

Update of Patient Selection and Therapeutic Strategy Using MitraClip

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Summary

Patients with advanced heart failure often accompany severe function mitral regurgitation refractory to optimal medical therapy. Degenerative mitral regurgitation also develops due to various degeneration of mitral valve. Surgical intervention to the mitral valve might be effective in some cases, but it is challenging for the high-risk cases. Recently, percutaneous edge-to-edge mitral valve repair using the MitraClip system, which enables us to approach the mitral valve at relatively low risk, has developed. Two major prospective randomized control trials have been conducted to investigate the clinical advantage of MitraClip system over optimal medical therapy in patients with severe mitral regurgitation; both showed controversial conclusions. Now is a time to consider optimal patient selection and therapeutic strategy using MitraClip system.

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Mitral regurgitation (MR) is the most frequent valvular disease.¹⁾ Mitral valve consists of the complex of mitral annulus, leaflets, chords, papillary muscle, and left ventricular myocardium. MR is distinguished by two major causes: (1) degenerative MR including mitral valve prolapse and mitral chordal rupture (Figure 1A, B) and (2) functional MR resulting from the tethering of mitral valve due to left ventricular remodeling or the mitral annular enlargement (Figure 1C, D).

Given that the prognosis of severe MR is worse when heart failure symptom develops, the early intervention to the mitral valve is highly recommended.²⁾ However, in the real-world practice, almost half of the patients with severe MR do not undergo the surgery, given their high-risk to receive the surgery due to high age, renal failure, and too reduced cardiac function.³⁾

There has been no definite therapeutic strategy for such high-risk patients, except for optimal medical therapies, such as beta-blocker, angiotensin-converting enzyme inhibitor, mineral corticoid antagonist,⁴⁾ and cardiac resynchronization therapy if applicable.⁵⁾ Surgical intervention has been considered for those refractory to these medications. However, such a surgical intervention is a Class IIb indication in the current guidelines, given that the beneficial effect of mitral valve surgery has not been proven by prospective randomized clinical trials.⁵⁾

Considering that there are many patients with severe MR refractory to medications or contraindicated to the surgery, a less invasive transcatheter intervention to the mitral valve has been innovated recently.

Percutaneous Transcatheter Edge-to-Edge Repair (MitraClip[®])

An edge-to-edge technique in the mitral valve repair was introduced by Alfieri, a cardiac surgeon, in 1991.⁶⁾ A transcatheter edge-to-edge repair of mitral valve, MitraClip system (Abbott Vascular, Abbott Park, IL, USA), has been innovated in 1998.

Following the first-in-man study of MitraClip in 2003, a CE mark was obtained for the use of degenerative and functional MR in Europe in 2008, followed by the US Food and Drug Administration approval for the degenerative MR in 2013. In Japan, the MitraClip was approved for degenerative and functional MR by the insurance reimbursement in 2018. Given the favorable result of COAPT trial,⁷⁾ the indication for the functional MR was also approved in the USA in 2018.

MitraClip system consists of a 24-Fr steerable guiding catheter and a clip delivery system with a clip located at the tip (Figure 2). The clip delivery system has two dials (medial-lateral direction and antero-posterior direction) to direct the clip toward the plane of mitral valve. The clip arm can be opened or closed by using the arm positioner knob attached to the clip delivery system. You can try clipping repeatedly before releasing the clip from the clip delivery system for the appropriate positioning.

During the MitraClip procedure, transesophageal echocardiography is a more useful tool to understand detailed anatomical device positioning than the fluoroscopic image. Echocardiologists and interventionists should collaborate with each other for the successful MitraClip pro-

