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# Percutaneous Mitral Valve Repair to Treat Secondary Mitral Regurgitation in Dilated Cardiomyopathy: Are the Hopes Greater than the Achievements?

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**COLUMN ARTICLE**

Mitral regurgitation may be primary when there is leaflet abnormality, whereas it is secondary to ischemic or dilated cardiomyopathy when there is a structurally normal valve leaflets that are unable to coapt completely because of damaged of the supporting mitral valve apparatus. There is a controversial agreement on how to manage these two types of mitral regurgitation. Current guidelines recommend early surgery for severe primary mitral regurgitation [1-3]. However, there are confronted opinions on the therapeutic management of secondary mitral regurgitation. Heart failure (HF) patients who have moderate to severe secondary mitral regurgitation due to left ventricular dysfunction and dilatation have a worse prognosis than those HF patients who have left ventricular dysfunction but without mitral regurgitation [4,5].It still remains unclear if mitral regurgitation is simply a marker of a diseased left ventricle or if it is a causative factor that contributes to left ventricular dilatation and progression of volume overload leading to poor clinical outcomes [6]. Optimal medical treatment for cardiomyopathy, as well as, cardiac resynchronization therapy can reduce the severity of secondary mitral regurgitation and are currently the only management strategies with a class I recommendation in recent clinical guidelines [2,3]. On the other hand, cardiac surgery for secondary mitral regurgitation has not been tested in clinical trials and there is no evidence for a clear benefit [7,8].

Only six years ago, an interventional percutaneous method to treat severe primary mitral valve regurgitation refractory to medical therapy was approved by the FDA. The medical device utilized is called MitraClip which was used to treat mitral valve regurgitation for individuals who should not have open-heart surgery. The device is implanted via a tri-axial transcatheter technique and involves suturing together the anterior and posterior mitral valve leaflets. MitraClip is the most widely used device for this porpoise with more than 80,000 implants performed to date worldwide. Observational studies suggest that MitraClip treatment of secondary mitral regurgitation is safe and associated with improved symptoms, quality of life, exercise

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tolerance, reverse remodeling, and functional status in HF patients [9-13]. After several observational studies and small clinical trials were published, the results of two larger randomized clinical trials that evaluated the potential clinical benefit of PMVR to treat mitral regurgitation in patients whose primary diagnosis was cardiomyopathy were available last year [14,15]. Thereafter, there was a clear paradigm shift in the management of secondary MR among patients with congestive heart failure owing to the publication of these two randomized clinical trials. In each trial, the MITRA-FR trial and the COAPT trial, symptomatic patients with left ventricular systolic dysfunction and moderately severe secondary mitral regurgitation were randomly assigned to PVMR plus guideline-directed medical therapy or medical therapy alone. The MITRA-FR trial was performed in France, and the COAPT trial in the United States and Canada. The MITRA-FR trial showed no significant difference in the composite primary outcome, namely, the rate of death from any cause or unplanned hospitalization for heart failure at 1 year between the trial groups. However, the COAPT trial showed a significantly lower rate of hospitalization for heart failure at 2 years, which was the primary outcome and, significantly lower all-cause mortality at 2 years as secondary outcome in the device group [14,15]. Due to these latter favorable results of the COAPT trial, the MitraClip indication was extended and approved by the FDA in March this year to patients with heart failure symptoms refractory to medical treatment in the presence of moderate-to-severe or severe secondary MR.

The differences in outcomes may be related to dissimilar medical management before and after enrollment in the two trials. In the COAPT trial, the heart-failure treatments were implemented at the maximum tolerated dose before randomization, and patients were subsequently excluded if their symptoms subsided or if the degree of mitral regurgitation decreased. This approach may have led to enrollment of more HF patients refractory to medical therapy in the COAPT trial than in the MITRA-FR trial. Indeed, patients in the COAPT trial had higher baseline levels of N-terminal pro–B-type natriuretic peptide, as well as a higher incidence of hospitalization for heart failure, than patients in the MITRA-FR trial. Moreover, a lower percentage of patients in the COAPT trial than the MITRA-FR trial had a higher percentage of patients with New York Heart Association functional class of I or II at 1 year; and patients in the COAPT trial had a greater increase in left ventricular end-diastolic volume at follow-up. Clearly, these facts point out to the fact that there were a greater number of sicker patients in the latter trial. Patients enrolled in the COAPT trial had heart failure symptoms that were frankly refractory to medical therapy, with a greater degree of mitral regurgitation and less left ventricular dilatation than the patients enrolled in the MITRA-FR trial [14,15]. In addition, there were differences in baseline echocardiographic features between the patient populations of the two trials. As assessed on the basis of the effective regurgitant orifice area, mitral regurgitation was more severe in the COAPT trial than in the MITRA-FR trial (41 mm2 vs. 31 mm2). Conversely, the left ventricular end diastolic volume was smaller in the COAPT trial. Another echocardiographic feature that could also influence procedural success is mitral valve anatomy. Whether eligibility differed on the basis of suitable mitral-valve leaflet anatomy is unclear. Considering that secondary mitral regurgitation is actually a disease of the left ventricle, the management of left ventricular dysfunction with guideline-directed pharmacological therapy and cardiac resynchronization therapy if suitable, should be performed before any percutaneous intervention involving the mitral valve is considered.

