Transcatheter Leaflet Repair for Functional MR

What will randomized trials mean for the future of mitral intervention?

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Treatment for functional mitral regurgitation (FMR) has remained controversial despite many years of surgical, medical, and now device therapies for this problem. FMR due to ischemic or dilated cardiomyopathy has been treated with surgery when associated with coronary artery disease, and the practice of treating MR in association with coronary artery bypass graft surgery using annuloplasty techniques is well established. Even more problematic is the use of surgical annuloplasty for isolated FMR associated with heart failure. Current guidelines give this indication a class II, level of evidence B recommendation, primarily based on retrospective observational studies.[1]

However, two recent randomized clinical trials of surgical annuloplasty conducted by the Cardiothoracic Surgical Trials Network (CTSN) both failed to meet their primary endpoint of reduced left ventricular (LV) end-systolic volume index.[2,3] In the CTSN severe trial, patients with severe FMR were randomized to an undersized annuloplasty ring or mitral valve replacement. There was a 58% recurrence of FMR at 2 years in the annuloplasty group, but the clinical benefits were similar in the two groups. In the CTSN moderate trial, there was no demonstrated benefit to adding an undersized annuloplasty ring to the treatment of patients undergoing coronary artery bypass grafting. The results of these trials challenge the value of surgical annuloplasty and have been added to the updated 2017 American Heart Association/American College of Cardiology valvular heart disease guidelines. In real-world practice, only about 10% of patients with isolated FMR are actually treated with surgery, with the remainder receiving medical therapy.[4]

MITRACLIP FOR FMR

The option of using the MitraClip device (Abbott Structural Heart) in these FMR patients has increasingly become attractive over the last several years. The majority of the more than 60,000 patients treated with MitraClip have FMR, with approximately 75% of the treated population in this disease category. Numerous reports have shown the relative safety of MitraClip in this setting, with successful clinical outcomes when measured by the need for repeat heart failure (HF) hospitalizations, functional class, and LV remodeling. The large number of FMR patients treated with MitraClip in clinical practice has yielded many registry reports and meta-analyses that suggest benefits of this approach.

The MitraClip procedure is based on surgical edge-to-edge mitral leaflet repair, which has mostly been used for degenerative MR (DMR) and has never been compared to medical therapy alone for either FMR or DMR. In fact, the only therapy for FMR shown to improve mortality compared to optimal medical therapy (OMT) in randomized clinical trials is cardiac resynchronization therapy (CRT) for eligible patients.[5] Furthermore, surgical annuloplasty for FMR has not been compared to OMT in meaningful randomized clinical trials. The uncertainty about the effectiveness of OMT is thus a major impediment to understanding which patients truly benefit from surgery or device treatment. This is a critical evidence gap. Randomized trial data that demonstrate clinical benefits of device treatment for FMR will define a clear role for these therapies. Negative outcomes for devices compared to OMT will raise the bar for future efforts with many devices, including MitraClip and other edge-to-edge therapies, catheter-based annuloplasty, and percutaneous mitral valve replacement.

ONGOING MITRACLIP STUDIES

Three randomized trials have been undertaken and completed to address this evidence gap. The COAPT and MITRA-FR trials both randomized patients with FMR to MitraClip or OMT (Figure 1). There are several

important differences between these trials. One of the most important is the choice of primary endpoint. The primary endpoint for the COAPT trial is recurrent HF hospitalizations, and for MITRA-FR, the combined endpoint is death from any cause and HF hospitalizations. The key consideration in this difference is the observation that mortality and recurrent HF hospitalizations are competing endpoints, as patients who die early in the course of the trial of course cannot undergo repeat hospitalizations. The MITRA-FR trial makes the assumption that treating FMR with MitraClip may have some effect on mortality favoring MitraClip, whereas COAPT assumes that these are older patients with comorbidities and that noncardiac mortality will be balanced between the two study groups, making HF hospitalizations a better discriminating measure. The primary effectiveness endpoint in COAPT has specifically been redefined during the course of the trial, finally stated as 24-month survival status and date of last known HF hospitalization when the last randomized subject test passed 395 days after enrollment. These trials, as well as the RESHAPE-HF2 trial, are compared in Table 1.