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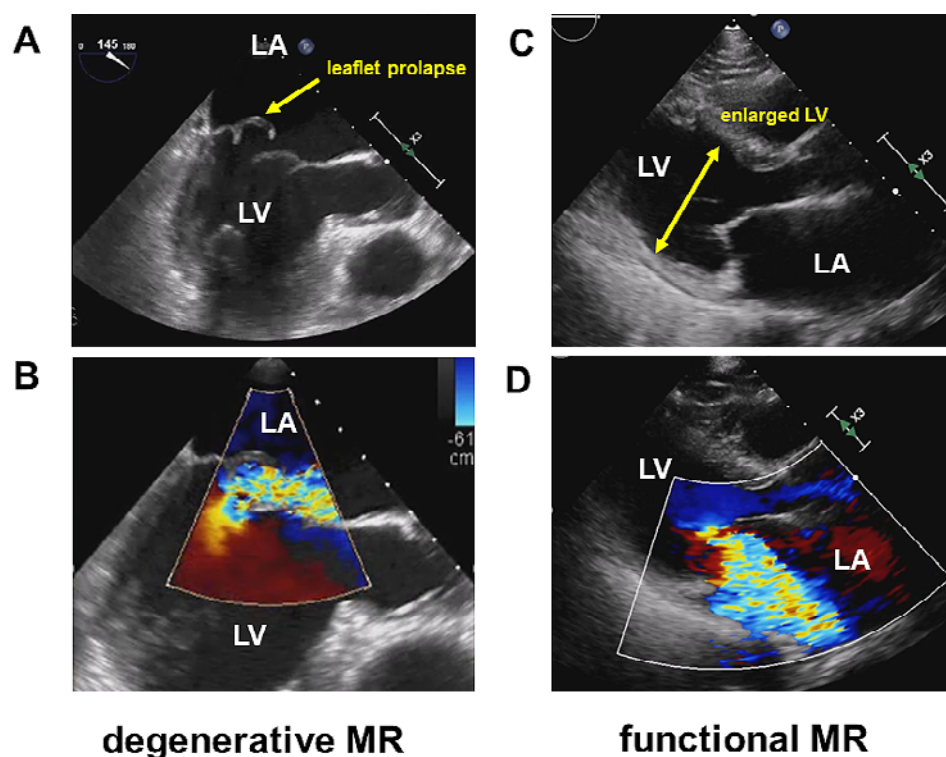


Figure 1. Two mechanisms of mitral regurgitation (MR): degenerative MR due to mitral valve leaflet prolapse with eccentric MR jet (A, B) and functional MR due to enlarged left ventricular cavity and tethering of mitral valve leaflet (C, D). LA indicates left atrium and LV indicates left ventricle

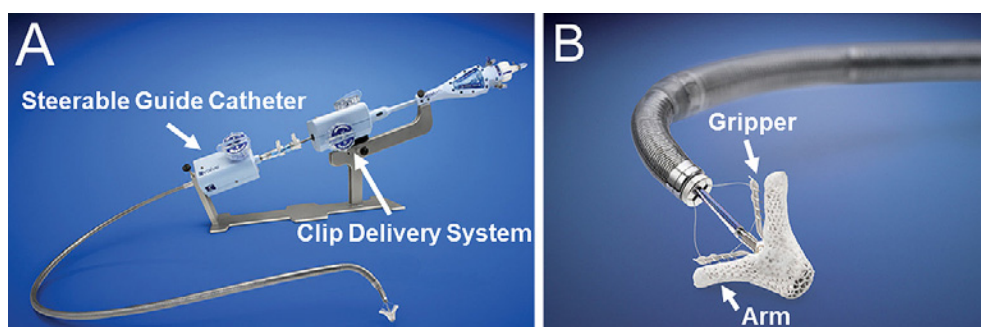


Figure 2. MitraClip system consisting of steerable guide catheter and clip delivery system (A) and a clip located on the tip of MitraClip system (B). Figures are used with permission from Abbott Vascular

cedure.

Following the procedure, approximately 8 mm of the idiopathic atrial septal defect remains, but most of them close gradually with a left to right shunt. If remained, transcatheter closure might be considered.⁸⁾ For the hemostasis of the right femoral vein, a figure-of-eight technique with one suture is an easy and secure procedure.⁹⁾

MitraClip® in Degenerative MR

Degenerative MR is a relatively common disease, which develops approximately 2% of the population.¹⁰⁾ It is caused by valvular or chordal degeneration with sys-

tolic excessive leaflet movement, due to fibroelastic deficiency, or diffuse myxomatous disease.¹¹⁾

The gold standard is surgical interventions including mitral valve repair or replacement, and the repair is recommended for its superiority in the long-term outcome.¹²⁾ However, approximately half of patients applicable to the surgical intervention do not undergo the surgery, given their high age, renal dysfunction, and a history of open-heart surgery.¹³⁾

MitraClip procedure, a less invasive transcatheter edge-to-edge mitral valve clipping, was innovated for such high-risk populations. Thus far, many studies have demonstrated the safety and efficacy of the MitraClip procedure.

Of note, Endovascular Valve Edge-to-Edge Repair Study II (EVEREST II) is the sole prospective multicenter randomized trial comparing MitraClip procedure with conventional surgical intervention.¹⁴⁾ In this study, 279 patients with symptomatic MR were randomized into the MitraClip arm and the surgical arm (repair or replacement). Of them, 73% was degenerative MR, and those with reduced cardiac function (left ventricular end-diastolic diameter over 55 mm or left ventricular ejection fraction below 25%) were excluded. The rate of recurrence of MR requiring reoperation was higher in the MitraClip arm over the surgical arm (20% versus 2%), whereas one-year and four-year severity of MR and mortality were statistically comparable between the arms. Major adverse events were also statistically not different between the two arms except for the lower incidence of transfusion in the MitraClip arm (13% versus 45%).

