Percutaneous Mitral Valve Intervention Using MitraClip for Functional Mitral Regurgitation and Heart Failure

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Summary

Functional mitral regurgitation (FMR) frequently coexists with left ventricular systolic dysfunction and advanced heart failure, and typically has poor clinical outcomes. Although various therapeutic options including cardiac resynchronization therapy and surgical mitral intervention, have been proposed, an optimal treatment strategy for functional mitral regurgitation has not yet been established. Over the last decade, transcatheter mitral valve repair using MitraClip has emerged as a novel alternative therapeutic option for functional mitral regurgitation. In 2018, the COAPT trial demonstrated that MitraClip treatment reduced rehospitalization due to heart failure and all-cause death in patients with functional mitral regurgitation and heart failure. As a consequence, the MitraClip has become a very promising potential treatment for functional mitral regurgitation. In this review, we discuss and summarize the current status and future perspectives of the treatment for functional mitral regurgitation and heart failure.

(F Int Heart J 2021; 62: 4-8)

Key words: Mitral regurgitation, Structural heart disease intervention, COAPT trial

Functional mitral regurgitation (FMR) currently is a widely discussed and researched topic in cardiovascular medicine. Based on pathological features, MR is categorized into degenerative and functional MR. Degenerative (primary) MR occurs secondary to lesions of the mitral valve (MV) leaflets, chordae tendineae and papillary muscles, whereas functional (secondary) MR occurs in the absence of organic MV disease. Left ventricular (LV) dilatation (remodeling) primarily caused by ischemic or dilated cardiomyopathy leads to apical and posterior displacement of the papillary muscles, MV leaflet tethering and annular dilatation and causes FMR in a structurally normal (or near-normal) MV.

Owing to the underlying mechanism, FMR is commonly observed in patients with LV systolic dysfunction (LVSD). Moreover, FMR causes further deterioration of LV function and results in unfavorable clinical outcomes caused by a progressive spiral of LV remodeling.

In association with underlying LV remodeling, FMR commonly coexists with heart failure (HF). Koelling, et al.1) reported that patients with FMR represent a high-risk subset of patients with LV dysfunction. Trichon, et al.2) reported similar results in that significant FMR was commonly observed in patients with LV dysfunction and HF, and FMR was independently associated with lower survival rates. FMR is more commonly observed in patients with advanced HF. For example, moderate-to-severe FMR occurs in approximately 33% of patients with advanced HF in whom cardiac resynchronization therapy (CRT) is indicated.3,4) Previous studies report that severe FMR occurred in 25% of patients with ischemic and nonischemic dilated cardiomyopathy and that a close association was observed between severe FMR and long-term clinical outcomes in patients with both ischemic and dilated cardiomyopathy.5,6) Moreover, our previous studies have shown that in Japanese patients, FMR was commonly observed in patients with HF and LV dysfunction, resulting in unfavorable clinical outcomes.6,7) We previously reported that significant FMR (moderate-to-severe) was associated with higher incidence rates of all-cause death (hazard ratio 2.2), cardiovascular death (hazard ratio 2.4), and hospital admissions for HF (hazard ratio 1.8). Additionally, significant FMR was observed in approximately 17% of patients with LV dysfunction (LV ejection fraction [EF] ≤ 40%) and was associated with a higher incidence of the composite end-point including all-cause death and/or hospital admission for HF (hazard ratio 1.6). These results indicate that FMR is an important and challenging issue in cardio-
vascular clinical practice in Japan (particularly, for HF and LV dysfunction).

**Therapeutic Strategy for Functional Mitral Regurgitation and Heart Failure**

To date, the optimal medical treatment for patients with FMR and LVSD is unknown. The cornerstone of treatment for FMR is treatment of underlying LV dysfunction and HF, including guideline-directed medical therapy (GDMT) for HF, as well as CRT.

GDMT for HF (in patients with reduced EF) is the first-line treatment for FMR. Beta-blockers and renin-angiotensin system inhibitors should be prescribed for all patients with FMR and LV dysfunction. Several studies have reported on the efficacy of beta-blockers in patients with FMR. A small randomized trial has reported that carvedilol treatment decreased the severity of FMR in patients with dilated cardiomyopathy. Levine, et al. showed that up-titration of renin-angiotensin system inhibitors could improve severe FMR in patients with dilated cardiomyopathy in association with reverse remodeling. However, the morbidity and mortality rates in patients with FMR remain high despite GDMT.

CRT also shows a positive effect in patients with FMR. CRT reduces FMR in patients with HF and left bundle branch block. Bommel, et al. reported a reduction in FMR in patients categorized as high-risk surgical patients undergoing CRT and that the improved FMR was associated with better survival. The Multicenter InSync Randomized Clinical Evaluation trial showed that CRT resulted in sustained reduction in FMR in patients with severe HF with reduced EF and a wide QRS complex. However, the improvement in severe FMR was observed in only approximately 50% of patients undergoing CRT.