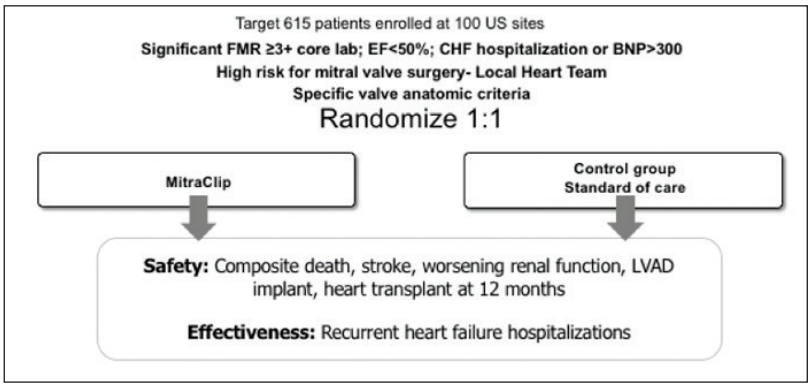

Figure 1. COAPT trial design. BNP, B-type natriuretic peptide; CHF, congestive heart failure; EF, ejection fraction; LVAD, left ventricular assist device.

Are there any signals from nonrandomized reports that shed light what we might expect from the randomized trials? A mortality benefit of MitraClip use has been suggested in a propensity-matched comparison with OMT. Giannini et al compared 60 patients treated with OMT with a propensity-matched cohort of 60 patients who underwent MitraClip treatment.[6] All were high surgical risk and had severe FMR. The mean patient age was 75 years and 67% were men. There was an ischemic etiology in 52% of patients. Median LV ejection fraction (LVEF) was 34%. All patients were symptomatic for dyspnea. In the MitraClip group, the procedure was associated with safety, with no occurrences of procedural or in-hospital mortality. After a median follow-up of 515 days, patients treated with MitraClip demonstrated overall significantly higher survival, survival free from cardiac death, and survival free of readmission due to cardiac disease than patients treated conservatively ($P = .007$, $P = .002$, and $P = .04$, respectively). One-year mortality in the MitraClip group was approximately 10%, in contrast to the 1-year mortality in the COAPT roll-in patients of 18.3% and 25.9% in the TVT Registry.[7]

A meta-analysis has also suggested a survival advantage for MitraClip compared to OMT. Benito-González et al analyzed five reports that enrolled a total of 1,271 patients; 720 were treated with MitraClip and 551 were managed conservatively.[8] A total of 269 all-cause mortality events at 1 year were reported: 15.14% (109/720) in the MitraClip arm and 29.04% (160/551) in the conservative group. A significant difference favoring MitraClip over OMT alone was observed (odds ratio, 0.44; 95% confidence interval, 0.30–0.64; $P < .0001$). No significant study heterogeneity ($P = .18$) or publication bias were detected ($P = .3$). The authors concluded that MitraClip is associated with an improvement in 1-year survival compared to standalone medical management.

Repeat hospitalizations for HF have decreased in observational studies of MitraClip.[9] The EVEREST II high-risk registry and REALISM continued access study's high-risk arm are prospective registries of patients who received the MitraClip device. Twelve-month outcomes in high-risk patients treated with percutaneous mitral valve edge-to-edge repair were reported for 351 patients. The annual hospitalization rate for HF decreased from 0.79% before the procedure to 0.41% after the procedure ($P < .0001$). Improvements in multiple clinical endpoints were also demonstrated. Patients were elderly (aged 76 ± 11 years), and 70% had FMR. From baseline to 12 months, LV end-diastolic volume improved from 161 ± 56 mL to 143 ± 53 mL ($P < .0001$) and LV end-systolic volume improved from 87 ± 47 mL to 79 ± 44 mL ($P < .0001$). New York Heart Association (NYHA) functional class improved from 82% in class III/IV at baseline to 83% in class I/II at 12 months ($P < .0001$). The 36-Item Short Form Health Survey physical and mental quality-of-life scores improved from baseline to 12 months ($P < .0001$). Kaplan-Meier survival estimate at 12 months was 77.2%. A similar reduction in hospitalizations for HF was shown in a DMR group of 127 patients treated with MitraClip.[10]