EVEREST High-Risk Registry, a sub-analysis of EVEREST II trial,¹⁵⁾ assessed 78 patients with predicted operative mortality risk $\geq 12\%$ who received MitraClip procedure or medical therapy. One-year survival was superior in the MitraClip group compared with the medical group (76% versus 55%) and the MitraClip group had lower 1-year heart failure recurrence rate compared with the medical group (16% versus 42%).

In the REALIS trial that included 127 inoperable patients with degenerative MR who received MitraClip procedure, one-year survival was over 70%. Given most of the survivors had residual MR 0-2, residual MR 0-2 is considered as a goal of MitraClip procedure thus far.¹⁶⁾

Given these results, the surgical intervention is recommended as a first choice for the severe degenerative MR, followed by the second choice MitraClip procedure for the high-risk or inoperable cases. The AHA/ACC guidelines recommend MitraClip procedure for those with symptomatic severe degenerative MR who have a reasonable life expectancy but a prohibitive surgical risk due to severe comorbidities (Class IIb).¹⁷⁾ ESC/EACTS guidelines also recommend MitraClip procedure in patients with symptomatic severe degenerative MR who fulfill the echocardiographic criteria of eligibility and are judged inoperable or at high surgical risk (Class IIb).⁵⁾

In Japan, although there is no recommendation in any guidelines, an appropriate use principle is proposed, which states that MitraClip should be considered in patients with symptomatic severe inoperable MR refractory to guideline-directed medical therapy, which has suitable anatomy for the procedure and a probability to improve MR.

MitraClip® in Functional MR

Functional MR develops in patients without any structural disorders. Instead, the dominant etiologies of functional MR are left ventricular remodeling due to cardiomyopathy and atrial remodeling due to long-term atrial fibrillation. In patients with left ventricular remodeling, the tethering of mitral leaflets is a dominant cause of functional MR. In patients with atrial remodeling, the worsening of coaptation of mitral leaflets due to the enlargement of the left atrium is a dominant cause of func-

tional MR.¹⁸⁾

Guideline-directed medical therapy is considered to treat background heart failure, but its impact in improving functional MR remains limited.¹⁹⁾ Cardiac resynchronization therapy is also considered in patients with functional MR, but the clinical implication remains controversial. Surgical intervention to the mitral valve is also considered. Its improvement in left ventricular remodeling and heart failure symptoms has been demonstrated, whereas its survival benefit remains undemonstrated.²⁰⁾ Therefore, AHA/ACC and ESC/EACTS guidelines recommend surgical intervention to the mitral valve alone as Class IIb. Furthermore, half of the patients with functional MR cannot receive guideline-directed surgical intervention given their reduced cardiac function.³⁾

MitraClip procedure has several advantages over the surgical procedure: (1) venous approach; (2) real-time assessment of MR during the repair; (3) clipping can be tried any time; and (4) no requirement of contrast medium.

A sub-analysis of the EVEREST II High-Risk Cohort was reported to show the clinical outcome of MitraClip procedure on the functional MR.²¹⁾ Patients with moderate or greater MR who had STS score above 12% underwent MitraClip procedure. Of them, 246/351 had functional MR. At discharge, 88% had mild or less MR, and 30-day mortality was 4.1%. At 12 months, the prevalence of mild or less MR, left ventricular diameter, and NYHA functional class all improved compared to the pre-procedural conditions.

Following the report, prospective randomized control trials comparing guideline-directed medical therapy versus MitraClip add-on arm were conducted to investigate the prognostic implication of MitraClip on the functional MR: MITRA-FR trial²²⁾ and COAPT trial⁷⁾ have been reported thus far.

MITRA-FR Trial

In the MITRA-FR trial, 304 patients with functional MR who had left ventricular ejection fraction 15-40%, regurgitant fraction ≥ 30 mL, and NYHA functional classes II-IV were randomized into the 152 medical arm and 152 MitraClip add-on arm. During the MitraClip procedure, cardiovascular complications developed in five patients and cardiac tamponade happened in two patients. At 12 months, there was no statistically significant difference in the primary composite endpoint, i.e., all-cause death and unplanned rehospitalization for heart failure.

