Transcatheter Edge-to-Edge Mitral Valve Repair in Functional Mitral Regurgitation. Does it Pass Muster? Still Leaving Plenty to Be Desired

Ovidio A. García-Villarreal, MD

The usefulness of percutaneous approaches in structural heart disease could be limited if they have been defined in terms of often unrealistic scenarios. Thus, the long-term outcomes and consequences need to be painstakingly analyzed. Much attention needs to be paid to the global magnitude of this issue. One such example is the transcatheter edge-to-edge mitral valve repair (TEER) and considerations of pivotal importance that arise from using this therapy to treat functional mitral regurgitation (FMR).

Traditionally, surgical treatment has been the best option for mitral valve (MV) repair. When comparing TEER to surgical MV repair, several salient details need to be considered. One of the main drawbacks of the edge-to-edge technique is that it has never been the first option for any surgical MV repair. Furthermore, the most important difference between the percutaneous technique and surgery is the absence of an annuloplasty prosthetic ring in the first option. Consequently, this factor renders the percutaneous procedure only partially effective. It must be emphasized in the strongest terms that it is insufficient to consider TEER without an annuloplasty ring. We must also acknowledge the important role of the annuloplasty, by means of a prosthetic ring in every MV repair.[1,2]. In fact, the lack of an annuloplasty ring is the most powerful predictor for failure after MV repair in the long term[3,4]. This rule is universal and, therefore, applies to any MV repair in the adult. Alfieri’s edge-to-edge technique that underpins the principle of TEER is no exception to this rule[5-9]. Nevertheless, it seems that all the implications of a ringless therapy such as TEER have not been completely addressed. Thus, we must define such limitations in the percutaneous approach for MV repair. Indeed, rules governing MV repair do not change just by shifting the approach. In fact, the percutaneous technique is constrained by the installation of a ringless TEER device. Due to TEER being a ringless therapy, dilatation of both commissures has been proposed as a possible explanation for the high occurrence of recurrent mitral regurgitation (MR) ≥ 2+ (23% at two years) observed in the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial[10].

The occurrence of FMR directly linked to coronary artery disease may constitute an ever-increasing potential indication for TEER. However, evidence supporting TEER in FMR is only limited to two controversial randomized controlled trials.

In the Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients with Severe Secondary Mitral Regurgitation (MITRA-FR) trial (in which primary funding was provided by the French Ministry of Health and Research National Program), TEER results were compared with medical treatment in patients with FMR. No statistically significant differences were observed between both groups for all-cause mortality (24.3% vs. 22.4%; hazard ratio (HR): 1.11; 95% confidence interval (CI), 0.69 to 1.77) and rehospitalization for heart failure (HF) (47.4% vs. 47.4%; HR: 1.13; 95% CI, 0.81 to 1.56) at one year of follow-up[11]. At two years of follow-up, there was no significant difference for the composite of death for any cause and HF rehospitalization (63.8% vs. 67.1%; HR 1.01, 95% CI 0.77-1.34). Rehospitalization for HF alone did not show important difference between groups (55.9% vs. 61.8%; HR 0.97, 95% CI 0.72–1.30)[12].

Contradictory results in favor of TEER were obtained in the COAPT trial, a study fully sponsored by the MitraClip™ device industry Abbott for TEER (MitraClipTM TMVr, Abbott, Santa Clara, USA) at 2 – 3- years of follow-up. Rehospitalization rate for HF was 35.8% for TEER and 67.9% in the control group (HR, 0.53; 95% CI, 0.40 to 0.70; P<0.001). In light of the above, important questions arise in respect of the best treatment for this special group of patients[13].

Special efforts have been made in order to narrow the gap between the ideal and the real outcomes observed in COAPT and MITRA-FR trials, respectively. Theoretical explanation by means of the disproportionate/proportionate FMR concept has been proposed to provide a better understanding of the aforementioned data disparities[14,15]. The central concept...
is the effective regurgitant orifice area/endpoint diastolic left ventricular (LV) volume ratio. The selected cut-off value is 0.14 (with LV ejection fraction of 30% and regurgitant fraction of 50%, meaning severe FMR). Thus, two main types of FMR can be identified, namely, those with preserved LV volume and significant MR (disproportionate), and those with diluted LV volume and large MR (proportionate). The former is typical of chronic ischemic MV regurgitation with posterobasal deformation of the left ventricle due to chronic coronary artery disease. The latter is generally observed in dilated cardiomyopathies, regardless of the underlying etiology. Hence, at a first glance, disproportionate FMR cases entail better prognosis. However, when moving from theory into practice, all these tools have failed to obtain a reasonable explanation about the differences between trials until now. By using this concept, Lindenfeld et al. [16] found no consistent differences between groups when comparing MITRA-FR-like vs. COAPT-like patients. Adamo et al. [17] demonstrated that the relative risk of HF hospitalization and death was independent from the presence of disproportionate FMR [18]. In a study of 241 cases of TEER, Ooms et al. [19] found no important difference for all-cause mortality and HF rehospitalization rates for disproportionate and proportionate FMR (30% vs. 37%, respectively). Hagendorff et al. [20] have clearly emphasized that the disproportionate FMR can only be explained by means of conflicting data on the reported echocardiographic values, such as those observed in the COAPT trial.

