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Managing Mitral Regurgitation in Heart Failure—Perspectives After COAPT

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Abstract

Purpose of review Functional mitral regurgitation (MR) in setting of cardiomyopathy causes significant morbidity and worsened survival. Surgical therapies have failed to demonstrate significant overall benefit for functional MR. More recently, major trials utilizing transcatheter therapies for functional MR have been completed and offer new avenues for intervention. This review evaluates and compares 2 major recent trials designed to test the benefit of edge-to-edge repair using the MitraClip system for severe functional MR.
Recent findings The Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) and Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation (MITRA-FR) trials were simultaneous trials evaluating the treatment of effect of MitraClip in the setting of severe functional mitral regurgitation. Results of the trials were quite different with COAPT demonstrating substantial clinical benefit including significantly improved survival compared with MITRA-FR in which no clinical benefit was derived.
Summary Key differences in the patient population between the COAPT and MITRA-FR trials help to explain the contrasting results between the 2 trials designed to test the same hypothesis. Patients in COAPT had higher severity of MR with less dilated ventricles compared with MITRA-FR. These results will help shape patient selection for who will most benefit from MitraClip therapy. Further transcather mitral valve therapies continue to evolve and will likely offer alternative therapies for MR as technology improves.

Introduction

Significant mitral regurgitation (MR) is known to portend to worse outcomes among patients with heart failure (HF) [1–3]. Generally, MR can be categorized as primary (degenerative) or secondary (functional). Primary MR occurs when pathology of the valve apparatus itself leads to an incompetent valve. Conversely, secondary MR occurs due to abnormal geometry and function of the left ventricle (LV) resulting in leaflet malcoaptation [1]. The abnormal LV impacts the valve apparatus including papillary muscles, chordae tendineae, and mitral leaflets resulting in MR. While surgical intervention for primary MR has been proven to be safe, efficacious, and life extending, this has not been shown to be the case for secondary (functional) MR. In fact, there is sparse evidence to suggest mortality benefit in patients with severe functional MR and significant LV dysfunction [4–7]. Current guidelines for severe secondary MR suggest consideration of surgical intervention (repair or replacement) only in the setting refractory symptoms despite optimized medical therapy for heart failure or concurrent open heart surgery (i.e., coronary artery bypass grafting (CABG) or aortic valve replacement (AVR)) [8, 9].

Advances in transcatheter valvular interventions

New advances in transcatheter therapies continue to evolve and provide new treatment options for patients with valvular heart disease. Randomized clinical trials (RCTs) published over the past decade regarding transcatheter aortic valve replacement (TAVR) have demonstrated that these therapies are safe and efficacious for patients with severe symptomatic aortic stenosis, irrespective of surgical risk strata [10–16]. However, transcatheter therapies for the mitral valve are less mature and continue to evolve. The first large RCT utilizing a transcatheter mitral valve repair (MitraClip) was the EVEREST II trial which randomized high surgical risk patients to either percutaneous edge-to-edge mitral valve repair with the MitraClip device or surgical intervention with either repair or replacement. Results of this trial showed that transcatheter edge-to-edge repair using the MitraClip system yielded less durable reduction in the degree of MR though did have superior safety profile compared with surgery [17]. However, this trial was a heterogeneous group of both primary and secondary MR which may have confounded the results. A subgroup analysis from the EVEREST II trial suggested that the percutaneous repair with MitraClip was favorable to surgery in patients with functional MR, though this data was exploratory given the low number of patients in the functional MR category.

Two major trials evaluating MitraClip for secondary mitral regurgitation

Over the past year, 2 large RCTs (COAPT [18••] and MITRA-FR [19••]) evaluating MitraClip in addition to optimal medical therapy for HF versus medical therapy alone have been published in patients with severe secondary MR. Previous registry data in patients receiving MitraClip for functional MR suggested clinical benefit; however, these trials have provided the first RCT level data. The results from the 2 major trials had starkly different results.

Results of the MITRA-FR and COAPT trials

The MITRA-FR trial results were presented at the August 2018 European Society of Cardiology (ESC) meeting in Munich. Despite a reduction in the MR among patients receiving MitraClip, there was no difference in the primary composite endpoint of the rate of death or hospitalization for HF at 1 year. More recently, 2 year follow-up data was presented at ESC 2019, again illustrating no clinical benefit in the group treated with MitraClip.