TABLE 1. FMR RANDOMIZED TRIALS

	COAPT	MITRA-FR	RESHAPE-HF2
No. of patients	555 at 85 sites in North America	288 at 22 sites	380 at 50 European sites
Control arm	GDMT ± CRT	GDMT ± CRT	GDMT ± CRT
FMR grade	≥ 3+ (EROA ≥ 30 mm^2 and/or Rvol > 45 mL by ECL)	Severe (EROA > 20 mm^2 + Rvol > 30 mL by ECL)	≥ 3+ (EROA ≥ 30 mm^2 and/or Rvol > 45 mL by ECL)
NYHA class	II, III, or ambulatory IV	II–IV	III or ambulatory IV
Other inclusion criteria	HF hospitalization within 12 mo or BNP ≥ 300 pg/mL or NT-proBNP ≥ 1,500 pg/mL within 12 mo; MV surgery not local SOC	HF hospitalization within 12 mo; not eligible for MV surgery	HF hospitalization < 12 mo or BNP ≥ 350 pg/mL or NT-proBNP ≥ 1,400 pg/mL < 90 days; ineligible for MV surgery
LVEF	≥ 20%–50%	≥ 15%–40%	≥ 15%–40%
LV volumes	LVESD ≤ 70 mm	–	LVEDD ≥ 55 mm
Efficacy endpoint	HF hospitalization 12 mo	Death or HF hospitalization at 12 mo	Death or HF hospitalization 12 mo
Safety endpoint	SLDA, device embolizations, endocarditis/mitral stenosis/device-related complications requiring nonelective cardiovascular surgery, LVAD, OHT	–	All-cause mortality, stroke, myocardial infarction, new renal replacement therapy, nonelective cardiovascular surgery for device-related complications
Duration of follow-up	5 y	2 y	1 y

Abbreviations: BNP, B-type natriuretic peptide; CRT, cardiac resynchronization therapy; ECL, echocardiographic core laboratory; EROA, effective regurgitant orifice area; FMR, functional mitral regurgitation; GDMT, guideline-directed medical therapy; HF, heart failure; LVAD, left ventricular assist device; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MV, mitral valve; NT-proBNP, N-terminal B-type natriuretic peptide; NYHA, New York Heart Association; OHT, orthotopic heart transplantation; Rvol, regurgitant volume; SLDA, single leaflet device attachment; SOC, standard of care.
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The COAPT trial used rigorous case review by a group of HF specialists to assess OMT, and patients could not be included until they had failed to respond to both OMT and, if candidates, CRT. This selection process was more rigorous than those used in any previous or subsequent trials. The definition of OMT in the COAPT trial minimally includes an ACE inhibitor (ACE-I) at stable doses for 30 days prior to enrollment, if tolerated, and a β blocker (carvedilol, sustained release metoprolol succinate, or bisoprolol) for 90 days prior to enrollment, if tolerated, with a stable up-titrated dose for 30 days prior to enrollment. This also includes an angiotensin II receptor blocker (ARB) at stable doses for 30 days prior to enrollment, if tolerated, when ACE-I is not tolerated. *Stable* is defined as no more than a 100% increase or a 50% decrease in dose. If the subject is intolerant to ACE-I, ARB, or β blockers, documented evidence must be available. In those intolerant to both an ACE-I and ARB, combination therapy with hydralazine and oral nitrate should be considered. Therapeutic equivalence for ACE-I substitutions is allowed within the enrollment stability timelines. Aldosterone inhibitor therapy should be added when NYHA class III or IV symptoms occur on standard therapy as per the RALES trial.[11] If aldosterone inhibitor therapy is administered in NYHA class II patients, it must be initiated and optimized prior to enrollment. Eplerenone requires dosage stability for 30 days prior to enrollment, similar to the other agents. Diuretics may be used as necessary. All HF therapeutics and dosages were documented in the electronic case report forms. Because most previous trials did not use such a rigorous approach to medical therapy, enrollment in COAPT was laborious, with a high screen failure rate. The first COAPT patient randomized in December 2012, with the last in June 2017. The requirement for rigorous medical therapy will help address the scientific question regarding the benefit of FMR correction, but these patients also may have MR and HF/LV

