore, MR in the COAPT trial was disproportionately greater compared with the degree of LV dilatation. Patients enrolled in the COAPT trial had 30% higher EROA and 30% smaller LV volumes compared with those in the MITRA-FR trial. In short, patients in the COAPT study had a greater degree of disproportionate MR observed.

The results from these 2 trials can be reconciled. Cohorts in the COAPT had more valvular dysfunction over ventricular dysfunction, and thus experienced a more severe degree of MR with less ventricular remodeling. The MitraClip was more effective in the patients who had less advanced left ventricular dysfunction with greater MR disproportionately. Preliminary subgroup analysis in the COAPT showed that in patients with EROA of 30 mm^2 or less, similar to those included in MITRA-FR, there was no benefit in 1-year all-cause mortality and heart failure-associated hospitalization, irrespective of indexed LVEDVs. This supports the idea that the relationship between the degree of MR and the level of LV dysfunction is an important factor in the success of an isolated transcatheter edge-to-edge repair.

Furthermore, in some situations, MR cannot be explained by ventricular dilation alone. Specific regional changes within the LV may affect the MV apparatus to a greater degree than global LV dyfunction.[51] EROA is dependent on both the LVEDV and LVEF, such that among patients with reduced LVEF 30% and left ventricular dilation (LVEDV 200 to 250 mL), an EROA of 20 mm^2 is common and reflects only a moderate degree of MR.[52] The patients who experienced a greater response to MV intervention were likely to have a less dilated LV and relatively larger EROA, where the ratio of EROA to LVEDV was higher among patients with disproportionate MR than those with proportionate MR.

Given these results from the MITRA-FR and COAPT trials, we can draw the following criteria for the MitraClip in patients with more than moderate-to severe functional MR:

1. EROA ≥ 30 mm^2 and/or regurgitant volume >45 mL;
2. LVEF (20% to 50%) and LV end-systolic diameter <70 mm;
3. Persistent heart failure symptoms (NYHA III/IV) despite optimal GDMT including cardiac resynchronization therapy, if indicated.

In March 2019, the FDA approved MitraClip for prohibitive surgical risk patients with functional MR who remain symptomatic despite optimal medical therapy. As COAPT has been the first clinical trial to show a survival benefit with intervention in this population, further trials will be important to understand whether surgery can show a similar impact in this group.

Ongoing Studies in Functional MR

Two upcoming studies will further shape our understanding of the optimal treatment in patients with functional MR (Table 1). The RESHAPE-HF2 trial (ClinicalTrials.gov Number NCT02444338) is an international study designed to provide additional evidence for the use of MitraClip in patients with chronic heart failure and clinically significant functional MR. The trial has been designed with MR inclusion criteria similar to that of COAPT. In terms of LV dysfunction, however, the criteria lie in between COAPT and MITRA-FR. This trial should hopefully provide additional information on the importance of LV dysfunction, as well as disproportionality of MR in patients with the functional disease.

Additionally, the MATTERHORN trial (ClinicalTrials.gov Number NCT02371512), currently being conducted in Germany, will explore efficacy and safety of the MitraClip vs. surgical management in the patients with functional MR with depressed LV function considered to be at high surgical risk.

Pitfalls of MitraClip and Future Directions

Despite the promise of this transcatheter technology, we must take this hype with a grain of salt. The double orifice valve created by the MitraClip device raises the concern of postprocedural mitral stenosis. A recent retrospective study by Neuss et al. showed that transmitral mean pressure gradient >5 mmHg after MitraClip was associated with higher mortality (P = 0.018) and combined endpoint of mortality and reintervention (P = 0.001).[53] Higher left atrial pressure index after MitraClip was predictive of worsening NYHA status and rehospitalization for heart failure.[54] An MV area ≥4 cm^2 or preprocedural mean transmitral pressure gradient >5 mmHg should be avoided to prevent the acceleration of stenosis. Additionally, the durability of the isolated transcatheter edge-to-edge repair without annuloplasty remains to be seen. This is a relevant concern given the suboptimal long-term results of surgical edge-to-edge repair performed in isolation.[55]

As residual MR is associated with higher mortality, less resolution of MR after MitraClip makes surgery favorable for the treatment of primary MR.[30,56–58] MitraClip should be reserved for high-risk or nonoperative patients until further evidence

Table 1. Upcoming Trials Examining the Use of MitraClip in Functional MR.