Only several weeks after the presentation of the negative MITRA-FR trial, the results of the COAPT trial were presented at the September 2018 TCT meeting in San Diego. In stark contrast to MITRA-FR, this trial strongly favored MitraClip plus medical therapy for HF over medical therapy alone. Reduction in the primary endpoint of HF hospitalization at 24 months was dramatically reduced in the MitraClip arm (35.8% vs 67.9%). All secondary pre-specified endpoints also favored MitraClip. Strikingly survival was greatly improved with 2 year mortality rates of 29.1% in the MitraClip arm versus 46.1% in the medical therapy alone arm. The number needed to treat to prevent 1 hospitalization was 3.1 and to save 1 life was 5.9—both exceedingly positive results in clinical medicine.

Making sense of the discordant results of the two major trials

Obviously, the conflicting results of these 2 major trials led to many questions regarding how similar trials designed to answer the same questions yielded different results. Careful examination of the trials including the design, patient selection, and timing can help reconcile the different results and broaden our understanding of the usefulness of MitraClip in those with functional MR.

Degree of mitral regurgitation

Inclusion criteria for the trials differed. In MITRA-FR, severe MR was defined as regurgitant volume (RV) of > 30 mL per beat or effective regurgitant orifice area (EROA) of greater than 20 mm^2 based on the current European guidelines for secondary MR. Conversely, the COAPT criteria required grade 3+ or 4+ MR based on the 2008 US guidelines (since updated) which use greater than 30 mm^2 EROA and greater than 45 mL of RV. This difference in the inclusion criteria led to differences in the studied populations. For example, the average EROA in MITRA-FR was 31 mm^2 compared with 41 mm^2 in COAPT. More than half (52%) of patients in MITRA-FR had EROA < 30 mm^2 while this characterized only 14% in the COAPT. Overall, COAPT patients had a substantially greater degree of MR than did the MITRA-FR patients.

Left ventricular size and function

There was also a difference in the LV size and function inclusion criteria. MITRA-FR included patients with an ejection fraction (EF) 15–40% without related LV size limitations criteria. COAPT used an EF range of 20–50%, though excluded severely dilated LVs (those with end diastolic diameter > 7 cm). Overall, EF was similar between the trials (33% in MITRA-FR versus 31% in COAPT), though patients in the MITRA-FR study generally had greater LV diameter, with average indexed LV end-diastolic volume (LVEDVi) of 135 mL/m^2 compared with 101 mL/m^2 in COAPT.

Medical management

There were differences in the protocol for optimization of HF medical therapy. COAPT required ongoing evaluation by HF specialists to optimize medical therapy to the maximally tolerated doses. The MITRA-FR did not track medical changes through the trial so information on drug titration is not available. Despite these protocol differences, rates of guideline-directed medical therapy (GDMT) were slightly higher in the MITRA-FR patients (ACEi/ARB/ARNI in 85% of MITRA-FR versus 67% of COAPT, BB in 89% MITRA-FR versus 91% in COAPT, and MRA in 55% of MITRA-FR versus 50% of COAPT). Data regarding dosing optimization is not available. Interestingly, there was a difference in the use of ACEi/ARB/ARNI between the intervention and control group in COAPT with more patients in the device group receiving this class of medication than the control group (72% versus 63%, $p = 0.03$). ACEi indicates angiotensin-converting enzyme inhibitor. ARB represents angiotensin receptor blocker. ARNI means angiotensin receptor-neprilysin inhibitor. BB stands for beta blocker, and MRA corresponds to mineralocorticoid receptor antagonist (Table 1).

Procedural outcomes and success

Overall, procedural success was very high in both trials (96% in MITRA-FR versus 98% in COAPT). Residual MR ≥ 3 + was higher in MITRA-FR than COAPT both acutely (9% versus 5%) and at 12 month follow-up (17% versus 5%). There were more overall clips used in COAPT (62% in COAPT with ≥ 2 clips versus 54% in MITRA-FR) (Table 2).

Table 1. Baseline patient characteristics in COAPT and MITRA-FR trials

	COAPT	MITRA-FR
Clinical		
Age (years)	72	70
Male (%)	64	75
DM (%)	37	29
HTN (%)	80	
Ischemic CMP (%)	61	59
NYHA III or IVa (%)	61	67
CRT (%)	36	27
Echo parameters		
EROA (mm2)	41	31
LVEDVi (mL/m2)	101	135
LVEF (%)	31	33
Medical therapy		
BB (%)	91	89
ACEi/ARB/ARNI (%)	67	85
MRA (%)	50	55

Table 2. Outcomes in COAPT and MITRA-FR trials

	COAPT	MITRA-FR
Procedural success, %	98	96
Number of clips, %		
1 clip	36	46
2 clips	55	45
3 + clips	8	9
Mortality		
1-year %		
Intervention	19.1	24.2
Control	23.2	22.4
2-year %		
Intervention	29.1	34.9
Control	46.1	34.2
HF hospitalization		
1-year %		
Intervention	19.1	48.7
Control	23.2	47.4
2-year %		
Intervention	35.7	55.9
Control	56.7	61.9