As with most of cardiac devices, early experience with the MitraClip highlighted several issues prompting further refinements [8,16,17]. In 2016, a second generation device (MitraClip NT) was launched featuring a redesigned clip delivery system with better steering and improved leaflet grasping. This feature allowed better performance in some degenerative anatomies like large flail gap, or when suboptimal clip trajectory is present. However, there remained an unmet need for further modifications of the clip and its delivery system to improve its ease of use and allow its application in complex anatomies. Therefore, in early 2018, two third-generation systems (MitraClip NTR and MitraClip XTR) were introduced to address these remaining issues. Although there are some differences in these two devices, both are equipped with an enhanced delivery system that allows superior steerability and

precise clip positioning. These unique features of these devices were expected to further optimize the edge-to-edge repair procedure, and to expand its applicability to a wider range of mitral valve anatomies [18]. However, data on its safety and incremental utility remain limited. In this regard, Praz., *et al*. [19] provided detailed evaluation on the safety and performance of MitraClip XTR in 107 patients treated at 3 European centers. The occurrence of device-associated complications at a higher rate than expected is a major finding of this study. Although no procedural death, stroke, or tamponade occurred, 6 patients (5.6%) had a device-related complication, resulting in 4 conversions to open surgery. These rates are higher than what was reported in contemporary trials and national registries [19-21]. The findings of the current study indicate that strict selection and use criteria are paramount. Additional investigations are needed to discern the role of both third-generation MitraClip devices in achieving optimal edge-to-edge repair in simple and complex anatomies. In order to better investigate the device in certain suitable mitral valve anatomy, the MitraClip EXPAND study was designed. This newly ongoing trial: "A Contemporary, Prospective Study Evaluating Real-world Experience of Performance and Safety for the Next Generation of MitraClip Devices; NCT03502811" will address the issue of using this device only in suitable anatomy. Thus, the outcomes of the EXPAND study will hopefully inform us on whether the safety hazard with XTR persists despite applying specific anatomic selection criteria.

Considering a newer device with different features, Lim., et al. [22] reported results of the CLASP study, a multicenter early-feasibility trial of a novel PASCAL transcatheter mitral repair device (Edwards LifeSciences, Irvine, California). This study, lead to the CE mark approval of this device system for the treatment of both primary and secondary MR in February 2019. The investigators presented early feasibility study data including 62 patients from 14 centers. These results add further knowledge to a previous study with this device [23]. Overall procedural success was high in early feasibility study with MR grade equal to or less than 2+ in 98% of the patients. Importantly, reduction of MR to grade 1+ or less was obtained in a high proportion of the treated patients (86%), a number that may be explained by the more liberal implantation of 2 devices in 49% of cases. Although PASCAL and MitraClip share similarities, the former may provide some advantages due to the wider paddles, the ability to independently grasp leaflets, and the presence of the central spacer. However, it remains to be seen whether more complex anatomies with larger flail segments, large prolapse, cleft, short posterior leaflet, or smaller mitral valve areas can be preferentially treated with the PASCAL system.

There are several other trials on the horizon investigating newer devices like the CARDIOBAND (Edwards Cardioband System ACTIVE Pivotal Clinical Trial [ACTIVE]; NCT03016975) and CARILLON (Assessment of the Carillon Mitral Contour System in Treating Functional Mitral Regurgitation Associated With Heart Failure [CARILLON]; NCT03142152) are annular technologies that are in pivotal clinical trial evaluation in the United States along with transcatheter replacement systems such as INTREPID (Transcatheter Mitral Valve Replacement With the Medtronic Intrepid TMVR System in Patients With Severe Symptomatic Mitral Regurgitation [APOLLO]; NCT03242642) and TENDYNE (Clinical Trial to Evaluate the Safety and Effectiveness of Using the Tendyne Mitral Valve System for the Treatment of Symptomatic Mitral Regurgitation [SUMMIT]; NCT03433274). Considering that approximately one third to one half of the patients either died or had continued heart failure symptoms that resulted in hospitalization at 1 year in the device group of each trials performed to date, these ongoing trials are really needed to identify the patients who have the greatest chance of benefiting. These ongoing trials will be paramount to define the appropriate use and indication for these novel devices. The optimal device should be selected according to the individual suitability to the patient´s mitral valve anatomy and the pursued MR reduction strategy. In addition, the possibility of combining different implants may develop new treatment strategies for patients with complex anatomy or borderline mitral valve area. There is no doubt that this approach will further expand the indication of the procedure and the inclusion of more patients eligible for transcatheter mitral valve repair. We are hoping better clinical results and outcome with the ongoing trials to improve the performance with new devices. Perhaps,

our hopes with these devices were much greater than the achievements. After all, humans by being imperfect cannot create a perfect device.

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