Editorial

Transcatheter edge-to-edge repair for secondary mitral regurgitation: what the clinician needs to know in the absence of robust data from international guidelines

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Vindhyal and colleagues (1) recently explored outcomes of transcatheter edge-to-edge repair (TEER) in patients with mitral regurgitation (MR), who experienced end-stage renal disease (ESRD) requiring dialysis. This elegant, retrospective, analysis of 463 patients is the first report from the United States Renal Data System (USRDS) database that evaluated patients 18 years or older with ESRD and received TEER after the new American Heart Association/American College of Cardiology (AHA/ACC) guidelines (2). The authors observed that although the in-hospital and 30-day mortality rates exceeded non-ESRD patients, the death rates were lower than previously reported. Furthermore, the authors emphasize that while recording a high 1-year mortality compared to non-ESRD patients with a high-risk patient profile, the absolute risks are still reasonable when adjusted for comorbidity. One shortcoming of the study identified the lack of data on anatomical and procedural details. This finding highlights the inability to identify patients who were declined TEER due to anatomical constraints (1).

In the last decade, the progress achieved in the field of cardiology has made use of continuous technological innovations that have increased diagnostic and therapeutic options. This incessant need for evolution has been countered by the demand of healthcare authorities to increasingly contain shipments (3,4). At the same time the growing need to move to patient-specific or patient-centered cardiology has prompted enhancement of international guideline recommendations to achieve immediate and long-term efficacy (2). The question is how to manage better this "conflict" of increasing opportunity, challenge and responsibility. The answer is multifactorial and involves the perspectives and responsibilities of the health practitioners concerned, the role, and the strict rules imposed within the heart team with attention to the ethical aspects which include without failing the patient.

The treatment of acquired structural heart valves diseases as well as that of other cardiac structures such as the left atrial appendage has undergone a revolution with the emergence of new platforms designed to perform the implantation of new devices embodying the rapidly evolving of transcatheter valve therapy (TVT) based treatment or minimally invasive approach (3,4). This revolution first involved transcatheter aortic valve implantation (TAVI) which demonstrated equivalent efficacy and safety compared to surgical aortic valve replacement in three different randomized trials involving the use of percutaneous balloon or self-expandable valves (5,6). Subsequently, the eligibility of TVT for to address MR arose. This procedure is directed towards the growing need for treating the rising prevalence

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of MR involving an aging population who experience notable comorbidities, making many subjects risky candidates for standard mitral valve surgery (SMVS) (7). The development of potentially low-risk procedures that decrease the MR severity vis-a-vis improve clinical outcomes is the primary target of transcatheter mitral valve (MV) interventions. We live in an age where effective transcatheter strategies are available for MR management despite its complex functional anatomy. In MV pathology, the characteristic of the lesions that occur in patients can vary widely, thus giving a different contribution with regard to the specificity of the onset and progression of MR. In fact, the pathological process can involve the leaflets, the annulus, chordae tendineae, the papillary muscles, and the underlying myocardium. Therefore, TVT repair techniques need to be directed to the leaflets, annulus, or chordae, both individually or in combination (8).

The first device that received Food and Drug Administration (FDA) approval for transcatheter repair improves edge-to-edge mitral leaflet coaptation by utilizing a clip or to oppose scallops of the anterior and posterior leaflets. In addition, the use of TEER was initially restricted to the management of symptomatic high/prohibitive risk patients with a severe primary MV regurgitation who were included in New York Heart Association (NYHA) functional class III or IV and who were referred to the interventional cardiologist to receive TEER. Subsequently, the indications although confined to a limited patient population because of the reasonable life expectancy, incorporated subjects with secondary mitral regurgitation (SMR) at prohibitive surgical risk and with a high rate of comorbidities (7,8). In a short time, two randomized clinical trials (RCTs), in the USA and Europe, were designed to evaluate the safety and efficacy of this technology for the treatment of patients with severe symptomatic functional MR [Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy (COAPT) (5) and Multicenter Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation (MITRA-Fr) (9)]. TEER for patients with SMR was more commonly used outside the USA (10,11). Several other transcatheter repair systems such as ring devices were rapidly developed and were made available for clinical use (3,12).