Overall take-home and interpretation

While both of these trials were designed to test the same fundamental hypothesis, the different results are likely the results of the differences in the populations studied. Patients in COAPT had smaller ventricles with more severe MR, while MITRA-FR had more advanced ventricular dilatation and remodeling with less overall MR. Classically, MR has been divided into either primary or secondary, but it is becoming more apparent that even within the subset of secondary MR there are varying degrees of valvular versus ventricular dysfunction. The concept of proportionate and disproportionate MR based on LV size and EROA was recently discussed by Grayburn et al. [20]. In essence, COAPT patients had MR that was significantly more severe in proportion to their LV dysfunction. MITRA-FR patients more commonly had a predominantly ventricular pathology relative to the degree of valvular dysfunction. Within this framework, it stands within reason that the patients with more predominantly valvular problem (COAPT) were those that benefit most from specific therapy on the mitral valve.

Future directions

Catheter-based interventions for mitral valve disease continue to evolve. The MitraClip device is now FDA-approved and has the CE mark for the treatment of both primary and secondary MR in selected patients as a percutaneous edge-to-edge repair system. It is the only current transcatheter therapy with FDA approval though several other devices have received the CE mark. Additionally, there are numerous other devices currently in various phases of study and investigation. The Carillon transcatheter mitral valve annuloplasty device (Cardiac Dimensions) has the CE mark and utilizes a delivery system through the coronary sinus without need for transseptal puncture. Cardioband (Edwards) is another annuloplasty device with the CE mark. Transcatheter mitral valve replacement systems delivering a bioprosthetic tissue valve in the mitral position (Intrepid system by Medtronic, Tendyne by Abbott) are currently in randomized clinical trials. The Pascal device (Edwards) is an alternative edge-to-edge repair system with independent mobile clips that now has the CE mark. Mitral repair using artificial cords (Harpoon) is under investigation. It clearly is an exciting time in the field of structural interventions of mitral valve disease. Certainly not all of the devices under investigation will turn out to be clinically beneficial, though the variety and depth of interventions being studied offers potential for many future treatments.

Conclusions

Severe functional mitral regurgitation in advanced HF causes significant morbidity and mortality. Surgical interventions for the management of severe functional MR with concurrent systolic heart failure have demonstrated limited clinical value and are reserved for those with refractory symptoms. The advent of less invasive means to reduce the mitral regurgitation using the MitraClip edge-to-edge repair system is revolutionary for patients living with severe functional MR.

When considering mitral valve interventions, proper patient selection is of paramount importance. Aggressive medical therapy to maximally tolerated doses of GDMT often results in significantly improved MR without necessitating procedural or surgical interventions. Medical therapy also continues to develop, with more recent options including the class additions of ARNIs and SGLT2 inhibitors in addition to cardiac resynchronization therapy (CRT) in selected patients. If severe functional MR remains despite maximized medical therapy, then catheter-based MitraClip can offer substantial improvement in both symptoms, reduce HF admissions, and improve survival. There is a concern that as MitraClip and other procedural interventions become more commercially available and widespread, there will "creep", that is, performing the procedure in patients who are not fully optimized in terms of medical therapy. Moving forward, it will be important to ensure mechanisms are in place to prevent the premature use of device therapy.

Lessons learned from the COAPT and MITRA-FR trials highlight the importance of selecting the right patients who will benefit from the use of MitraClip. Patients with more advanced LV dilatation and comparatively less degree of MR are less likely to benefit from MitraClip than those patients with higher degrees of MR and ventricles that are not as dilated. Ongoing close follow-up and continued medical therapy for HF even after device implant continues to play a key role.

Currently, the MitraClip is the only catheter device proven to have robust clinical benefit for functional MR. Optimistically, one can envision a time where there are multiple devices available for mitral valve repair or replacement. Combination therapy (e.g., edge repair with MitraClip plus annuloplasty) may provide the optimal results in a given patient, and this is an area for future discovery. Certainly, this is an exciting time in the world of structural heart interventions.

With the continuing expansion of potential treatment options, the role of heart team will gain ever more importance in choosing the correct treatment option for an individualized patient. Treatment of mitral valve pathology is more nuanced and complex than the aortic valve making each team members' input imperative. The perspectives and expertise of the interventional cardiologists, heart failure specialists, cardiac imaging specialists, and cardiac surgeons will help to determine the best treatment option for an individual patient being mindful of their clinical status, anatomic limitations, and the technical aspects of the given procedure.

Compliance with Ethical Standards

Conflict of Interest

Jarrod Betz, Scott M Lilly, and William T Abraham each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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