It is important to clarify the distinction in the guideline-directed medical therapy (GDMT) between the two trials, in order to dispel the popular misconception about the similar equivalence between them. While post-procedural GDMT has been largely questioned in COAPT, intensive medical treatment was carried out and maintained in nearly 80% of cases in MITRA-FR. Thus, medical management was quite different in both trials, especially after randomization [20]. In the COAPT trial, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or angiotensin/nephrilisin receptor inhibitors were significantly underused in the medical therapy alone arm than in the TEER group throughout the whole trial period [21]. Taken together, these data tend to create a major distortion towards the most optimum balance in both arms of the COAPT. Hence, it could explain the wide different outcomes in both trials. In the same COAPT trial, within the group of patients whose MR did not improve 30 days after the start of medical treatment, 33% and 40% — at one year and two years, respectively — had significant improvement in reducing the severity of MR. This strongly questions the efficacy of the medical treatment used within the COAPT trial. Finally, if the pool of medications and doses used in COAPT (sacubitril/valsartan used in < 5% of cases, mineralocorticoid antagonist in 50%, and sodium-glucose cotransporter inhibitor in 0%) is compared with current treatment protocols, we can state that such medical therapies in the COAPT are, at present, inadequate and obsolete. Moreover, in stark contrast to what current clinical guidelines for the management of HF recommend as an aggressive medical treatment from the outset, reaching maximum doses as necessary [22], the GDMT utilized in the COAPT trial leaves much to be desired.

Post-COAPT trial data considerations with respect to the absence of open, unbiased data transparency, alongside a lack of reproducibility in low-volume centers and the stringent patient selection criteria, make extrapolation to the majority of the population with FMR highly unlikely. Therefore, concern about the accuracy of all conclusions from the COAPT trial must be urged, and assiduous caution exercised when interpreting the results. Nonetheless, based on the COAPT results, the most recent European and American clinical guidelines for the management of valvular heart disease consider a Class IIa recommendation for TEER in FMR, in the absence of coronary artery disease. This recommendation is also applicable for cases of HF in stage D without an adequate response to GDMT [23,24]. The obvious conclusion that the COAPT results can be applied to most of the patients with FMR is, therefore, biased and unfounded. The author of this article considers that before accepting this recommendation, all available information should be revisited again in an impartial manner. In fact, the author has repeatedly suggested that this TEER recommendation for FMR should be a Class IIb recommendation, and limited to a very selective pool of patients [25,26].

Much of the rationale for supporting TEER and downplaying MV repair surgery in FMR arises from research by Goldstein et al. and the Cardiothoracic Surgical Trials Network investigators, which demonstrated that the recurrent MR rate after MV restrictive annuloplasty was up to 58.8% at a two-year follow-up [27]. However, it is extremely important that this information be carefully considered. Firstly, specific echocardiographic parameters for MV repair in FMR were not included in this study. Significantly, systolic sphericity index > 0.7, LV end-systolic volume > 140 mL, LV diastolic diameter > 65 mm, LV systolic diameter > 51 mm, posterior papillary-fibrosa distance > 40 mm, interpapillary distance > 20 mm, coaptation depth > 1.1 mm, tenting area > 2.5 mm², and posterior leaflet angle > 45° are considered as predictors of failure after restrictive annuloplasty in FMR [28]. The second fact is that no etiology-specific designed annuloplasty rings were utilized in the trial. The GeoForm annuloplasty ring (Edwards Lifesciences, Irvine, California, USA) and IMR ETlogix ring (CMA IMR ETlogix ring®; Edwards Lifesciences, Irvine, California, USA), instead of the classic Physio annuloplasty ring (Edwards Lifesciences, Irvine, California, USA), have demonstrated a lower rate of MV regurgitation recurrence after operation in FMR [29,30].