TEER allows restoration of edge-to-edge leaflet coaptation using a clip and was described by Alfieri *et al.* who first performed the procedure for surgical MV repair (13). The technique essentially results in a MV with a double orifice that promotes a substantial reduction in the severity of MR. The promising initial results revealed that successful procedures resulted in improved hemodynamics and patient outcomes (14). Importantly, suitable patient screening depends critically on meticulous clinical and echocardiographic evaluation both during and after the procedure with algorithms to facilitate training. The TEER was rigorously evaluated, and the operator and institution criteria for implementation were published in an expert consensus document (15). This procedure was quickly taken up by interventional cardiologists at over 200 sites across the USA (12) (*Figure 1*).

Left ventricular (LV) remodeling is a poor prognostic indicator for ischemic cardiomyopathy can be reversible with revascularization of viable myocardium (16,17). The management of SMR advocates significant challenges that patients with ESRD may appear even more difficult to manage in the absence of direct recommendations from international guidelines. SMR is a pathological process that involves the LV rather than attributable to the MV. Thus, therapy is primarily directed toward addressing this LV disorder. Medical therapy involves administration of neurohormonal antagonists and cardiac resynchronization devices may help promote the reversal of the adverse remodeling process. Again, in a large percentage of patients, the combination of these interventions can support the consequent reduction of LV volumes by improving the severity of MR (18). In contrast, SMVS aimed at reversing MV failure have reported disappointing results. In 2 reports of RCT, patients with moderate or severe ischemic MR with relatively preserved left ventricular ejection fraction (LVEF) within 40%, did not disclose pre-specified benefit on cardiac geometry either by performing MV repair with undersized ring annuloplasty or via SMVS with chordal sparing preservation. For these patients, favorable long-term effects on clinical outcomes and the absence of a high recurrence rate of mitral insufficiency (MI) were not demonstrated (19). As a result, secondary MR management is primarily based on drug administration and device implantation to advocate the restoration of LV structure and function, rather than using SMVS to reduce MR.

In a recent study, Okuno *et al.* (20) reported 2-year outcomes comparing SMVS using restrictive mitral annuloplasty (RMA) *vs.* TEER for SMR in 202 matched patients. At 2 years, freedom for all-cause mortality was 75.7% in recipients of TEER compared to 77.0% in the RMA group (hazard ratio, 0.97; 95% confidence interval: 0.55–1.71; P=0.909). The risk of severe heart failure (HF) is another complication due to the procedure strategy worthy

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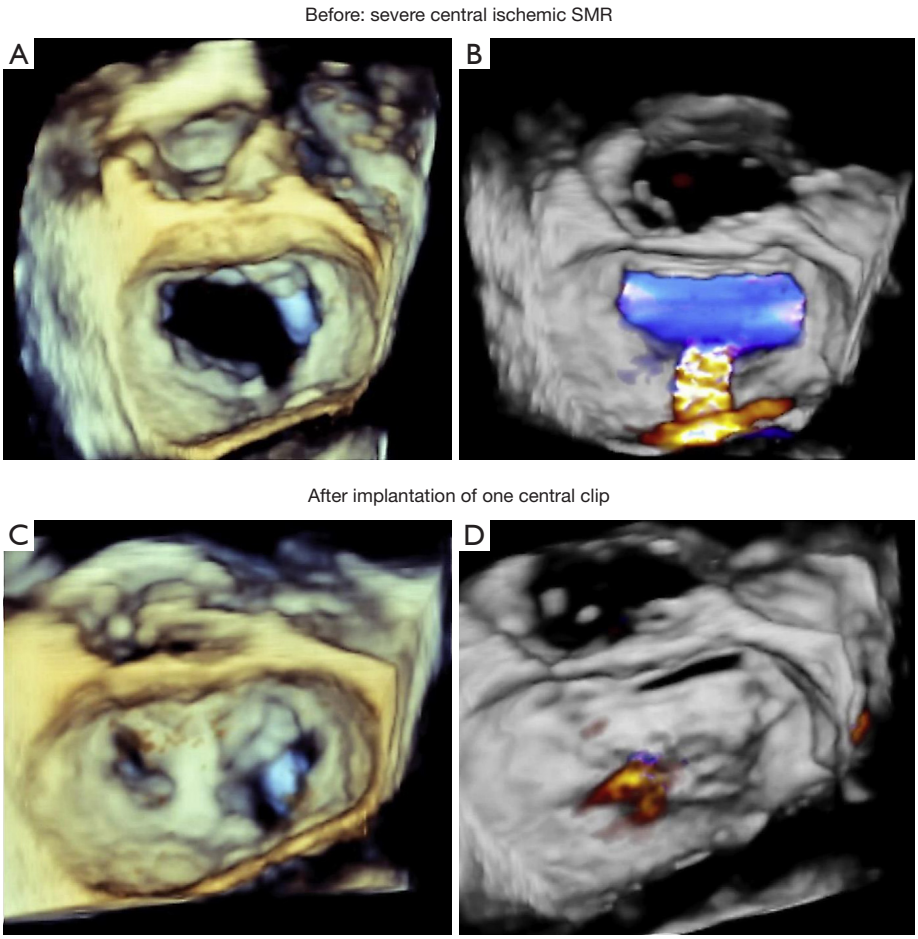