dysfunction that is too far advanced to benefit from reduction in FMR. Could the resulting patient population of nonresponders to OMT represent patients who are less likely to respond to any therapy?

The COAPT trial included over 70 contributing sites. The MitraClip experience level varied among sites, and this is also an important consideration. In the EVEREST II randomized trial, the procedure was in its infancy and all the operators were inexperienced. Single leaflet detachment occurred in nearly 5% of patients and failure to implant a device occurred in 9%.[12] Procedure results have substantially improved since this report, but newer operators of course still have a learning curve.

The COAPT trial also required consideration for CRT among candidates for this therapy. Patients with an LVEF ≤ 35%, sinus rhythm, and NYHA functional class III or ambulatory class IV symptoms despite recommended OMT, as well as those who have cardiac dyssynchrony defined as a QRS duration ≥ 0.12 seconds, were recommended to receive CRT with or without an implantable cardioverter defibrillator, unless contraindicated. Patients who failed to improve after CRT were then included in the randomized trial. The COAPT roll-in experience suggests that as many as 25% or more of patients in the trial will be CRT nonresponders. This group will necessarily have LVEF at the lower end of the range accepted in the trial.

Auricchio et al reported on 51 symptomatic CRT nonresponders with FMR grades ≥ 2 who underwent MitraClip treatment.[13] After a median of 14 months of follow-up, NYHA class progressively improved and the proportion of patients with significant residual FMR (grade ≥ 2) progressively decreased ($P < .001$). Significant reverse LV remodeling and improved LVEF were detected at 6 months, with further improvement at 12 months. The authors concluded that FMR treatment with the MitraClip in CRT nonresponders was feasible, safe, and demonstrated improved functional class, increased LVEF, and reduced LV volumes in approximately 70% of these study patients.

Giaimo et al reported outcomes in 30 CRT patients with persistent FMR after CRT.[14] All patients were treated with CRT for at least 6 months and remained in NYHA class III or IV despite OMT with residual moderate-to-severe or severe FMR. There was a significant improvement in NYHA class from baseline to 6 months after the MitraClip procedure, which was sustained at 12 and 24 months. The degree of FMR significantly improved throughout the 12 months of follow-up. There was LV remodeling with significant reduction of end-systolic volume and an increase of LVEF at 6 and 12 months, but the opposite trend was noted between 12 and 24 months, suggesting that the result may not be durable. Neither of these studies addressed the trial endpoints for COAPT and MITRA-FR of changes in mortality or HF hospitalizations.

CONCLUSION

The uncertainties reflected in the nonrandomized observational experiences with MitraClip for FMR highlight the importance of randomized trial data to define the clinical benefits of this therapy. On the other hand, the design of such trials is also demanding. Trials enrolling patients who are not responding to OMT may select patients with advanced HF who are not responsive to unloading therapy. One should ask, why should they respond to mitral valve interventions? Reducing volume overload can induce reverse remodeling, but only if applied early enough in the cycle of FMR as a consequence of LV dilatation and dysfunction. There is evidence in the surgical literature and in animal models of FMR to suggest that early intervention is needed to induce reverse LV remodeling.[15,16]

The outcomes from the upcoming reports of MITRA-FR and COAPT will be affected by the patient populations that were ultimately included, the success of the MitraClip procedures, and the effectiveness of OMT. The trial results will have a great impact on clinical practice broadly, the use of MitraClip in practice, and the requirements for trials that are evaluating other devices for treating FMR. ■

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