	RESHAPE-HF2	MATTERHORN
Expected completion	March 2021	December 2019
Study type	Randomized	Randomized
Country	Czechia, Denmark, Germany, Greece, Italy, Poland, Portugal, Spain, United Kingdom	Germany
Enrollment	420	210
Aim	MitraClip + GDMT vs GDMT	MitraClip vs surgery
Inclusion	Functional MR (moderate-severe/severe) Optimization for ESC/HFA therapy LVEF 15%-35% (NYHA II) LVEF 15%-45% (NYHA III-IV)	Functional MR (Significant) LVEF ≥ 20% High surgical risk NYHA II-IV on GDMT
Exclusion	Degenerative MR Transplanted heart Acute coronary syndrome TIA/stroke Any cardiovascular surgery Mitral valve surgery candidates Renal replacement therapy 6MWT > 475 m Mitral valve area < 4.0 cm^2	Severe TR Other severe valve disorders Coronary revascularization within 1 month CRT within 1 month
Follow-up	24 months	12 months
Primary outcome	CV death Rehospitalization for HF	Death Rehospitalization for HF Reintervention Ventricular assist device Stroke
Secondary outcome	MR reduction at 12 and 24 months 6MWT at 6, 12, and 24 months CV hospitalizations/death at 24 months KCCQ at 12 months NYHA I/II at 6, 12, and 24 months PGA at 6, 12, and 24 months	MR (+3−4) recurrence 6 MWT NYHA MLHFQ score LV remodeling Change in BNP Length of stay ICU/HD

6MWT, 6 minute walk test; BNP, B-type natriuretic peptide;CRT, cardiac resynchronization therapy; CV, cardiovascular; ESC/HFA, Heart Failure Association of the European Society of Cardiology; GDMT, guideline-directed medical treatment; HD, hospital days; HF, heart failure; ICU, intensive care unit; KCCQ, Kansas City Cardiomyopathy Questionnaire; LV, left ventricular; LVEF, left ventricular ejection fraction; MLHFQ, Minnesota Living with Heart Failure Questionnaire; MR, mitral regurgitation; NYHA, New York Heart Association functional class; PGA, patient global assessment; TIA, transient ischemic attack; TR, tricuspid regurgitation.

exists. This may change in due course depending on the results of upcoming trials. On the other hand, in patients with functional MR, no study has yet shown a benefit of isolated surgical MV repair or replacement.[35,36] These patients tend to be higher-risk with underlying cardiomyopathy. Given the challenges faced in this population, and the results of the COAPT trial, MitraClip combined with GDMT will become the treatment of choice in these patients. Surgery will still have a role in patients requiring concomitant procedures in the setting of functional MR, keeping in mind that it may only improve symptoms but not overall long-term mortality. In both primary and functional MR, further technological innovations such as newer generation devices and combined use with transcatheter annuloplasty with leaflet clips will likely extend indications for transcatheter therapies in the future.

Is MitraClip a Complement or Replacement to Mitral Surgery?

As technology advances, patients receive the benefit of minimally invasive procedures that result in faster recovery and improved quality of life both in the short term and long term. MitraClip is a minimally invasive procedure that often results in patients being discharged the next day. However, minimal invasiveness should not be chosen over the long-term benefit of more invasive treatment. If the patient is a reasonable surgical candidate, one should undergo surgical MV repair to receive the benefit of this procedure. The industry is discussing a randomized control study between surgery and MitraClip for intermediate-risk primary MR patients, and it remains to be seen where the line will be in terms of risk stratification. In secondary MR, although we can draw possible patient criteria from reconciliation of COAPT and