Figure 1 Patient with SMR who received TEER. 3D-TEE (A) and 3D-TEE (B) color en-face view showing central SMR. (C) A 3D-TEE en-face view after a successful procedure with implantation of 2 central MitraClips (Abbott Vascular, Menlo Park, CA, USA). (D) Transthoracic echocardiographic 3-chamber view shows persistent good results at 1 year with residual mild mitral regurgitation and a gradient at 4 mm. SMR, secondary mitral regurgitation; TEER, transcatheter edge-to-edge repair; 3D, three-dimensional; TEE, transesophageal echocardiography.

of consideration. The authors also noted less prevalent symptoms of severe HF at 2 years in the RMA group *vs.* the TEER group at 2 years (NYHA functional class III or IV: 13.5% *vs.* 29.5%; P=0.032). They reported a higher proportion of the RMA recipients with decreased SMR to none or mild at discharge (90.8% *vs.* 72.0%; P<0.001) and 2 years (86.5% *vs.* 59.6%; P<0.001). The improvement of MR was consistent among patients with RMA who achieved none or mild MR at discharge with only 7 patients (10.1%) in this group progressing to moderate or greater MR compared to 15 patients (34.9%) in the TEER group at 2 years (P=0.003). Similarly, LVEF improved (10.1%±11.1%; P<0.001) after RMA (LVEF at 2 years: 45.7%±12.8%) compared to TEER (–1.3%±8.9%; P=0.260) (LVEF at 2 years: 34.0%±13.2%) (20).

The results of Okuno and colleagues (20) project contradictions in the 2020 AHA/ACC guidelines for the indication for TEER in SMR that is advocated [Class of Recommendation (COR) II-b and level of evidence (LOE) B-R2]. Propensity-matched cohorts of SMVR *vs.* TEER for SMR were used and the results were reported soon after the AHA/ACC and European Society of Cardiology (ESC) guidelines were released. They revealed no significant difference in survival (P=0.909); however, the use of RMA with coronary revascularization has proved superior to TEER for decreasing MR, improving LVEF, and reducing NYHA class III–IV (20).

The Cardiothoracic Surgical Trials Network (CTSN)

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trial sub-analysis included 75% concomitant coronary artery bypass grafting (CABG) surgery cases as well, negating the potential improvement in regional wall motion for 25% of patients (19). The use of sub-valvular MV procedure alongside a valvular procedure of restrictive repair has proven to be safe and effective compared to RMA alone in ischemic and non-ischemic cohorts in several studies (16,17,21,22). The use of double-level repair with valvular and sub-valvular handling of the MV apparatus has been described in the papillary muscle approximation RCT (PMA-RCT). Ninety-six patients with severe secondary ischemic MR underwent revascularization combined with isolated restrictive mitral repair or PMA with RMA in a 5-year follow-up. Left ventricular end diastolic dimension (LVEDD) improved at 5-year follow-up (5.8±4.1 and –0.2±2.3 mm, respectively; P<0.001) preserving the benefit attained in the immediate post-operative period with freedom from major adverse cardiac and cerebrovascular events (P=0.004) (16). In the COAPT study an improvement of LV remodeling secondary to the use of TEER was not observed (LVEDV: 194.4±69.2 *vs.* 192.2±76.5 mL) (5) despite TEER recipients noting improvements in MR severity at 3 years, functional capacity, and quality-of-life measures compared to guideline-directed medical therapy (GDMT) alone (5). The benefit of using the TEER procedure over GDMT was noted in 58 patients who had previously received GDMT-only administration and who subsequently switched to TEER management. For this cohort, the subsequent composite rate of death or hospitalization for HF was reduced compared with GDMT alone (P=0.006) (5).