COAPT Trial

In the COAPT trial, 614 patients with functional MR who had left ventricular ejection fraction 25-50%, moderate or greater MR, and NYHA functional classes II-IV were randomized into 312 medical arm and 302 MitraClip add-on arm. The MitraClip add-on arm had a better 24-month heart failure readmission rate than the medical arm (38.5% versus 67.9%, $P < 0.001$). All-cause mortality during the 24-month observational period was also significantly lower in the MitraClip add-on arm than in the

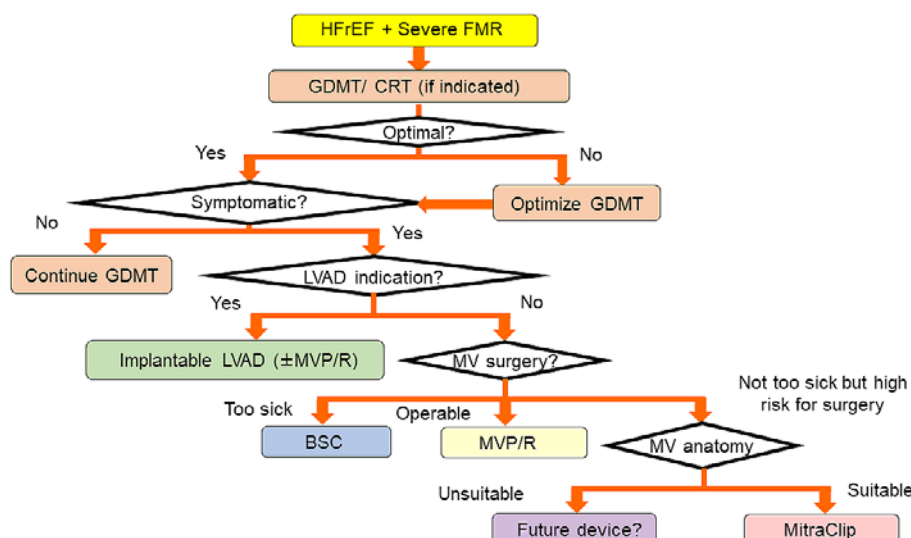


Figure 3. Therapeutic algorithm in patients with reduced left ventricular ejection fraction and functional MR. HFrEF indicates heart failure with reduced ejection fraction; FMR, functional mitral regurgitation; GDMT, guideline-directed medical therapy; LVAD, left ventricular assist device; BSC, best supportive care; MVP, mitral valve prolapse; and MVR, mitral valve replacement

medical arm (29.1% versus 46.1%, $P < 0.001$).

Future Concerns

There are several discussions to explain these opposite results:²³⁾ (1) doubled sample size; (2) difference in the observational period (one year versus two years); (3) MITRA-FR trial had more enlarged left ventricle ($135 \pm 35 \text{ mL/m}^2$ versus $101 \pm 34 \text{ mL/m}^2$) and reduced left ventricular ejection fraction (15-40% versus 20-50%) than the COAPT trial; and (4) the degree of MR was lower in the MITRA-FR trial than the COAPT trial (effective regurgitant orifice area, $31 \pm 10 \text{ mm}^2$ versus $41 \pm 15 \text{ mm}^2$). Given these differences, left ventricular function was a dominant prognostic factor in the MITRA-FR trial, whereas MR itself was a dominant prognostic factor in the COAPT trial. In other words, the impact of MitraClip might be less dominant in the MITRA-FR trial than the COAPT trial. Furthermore, medications were not optimized in the MITRA-FR trial, whereas was more optimized in the COAPT trial.

Currently, the indication of MitraClip in patients with functional MR is (1) symptomatic MR refractory to guideline-directed medical therapy, (2) high operative risk, (3) left ventricular ejection fraction above 30%, (4) severe MR, and (5) anatomical feature applicable to the procedure.⁵⁾ Considering the current evidence, an algorithm to consider intervention to the functional MR in patients with reduced left ventricular ejection fraction might be proposed (Figure 3).⁵⁾

One of the next concerns would be the therapeutic strategy for less sick heart failure cohort (e.g., cardiac resynchronization therapy nonresponders independent on the continuous inotropes infusion). For them, the left ventricular assist device might not be an aggressive indication, whereas it might be unknown whether MitraClip alone is

sufficient to manage their heart failure. Another concern is an intervention to the secondary tricuspid regurgitation due to the MR. An innovation of next-generation device for the MR with anatomy not suitable for the current MitraClip system would also be a future concern. Benefit of MitraClip system in the cost-effectiveness versus medical therapy also remains future concerns.

Disclosure

Conflicts of interest: None.

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