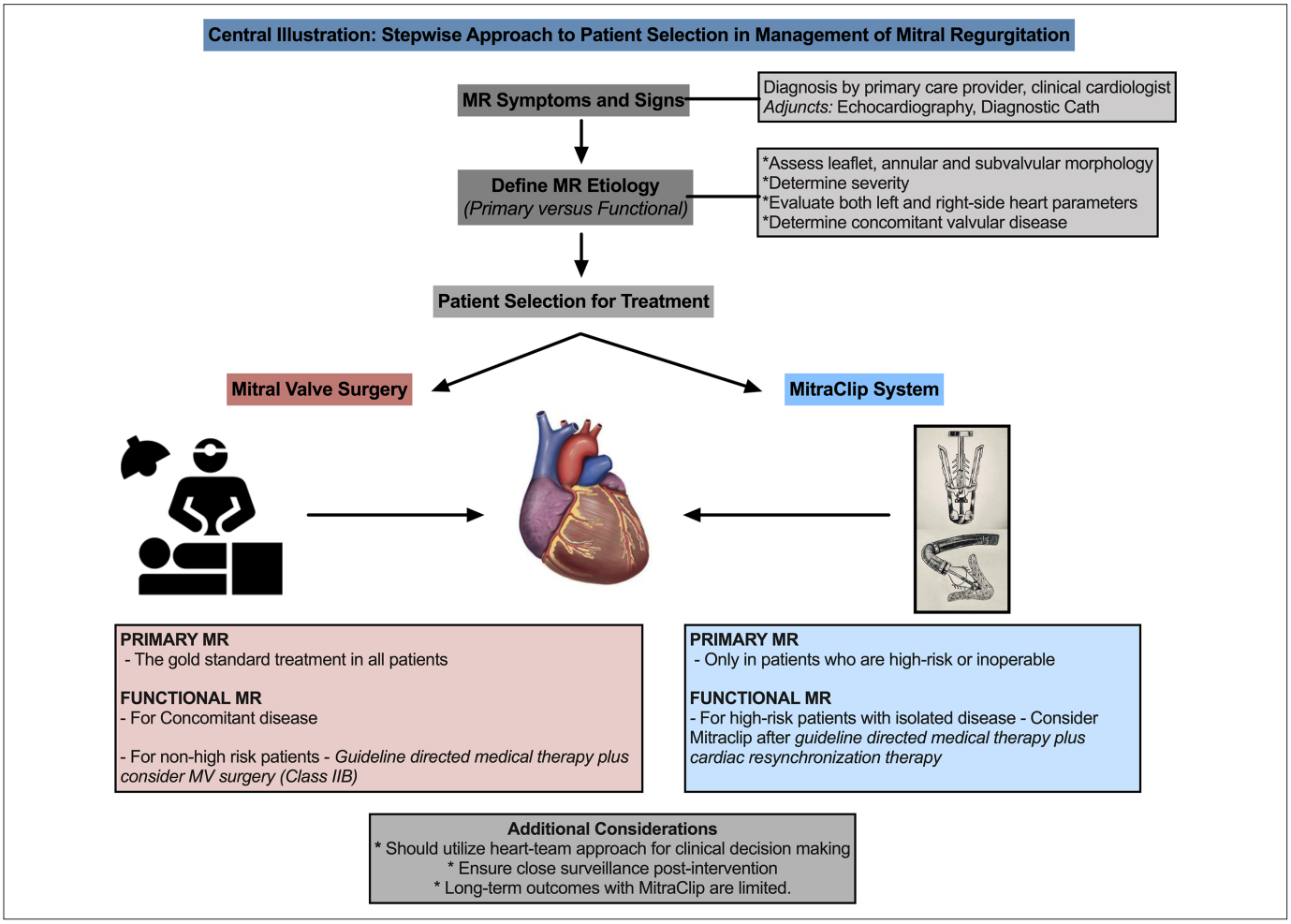

Fig. 3. Summary of surgical and percutaneous treatment strategy for MR. MR, mitral regurgitation; MV, mitral valve.

MITRA-FR, both trials compared MitraClip to GDMT alone, without any surgical arm. Thus, we should be cautious when drawing conclusions about comparisons between surgery and MitraClip in this patient cohort. In patients with functional disease amenable to surgical repair, surgery should still be strongly considered. Additionally in patients who require surgical revascularization, surgical MV replacement should be considered vs. repair. For now, if a patient has isolated secondary MR who is at high risk for surgery, one should be considered for MitraClip following GDMT.

For all etiologies, MitraClip technology is not a replacement for MV surgery but should be a complement. Moving forward it will be crucial to provide both surgical and transcatheter treatment as a heart team to improve outcomes. Also the stakes for the surgeons will be heightened for performing good mitral surgery, as we will be required to meet the high expectations from the patients and the MitraClip world.