Okuno and colleagues reported that RMA was superior to TEER repair at 24 months (20). Randomized control trials have demonstrated that RMA had a greater MR recurrence rate at 2- and 5-year follow-ups (58.8% and 55.9%) (18,23). RMA tends to be more successful in patients with smaller preoperative left ventricular end systolic dimension (LVESD) and reduced apical tethering of the leaflets. Seventy-four patients enrolled in the CTSN trial with severe ischemic mitral regurgitation (IMR) with no MR recurrence had significantly smaller left ventricles at 2-year follow-up as compared to those patients with recurrent MR post-RMA alone (43±26 *vs.* 63±27 mL/m^2. The left ventricular end-systolic volume measures remained lower than patients who underwent surgical MV replacement (61±39 mL/m^2) (19).

The double-level repair in the PMA-RCT achieved geometric recovery by normalization of three measures: interpapillary muscle distance, tenting area, and anteroposterior annular dilatation. The repair aims to restore the altered spatial relationship of the different elements of the MV apparatus by addressing the valve and ventricle in SMR (Carpentier IIIb classification) (16,17,21,22). The role of the papillary muscles was also the subject of the Osaka group (24). Kainuma and colleagues noted that RMA in isolation failed to relieve leaflet tethering which then influenced the recovery of interpapillary muscles distance (IPMD) due to the improvement of LVEDD. IPMD was the main factor for MR recurrence. These benefits are boosted by post-RMA reverse LV remodeling causing a reduction in IPMD (31±6 to 25±5 mm), potentially offsetting the increment in posterior leaflet angle (24). Thus, double-level repair incorporating surgical handling of dislocated papillary muscles is more suitable than the edge-to-edge TVT procedure in patients with SMR due to nonischemic cardiomyopathy (Carpentier class I). These patients have dilatation of the MV annulus, lateral displacement of the anterior and posterior papillary muscle and symmetrical tethering of the leaflets alongside apical tenting of the anterior leaflet, resulting in central jets which cannot be fixed using RMA alone (16,19,23). Patients with nonischemic cardiomyopathy and severe left ventricular dilation, alongside moderate-to-severe MR, had worse outcomes in the COAPT (5) and in MITRA-Fr (9) trials. These were similar to proportionate MR, therefore did not have a favorable response to TEER (2,5,9,23).

There are currently 5 AHA/ACC recommendations classified as LOE B-R or B-NR, indicating moderate quality of studies not supported by robust evidence on the efficacy and safety of TEER. The available literature reveals a scarcity of RCTs designed with large numbers of patients enrolled that include candidates receiving TEER, MV replacement, or MV repair with/without sub-valvular procedure. Specifically, the AHA/ACC guidelines refer to two RCTs based on TEER with 3-year results reported only for the COAPT study (5) and the analysis of the new pathophysiological picture of the pathological mechanism for SMR (2,16-18,22,24). None of these recommendations were based on longer follow-ups (2,5,9,22). However, there is no robust evidence today based on usefulness, effectiveness, and benefit supported by more than 1 RCT or meta-analyses recommending double-level repair.

The MATTERHORN study (Multicenter Randomized, Controlled Study to Assess Mitral vAlve reconsTrucTion for advancEd Insufficiency of Functional or iscHemic ORigiN), for which results are expected, considers composite of