Surgical MV repair is the established standard treatment for degenerative MR and is a class I recommendation for degenerative MR. However, the effects of MV surgery including MV repair and replacement on FMR remain uncertain. MV surgery is effective for acute reduction of FMR, and Bach, et al. reported that MV surgery improved LVEF and cardiac output with symptomatic improvement of HF in patients with dilated cardiomyopathy. However, several studies have shown that MV surgery did not improve survival rates in patients with FMR. Wu, et al. reported no clear mortality benefit conferred by MV annuloplasty for significant MR with severe LV dysfunction. Compared with MV repair, chordal-sparing MV replacement results in sustained improvement in MR; however, no significant difference was observed between these procedures with respect to LV reverse remodeling or survival rates. Smith, et al. reported that the addition of MV repair to coronary artery bypass graft surgery did not improve survival rates in patients with moderate ischemic MR. Therefore, per the latest guidelines, the recommendation level for MV surgery in patients with FMR is not high (class IIb).

**MitraClip for Functional Mitral Regurgitation and Heart Failure**

Over the last decade, transcatheter mitral valve repair (TMVR) has emerged as a novel alternative in patients with severe MR who are considered high-risk or prohibitively high-risk patients for conventional MV surgery. The MitraClip device (Abbott Vascular, Santa Clara, CA, USA) is the most commonly used among the various devices available for TMVR. MitraClip is a polyester-covered cobalt-chromium clip inserted via the femoral vein. This technique mimics the Alfieri stitch (“double-orifice” repair). MitraClip is inserted into the left atrium via the trans-septal route, and this device grasps the free edges of the anterior and posterior MV leaflets. Grasping both MV leaflets using MitraClip creates a “double-orifice” and serves as a useful minimally invasive technique to reduce MR.

The Endovascular Valve Edge-to-Edge Repair Study II (EVEREST II) trial included 278 patients with grades 3+/4+ MR who were randomized into the MitraClip group or MV surgery group. The MitraClip technique was significantly safer than MV surgery, and the New York Heart Association functional class and overall survival rates were similar between the aforementioned groups over a 4-year follow-up. Subsequent prospective studies such as the ACCESS-Europe-A Two-Phase Observational Study of the MitraClip System in Europe (ACCESS-EU) registry and the transcatheter mitral valve interventions (TRAMI) registry reported acceptable outcomes with respect to HF symptoms; however, to date, the beneficial effects of MitraClip on long-term outcomes remain unproven. Moreover, these registries included patients with both degenerative MR and FMR; therefore, the efficacy of the MitraClip device for FMR remains debatable.

Notably, approximately 70% of the patients investigated in the real-world registries including the ACCESS-EU and the TRAMI registry showed FMR etiology. Functional MR commonly occurs concomitantly with advanced HF and LV remodeling; therefore, MitraClip is considered a useful therapeutic option even in patients with HF. Nevertheless, the clinical benefit of MitraClip in treating FMR remains unclear; therefore, based on the latest European Guidelines, the recommendation level for MitraClip for FMR remains low (recommendation class IIb, evidence level C). Among the patients included in the EVEREST II trial, only 27% showed FMR. Therefore, when the MitraClip was approved by the United States Food and Drug Administration (FDA) in 2013, the indication for its use was limited to patients with degenerative MR with a prohibitively high risk for MV surgery. From this perspective, clinical evidence supporting MitraClip in patients with FMR and HF is strongly warranted.

In 2018, 2 randomized trials investigating the efficacy of MitraClip for FMR presented pivotal results. The Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation (MitraClip FR) study, which included 304 patients and compared GDMT with GDMT plus MitraClip for FMR and HF; reported no difference in the primary composite endpoint including rehospitalization for HF and all-cause death after 1 year.
In contrast, the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial, which included 614 patients and compared GDMT with GDMT plus MitraClip for FMR and HF, reported a significant reduction in rehospitalization for HF (hazard ratio 0.53) and all-cause death (hazard ratio 0.62) in the MitraClip group after 2 years.27 Despite the similar study design, the results of the MITRA-FR and COAPT trials are completely different.