Conclusions

Surgery remains the gold standard therapy in low- and intermediate-risk patients with primary MR. Given the increasing prevalence of MR in those with advanced age and prohibitive surgical risk, however, the MitraClip may offer a treatment alternative (Fig. 3). These indications may expand as new technology is introduced. In the case of functional MR, there is an ongoing challenge to fully understand the role of MitraClip, given the complex and heterogeneous nature of this population. Currently, only carefully selected patients with functional MR and a profile similar to those enrolled in COAPT would derive benefit from MitraClip. Long-term data are not yet available and many questions remain regarding how and in whom to apply this device. MitraClip is a complement to MV surgery, and the emphasis on the heart team approach will be more important in the future to provide the best care for the patients.

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References

1. Nkomo VT, Gardin JM, Skelton TN, et al. Burden of valvular heart diseases: a population-based study. *Lancet* 2006; 368: 1005–1011.
2. Enriquez-Sarano M, Akins CW and Vahanian A. Mitral regurgitation. *Lancet* 2009; 373: 1382–1394.
3. Grossi EA, Bizekis CS, LaPietra A, et al. Late results of isolated mitral annuloplasty for "functional" ischemic mitral insufficiency. *J Card Surg* 2001; 16: 328–332.
4. Enriquez-Sarano M, Schaff HV, Orszulak TA, et al. Congestive heart failure after surgical correction of mitral regurgitation. A long-term study. *Circulation* 1995; 92: 2496–2503.
5. Mirabel M, Iung B, Baron G, et al. What are the characteristics of patients with severe, symptomatic, mitral regurgitation who are denied surgery? *Eur Heart J* 2007; 28: 1358–1365.
6. Denti P, Buzzatti N and La Canna G. State of the Art of the MitraClip Therapy: Who, When, and How? In: Alfieri O, De Bonis M and La Canna G (eds) *Edge-to-Edge Mitral Repair: From a Surgical to a Percutaneous Approach*. Cham: Springer International Publishing, 2015, pp.137–146.
7. Alfieri O, Maisano F, De Bonis M, et al. The double-orifice technique in mitral valve repair: a simple solution for complex problems. *J Thorac Cardiovasc Surg* 2001; 122: 674–681.
8. Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med* 2018; 379: 2307–2318.
9. Reichenspurner H, Schillinger W, Baldus S, et al. Clinical outcomes through 12 months in patients with degenerative mitral regurgitation treated with the MitraClip(R) device in the ACCESS-EUrope Phase I trial. *Eur J Cardiothorac Surg* 2013; 44: e280–e288.
10. Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med* 2018; 379: 2307–2318.
11. Obadia JF, Messika-Zeitoun D, Leurent G, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med* 2018; 379: 2297–2306.
12. Kalbacher D, Schafer U, Bardeleben RS, et al. Long-term outcome, survival and predictors of mortality after MitraClip therapy: results from the German Transcatheter Mitral Valve Interventions (TRAMI) registry. *Int J Cardiol* 2019; 277: 35–41.