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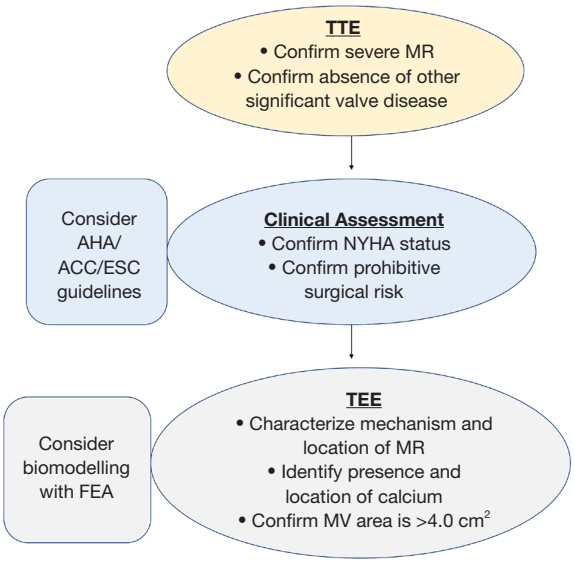

Figure 2 Algorithm for determining eligibility for TEER. TTE, transthoracic echocardiography; AHA, American Heart Association; ACC, American College of Cardiology; ESC, European Society of Cardiology; NYHA, New York Heart Association; FEA, finite element analysis; TEE, transesophageal echocardiography; MR, mitral regurgitation; MV, mitral valve; TEER, transcatheter edge-to-edge repair.

death, rehospitalization for HF, reintervention, such as repeat operation or repeat intervention, assist device implantation and stroke 12 months post-intervention as the primary endpoint. Other RCTs under review demonstrated efficacy and safety in the treatment of SMR using advanced technology devices. None of these involve the papillary muscles by performing approximation or relocation procedures which is a crucial point for obtaining a lasting repair in the presence of alteration of the functional spatial relationships of the various components of the MV apparatus.

Recently, a sub-analysis of the COAPT RCT evaluated the prognostic implications of MV geometry for patients with SMR. Namazi *et al.* (23) reported that patients with HF and severe SMR, a large anteroposterior mitral annular diameter and greater effective regurgitant orifice area were the most significant echocardiographic predictors of HF and death in patients treated with GDMT alone and with the MitraClip.

The CLASP RCT (n=124) (CLASP Study Edwards PASCAL TrAnScatheter Mitral Valve RePair System Study) used the PASCAL system for functional, degenerative, and mixed etiologies of MV disease. This study noted good survival with a significant reduction in hospitalization due to HF in both 1- and 2-year follow-ups. Patients also had a significant reduction in MR associated with reverse positive left ventricular remodeling alongside improved functional status and exercise capacity (25,26). The CLASP IID/IIF (n=1,275) will pit the PASCAL system and the MitraClip system for MV repair for regurgitant and degenerative valves.

Further multicenter randomized studies with longer follow-up (5 years) are needed in the near future to compare outcomes using the transcatheter methods *vs.* a double-level valve repair. In addition, a patient-specific computer simulation may offer a substantial empirical contribution to further improve the results of catheter-based treatment of acquired structural heart disease (3,4) (*Figure 2*).