The diametrically opposite results between the MITRA-FR and COAPT trials could be attributed to the following features: (1) The degree of baseline MR and the LV volume differed between patients included in the MITRA-FR and COAPT trials. The severity of MR at baseline levels was greater in patients enrolled in the COAPT trial than in patients enrolled in the MITRA-FR trial (mean effective regurgitant orifice area 41 ± 15 mm² versus 31 ± 10 mm²). Additionally, the degree of LV dilatation was lesser in patients enrolled in the COAPT trial than in patients enrolled in the MITRA-FR trial (101 ± 34 mL/m² versus 135 ± 35 mL/m²). These findings suggest a significantly more severe degree of MR but a smaller LV volume in patients enrolled in the COAPT trial than in patients enrolled in the MITRA-FR. Grayburn, et al. reported that the COAPT trial primarily included patients with “proportionate” MR and that these patients benefitted from MitraClip, whereas the MITRA-FR trial primarily included patients with “proportionate MR” who did not benefit from MitraClip.20 (2) Efficacy of MitraClip in MR reduction was superior in the COAPT trial. Postprocedural MR grade ≥ 3+ after MitraClip occurred more commonly in the MITRA-FR than in the COAPT trial (9% versus 5%). Additionally, MR grade ≥ 3+ a year after MitraClip was also more common in the MITRA-FR than in the COAPT trial (17% versus 5%). Differences in MR reduction could contribute to the differences in clinical outcomes observed between the trials. (3) Procedural complications occurred more commonly in the MITRA-FR than in the COAPT trial (15% versus 9%). Thus, we need to carefully interpret the different results of the COAPT trial and the MITRA-FR trial. However, it can be concluded that MitraClip can serve as an effective treatment for a “specific subset” of patients with FMR and HF, and the optimal patient selection criteria is the next issue to be discussed. The Randomized Study of the MitraClip Device in Heart Failure Patients With Clinically Significant Functional Mitral Regurgitation (RESHAPE-HF2) trial (NCT02444338) is currently underway in Europe to assess a similar proposition (the efficacy of MitraClip for FMR). Hopefully, the results of this RESHAPE-HF2 trial (which are expected in the near future) will provide a better understanding of this issue. Moreover, the Multicenter, Randomized, Controlled Study to Assess Mitral vAlve reconstrucTion for advanceD Insufficiency of Functional or ischemic OrigiT Device (NCT02371512), which compares clinical outcomes between patients with MR undergoing MV surgery and MitraClip, is currently underway. This study is also of clinical interest.

Future Perspectives in Japan

Since April 2018, MitraClip has been commercially available as a novel therapeutic option for MR in Japan. The etiology that warrants MitraClip use in Japanese patients is FMR and HF (similar to the indications for patients in Europe). Nevertheless, MitraClip is contraindicated in Japan in patients with LVEF < 30% based on the inclusion criteria outlined in a Pharmaceuticals and Medical Devices Agency-approved trial.29 In contrast, LVEF values do not serve as deciding indications/contraindications for MitraClip in Europe and the United States. Epidemiological data indicate that MV surgery was contraindicated in approximately 50% of patients with severe symptomatic MR, which was primarily attributed to impaired LV function.30 Moreover, Bach, et al. reported that only 16% of patients with FMR underwent MV surgery.31 Therefore, an unmet medical need exists in the management of patients with FMR with impaired LV function, and the MitraClip device is expected to address this unmet medical need. Moreover, based on the results of the COAPT trial, the FDA approved MitraClip use for FMR and HF in March 2019. Therefore, MitraClip is expected to gain wider acceptance to treat FMR and HF not only in Europe but also in the United States. From this perspective, the Japanese guideline excluding patients with LVEF < 30% is arguable. This unique contraindication in Japan apparently stems from the fact that baseline LV dysfunction is associated with poor outcomes after MV surgery,32 and MV surgery is not strongly recommended (class IIb recommendation) for severe degenerative MR in patients with LVEF ≤ 30%.33 However, previous studies have shown that MitraClip clinically benefits even patients with reduced LVEF.34,35 The COAPT trial also showed that MitraClip improved clinical outcomes in patients with FMR and HF with LVEF < 30%.36 Furthermore, the efficacy of the MitraClip device was confirmed even in CRT nonresponders (mean LVEF 19%)37 and patients with end-stage HF (mean LVEF 27%).38 With regard to the current status of management of patients with advanced HF in Japan, the waiting period for heart transplantation remains long, and to date, implantation of a ventricular assist device as destination therapy is not approved. Therefore, practical treatment options remain limited for patients with advanced HF in Japan. In this current scenario, MitraClip is a novel therapeutic option not only to treat severe MR but also in patients with advanced HF with FMR. However, data from 2 German studies has shown that approximately 50% of patients with FMR and HF who underwent MitraClip in Germany would be ineligible to undergo MitraClip in Japan owing to low LVEF.39 Therefore, it is necessary to reconsider the indications/contraindications for MitraClip in patients with reduced LVEF in Japan. Notably, previous studies have reported several cardiac and non-cardiac prognostic factors (other than LVEF) in patients undergoing MitraClip.40-46 Thus, patient selection criteria for MitraClip should be carefully evaluated based on the clinical characteristics of each patient. In addition to the MitraClip device, numerous emerging devices for TMVR or MV replacement are available.47 Further investigation is warranted not only with respect to MitraClip
but also for these novel emerging devices. Several questions remain unanswered including the optimal timing of intervention (early versus too late), the effect of MV intervention in patients with end-stage HF, and the optimal medical management before and after MV intervention. Despite several challenges that need to be overcome, efforts must be continued for the advancement of medical treatment for patients with FMR and HF.

Disclosure

Conflicts of interest: None.

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