13. Grigioni F, Enriquez-Sarano M, Ling LH, et al. Sudden death in mitral regurgitation due to flail leaflet. *J Am Coll Cardiol* 1999; 34: 2078–2085.
14. Kligfield P, Hochreiter C, Niles N, et al. Relation of sudden death in pure mitral regurgitation, with and without mitral valve prolapse, to repetitive ventricular arrhythmias and right and left ventricular ejection fractions. *Am J Cardiol* 1987; 60: 397–399.
15. Nishimura RA, Otto CM, Bonow RO, et al. AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2017; 70: 252–289.
16. Nishimura RA, Otto CM, Bonow RO, et al. AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Thorac Cardiovasc Surg* 2014; 148: e1–e132.
17. Nishimura RA, Otto CM, Bonow RO, et al. AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2017; 135: e1159–e1195.
18. Nishimura RA, Otto CM, Bonow RO, et al. AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; 63: e57–e185.
19. Chikwe J, Toyoda N, Anyanwu AC, et al. Relation of mitral valve surgery volume to repair rate, durability, and survival. *J Am Coll Cardiol* 2017; 69: 2397–2406.
20. O'Gara PT, Grayburn PA, Badhwar V, et al. ACC expert consensus decision pathway on the management of mitral regurgitation: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *J Am Coll Cardiol* 2017; 70: 2421–2449.
21. Gammie JS, Sheng S, Griffith BP, et al. Trends in mitral valve surgery in the United States: results from the Society of Thoracic Surgeons Adult Cardiac Surgery Database. *Ann Thorac Surg* 2009; 87: 1431–1437.
22. Enriquez-Sarano M, Schaff HV, Orszulak TA, et al. Valve repair improves the outcome of surgery for mitral regurgitation. A multivariate analysis. *Circulation* 1995; 91: 1022–1028.
23. Gillinov AM, Blackstone EH, Nowicki ER, et al. Valve repair versus valve replacement for degenerative mitral valve disease. *J Thorac Cardiovasc Surg* 2008; 135: 885–893.
24. Suri RM, Schaff HV, Dearani JA, et al. Survival advantage and improved durability of mitral repair for leaflet prolapse subsets in the current era. *Ann Thorac Surg* 2006; 82: 819–826.
25. Zhou YX, Leobon B, Berthoumieu P, et al. Long-term outcomes following repair or replacement in degenerative mitral valve disease. *Thorac Cardiovasc Surg* 2010; 58: 415–421.
26. Daneshmand MA, Milano CA, Rankin JS, et al. Mitral valve repair for degenerative disease: a 20-year experience. *Ann Thorac Surg* 2009; 88: 1828–1837.
27. McNeely CA and Vassileva CM. Long-term outcomes of mitral valve repair versus replacement for degenerative disease: a systematic review. *Curr Cardiol Rev* 2015; 11: 157–162.
28. Nickenig G, Estevez-Loureiro R, Franzen O, et al. Percutaneous mitral valve edge-to-edge repair: in-hospital results and 1-year follow-up of 628 patients of the 2011-2012 Pilot European Sentinel Registry. *J Am Coll Cardiol* 2014; 64: 875–884.
29. Sorajja P, Mack M, Vemulapalli S, et al. Initial experience with commercial transcatheter mitral valve repair in the United States. *J Am Coll Cardiol* 2016; 67: 1129–1140.
30. Feldman T, Foster E, Glower DD, et al. Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med* 2011; 364: 1395–1406.