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References

1. Vindhyal MR, Vasudeva R, Chan WC, et al. Transcatheter edge to edge mitral valve repair in patients with end-stage renal disease on dialysis: an analysis from the United States Renal Data System. Ann Transl Med 2023;11:277.
2. Writing Committee Members, Otto CM, Nishimura RA, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol 2021;77:450-500.
3. Nappi F, Nenna A, Chello M. Structural Heart Valve Disease in the Era of Change and Innovation: The Crosstalk between Medical Sciences and Engineering. Bioengineering (Basel) 2022;9:230.
4. Nappi F, Attias D, Avtaar Singh SS, et al. Finite element analysis applied to the transcatheter mitral valve therapy: Studying the present, imagining the future. J Thorac Cardiovasc Surg 2019;157:e149-51.
5. Mack MJ, Lindenfeld J, Abraham WT, et al. 3-Year Outcomes of Transcatheter Mitral Valve Repair in Patients With Heart Failure. J Am Coll Cardiol 2021;77:1029-40.
6. Popma JJ, Deeb GM, Yakubov SJ, et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. N Engl J Med 2019;380:1706-15.
7. Lim DS, Reynolds MR, Feldman T, et al. Improved functional status and quality of life in prohibitive surgical risk patients with degenerative mitral regurgitation after transcatheter mitral valve repair. J Am Coll Cardiol 2014;64:182-92.
8. Maisano F, Alfieri O, Banai S, et al. The future of transcatheter mitral valve interventions: competitive or complementary role of repair vs. replacement? Eur Heart J 2015;36:1651-9.
9. Iung B, Armoiry X, Vahanian A, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation: outcomes at 2 years. Eur J Heart Fail 2019;21:1619-27.
10. Maisano F, Franzen O, Baldus S, et al. Percutaneous mitral valve interventions in the real world: early and 1-year results from the ACCESS-EU, a prospective, multicenter, nonrandomized post-approval study of the MitraClip therapy in Europe. J Am Coll Cardiol 2013;62:1052-61.
11. Schillinger W, Hünlich M, Baldus S, et al. Acute outcomes after MitraClip therapy in highly aged patients: results from the German TRAnscatheter Mitral valve Interventions (TRAMI) Registry. EuroIntervention 2013;9:84-90.
12. Grover FL, Vemulapalli S, Carroll JD, et al. 2016 Annual Report of The Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. J Am Coll Cardiol 2017;69:1215-30.
13. Alfieri O, Maisano F, De Bonis M, et al. The double-orifice technique in mitral valve repair: a simple solution for complex problems. J Thorac Cardiovasc Surg 2001;122:674-81.
14. Hahn RT. Transcathether Valve Replacement and Valve Repair: Review of Procedures and Intraprocedural Echocardiographic Imaging. Circ Res 2016;119:341-56.
15. O'Gara PT, Calhoon JH, Moon MR, et al. Transcatheter therapies for mitral regurgitation: a professional society overview from the American College of Cardiology, the American Association for Thoracic Surgery, Society for Cardiovascular Angiography and Interventions Foundation, and the Society of Thoracic Surgeons. J Am Coll Cardiol 2014;63:840-52.
16. Nappi F, Lusini M, Spadaccio C, et al. Papillary Muscle Approximation Versus Restrictive Annuloplasty Alone for Severe Ischemic Mitral Regurgitation. J Am Coll Cardiol 2016;67:2334-46.
17. Nappi F, Spadaccio C, Nenna A, et al. Is subvalvular repair worthwhile in severe ischemic mitral regurgitation? Subanalysis of the Papillary Muscle Approximation trial. J Thorac Cardiovasc Surg 2017;153:286-295.e2.
18. Nasser R, Van Assche L, Vorlat A, et al. Evolution of Functional Mitral Regurgitation and Prognosis in Medically Managed Heart Failure Patients With Reduced Ejection Fraction. JACC Heart Fail 2017;5:652-9.
19. Goldstein D, Moskowitz AJ, Gelijns AC, et al. Two-Year Outcomes of Surgical Treatment of Severe Ischemic Mitral Regurgitation. N Engl J Med 2016;374:344-53.
20. Okuno T, Praz F, Kassar M, et al. Surgical versus transcatheter repair for secondary mitral regurgitation: A propensity score-matched cohorts comparison. J Thorac Cardiovasc Surg 2023;165:2037-2046.e4.
21. Pausch J, Sequeira Gross T, Müller L, et al. Subannular repair for functional mitral regurgitation type IIIb in patients with ischaemic versus dilated cardiomyopathy. Eur J Cardiothorac Surg 2021;60:122-30.
22. Nappi F, Antoniou GA, Nenna A, et al. Treatment options for ischemic mitral regurgitation: A meta-analysis. J Thorac Cardiovasc Surg 2022;163:607-622.e14.
23. Namazi F, Delgado V, Pio SM, et al. Prognostic implications of mitral valve geometry in patients with

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secondary mitral regurgitation: the COAPT trial. Eur Heart J Cardiovasc Imaging 2022;23:1540-51.
24. Kainuma S, Funatsu T, Kondoh H, et al. Beneficial effects of restrictive annuloplasty on subvalvular geometry in patients with functional mitral regurgitation and advanced cardiomyopathy. J Thorac Cardiovasc Surg 2018;156:630-638.e1.
25. Praz F, Spargias K, Chrissoheris M, et al. Compassionate use of the PASCAL transcatheter mitral valve repair system for patients with severe mitral regurgitation: a multicentre, prospective, observational, first-in-man study. Lancet 2017;390:773-80.
26. Webb JG, Hensey M, Szerlip M, et al. 1-Year Outcomes for Transcatheter Repair in Patients With Mitral Regurgitation From the CLASP Study. JACC Cardiovasc Interv 2020;13:2344-57.

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