31. Anyanwu AC and Adams DH. Evaluating catheter-based mitral valve therapies: lessons learned and future directions. *J Am Coll Cardiol* 2015; 66: 2855–2859.
32. Buzzatti N, Maisano F, Latib A, et al. Comparison of outcomes of percutaneous MitraClip versus surgical repair or replacement for degenerative mitral regurgitation in octogenarians. *Am J Cardiol* 2015; 115: 487–492.
33. Buzzatti N, Van Hemelrijck M, Denti P, et al. Transcatheter or surgical repair for degenerative mitral regurgitation in elderly patients: a propensity-weighted analysis. *J Thorac Cardiovasc Surg* 2019; 158: 86–94.
34. Lim DS, Reynolds MR, Feldman T, et al. Improved functional status and quality of life in prohibitive surgical risk patients with degenerative mitral regurgitation after transcatheter mitral valve repair. *J Am Coll Cardiol* 2014; 64: 182–192.
35. Wu AH, Aaronson KD, Bolling SF, et al. Impact of mitral valve annuloplasty on mortality risk in patients with mitral regurgitation and left ventricular systolic dysfunction. *J Am Coll Cardiol* 2005; 45: 381–387.
36. D'Agostino RS, Jacobs JP, Badhwar V, et al. The Society of Thoracic Surgeons Adult Cardiac Surgery Database: 2019 update on outcomes and quality. *Ann Thorac Surg* 2019; 107: 24–32.
37. Michler RE, Smith PK, Parides MK, et al. Two-year outcomes of surgical treatment of moderate ischemic mitral regurgitation. *N Engl J Med* 2016; 374: 1932–1941.
38. Nishimura RA, Otto CM, Bonow RO, et al. AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; 63: e57–e185.
39. Diodato MD, Moon MR, Pasque MK, et al. Repair of ischemic mitral regurgitation does not increase mortality or improve long-term survival in patients undergoing coronary artery revascularization: a propensity analysis. *Ann Thorac Surg* 2004; 78: 794–799.
40. Wong DR, Agnihotri AK, Hung JW, et al. Long-term survival after surgical revascularization for moderate ischemic mitral regurgitation. *Ann Thorac Surg* 2005; 80: 570–577.
41. Mihaljevic T, Lam BK, Rajeswaran J, et al. Impact of mitral valve annuloplasty combined with revascularization in patients with functional ischemic mitral regurgitation. *J Am Coll Cardiol* 2007; 49: 2191–2201.
42. Smith PK, Puskas JD, Ascheim DD, et al. Surgical treatment of moderate ischemic mitral regurgitation. *N Engl J Med* 2014; 371: 2178–2188.
43. Goldstein D, Moskowitz AJ, Gelijns AC, et al. Two-year outcomes of surgical treatment of severe ischemic mitral regurgitation. *N Engl J Med* 2016; 374: 344–353.
44. De Rosa R, Silverio A, Baldi C, et al. Transcatheter repair of functional mitral regurgitation in heart failure patients- a meta-analysis of 23 studies on MitraClip implantation. *Circ J* 2018; 82: 2800–2810.
45. Ailawadi G, Lim DS, Mack MJ, et al. One-year outcomes after MitraClip for functional mitral regurgitation. *Circulation* 2019; 139: 37–47.
46. Braun J, van de Veire NR, Klautz RJ, et al. Restrictive mitral annuloplasty cures ischemic mitral regurgitation and heart failure. *Ann Thorac Surg* 2008; 85: 430–436.
47. De Bonis M, Lapenna E, La Canna G, et al. Mitral valve repair for functional mitral regurgitation in end-stage dilated cardiomyopathy: role of the "edge-to-edge" technique. *Circulation* 2005; 112(9 Suppl): I402–I408.
48. Feldman T, Kar S, Elmariah S, et al. Randomized comparison of percutaneous repair and surgery for mitral regurgitation: 5-year results of EVEREST II. *J Am Coll Cardiol* 2015; 66: 2844–2854.
49. Baumgartner H, Falk V, Bax JJ, et al. ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J* 2017; 38: 2739–2791.
50. Grayburn PA, Sannino A and Packer M. Proportionate and disproportionate functional mitral regurgitation: a new conceptual framework that reconciles the results of the MITRA-FR and COAPT trials. *JACC Cardiovasc Imaging* 2019; 12: 353–362.
51. Grayburn PA, Carabello B, Hung J, et al. Defining "severe" secondary mitral regurgitation: emphasizing an integrated approach. *J Am Coll Cardiol* 2014; 64: 2792–2801.
52. Buck T and Plicht B. Real-time three-dimensional echocardiographic assessment of severity of mitral regurgitation using proximal isovelocity surface area and vena contracta area method. Lessons we learned and clinical implications. *Curr Cardiovasc Imaging Rep* 2015; 8: 38.
53. Neuss M, Schau T, Isotani A, et al. Elevated mitral valve pressure gradient after MitraClip implantation deteriorates long-term outcome in patients with severe mitral regurgitation and severe heart failure. *JACC Cardiovasc Interv* 2017; 10: 931–939.
54. Kuwata S, Taramasso M, Czopak A, et al. Continuous direct left atrial pressure: intraprocedural measurement predicts clinical response following MitraClip therapy. *JACC Cardiovasc Interv* 2019; 12: 127–136.
55. Schueler R, Momcilovic D, Weber M, et al. Acute changes of mitral valve geometry during interventional edge-to-edge repair with the MitraClip system are associated with midterm outcomes in patients with functional valve disease: preliminary results from a prospective single-center study. *Circ Cardiovasc Interv* 2014; 7: 390–399.
56. Paranskaya L, D'Ancona G, Bozdag-Turan I, et al. Residual mitral valve regurgitation after percutaneous mitral valve repair with the MitraClip(R) system is a risk factor for adverse one-year outcome. *Catheter Cardiovasc Interv* 2013; 81: 609–617.
57. Buzzatti N, De Bonis M, Denti P, et al. What is a "good" result after transcatheter mitral repair? Impact of 2+ residual mitral regurgitation. *J Thorac Cardiovasc Surg* 2016; 151: 88–96.
58. Sorajja P, Vemulapalli S, Feldman T, et al. Outcomes with transcatheter mitral valve repair in the United States: an STS/ACC TVT Registry report. *J Am Coll Cardiol* 2017; 70: 2315–2327.