The consequences of applying a therapy without anticipating long-term results can be devastating. In the CUTTING-EDGE study, 332 cases that underwent MR surgery after failed TEER were analyzed. Operative mortality was 16.6%, and 92.5% of cases ended with MV replacement [31]. Chikwe et al. [32] reported 524 patients underwent MR surgery after failed TEER. Operative mortality was 10.2%, and 95% of these patients underwent MV replacement. The Transcatheter Mitral Valve Therapy STS/ACC/TVT Registry reed an occurrence of recurrent MR ≥ 3+ of 8.7% at just 30 days after TEER [33]. An analysis from data of the Heart Failure Network Rhineland registry showed MR ≥ 3+ of 9.8% at one year after TEER [34]. An analysis from data of the Heart Failure Network Rhineland registry showed MR ≥ 3+ of 9.8% at one year after TEER [34]. An analysis from data of the Heart Failure Network Rhineland registry showed MR ≥ 3+ of 9.8% at one year after TEER [34]. An analysis from data of the Heart Failure Network Rhineland registry showed MR ≥ 3+ of 9.8% at one year after TEER [34]. An analysis from data of the Heart Failure Network Rhineland registry showed MR ≥ 3+ of 9.8% at one year after TEER [34]. An analysis from data of the Heart Failure Network Rhineland registry showed MR ≥ 3+ of 9.8% at one year after TEER [34]. An analysis from data of the Heart Failure Network Rhineland registry showed MR ≥ 3+ of 9.8% at one year after TEER [34]. An analysis from data of the Heart Failure Network Rhineland registry showed MR ≥ 3+ of 9.8% at one year after TEER [34]. An analysis from data of the Heart Failure Network Rhineland registry showed MR ≥ 3+ of 9.8% at one year after TEER [34]. An analysis from data of the Heart Failure Network Rhineland registry showed MR ≥ 3+ of 9.8% at one year after TEER [34]. An analysis from data of the Heart Failure Network Rhineland registry showed MR ≥ 3+ of 9.8% at one year after TEER [34]. An analysis from data of the Heart Failure Network Rhineland registry showed MR ≥ 3+ of 9.8% at one year after TEER [34]. An analysis from data of the Heart Failure Network Rhineland registry showed MR ≥ 3+ of 9.8% at one year after TEER [34].
REFERENCES

1. Carpentier A, Deloche A, Daupain J, Soyer R, Blondeau P, Pivnicka A, et al. A new reconstructive operation for correction of mitral and tricuspid insufficiency. J Thorac Cardiovasc Surg. 1971;61(1):1-13.

2. Carpentier A. Cardiac valve surgery—the “French correction”. J Thorac Cardiovasc Surg. 1983;86(3):323-37.

3. David TE, Armstrong S, McCrindle BW, Manlhiot C. Late outcomes of mitral valve repair for mitral regurgitation due to degenerative disease. Circulation. 2013;127(14):1485-92. doi:10.1161/CIRCULATIONAHA.112.000699.

4. Suri RM, Schaff HV, Michelena HI, Huebner M, Nishimura RA, et al. Effect of recurrent mitral regurgitation following degenerative mitral valve repair: long-term analysis of competing outcomes. J Am Coll Cardiol. 2016;67(5):488-98. Erratum in: J Am Coll Cardiol. 2016;67(16):1976-8. doi:10.1016/j.jacc.2015.10.098.

5. Alfiere O, Maisano F, De Bonis M, Stefano PL, Torracca L, Oppizzi M, et al. The double-orifice technique in mitral valve repair: a simple solution for complex problems. J Thorac Cardiovasc Surg. 2001;122(4):674-81. doi:10.1067/mct.2001.117277.

6. De Bonis M, Lapenna E, Taramasso M, La Canna G, Buzzatti N, Pappalardo F, et al. Very long-term durability of the edge-to-edge repair for isolated anterior mitral leaflet prolapse: up to 21 years of clinical and echocardiographic results. J Thorac Cardiovasc Surg. 2014;148(5):2027-32. doi:10.1016/j.jtcvs.2014.03.041.

7. De Bonis M, Lapenna E, Maisano F, Barili F, La Canna G, Buzzatti N, et al. Long-term results (≤18 years) of the edge-to-edge mitral valve repair without annuloplasty in degenerative mitral regurgitation: implications for the percutaneous approach. Circulation. 2014;130(11 Suppl 1):S19-24. doi:10.1161/CIRCULATIONAHA.113.007885.

8. De Bonis M, Lapenna E, Pozzoli A, Giacomini A, Alfiere O. Edge-to-edge surgical mitral valve repair in the era of MitraClip: what if the annuloplasty ring is missed? Curr Opin Cardiol. 2015;30(2):155-60. doi:10.1097/HCO.0000000000000148.

9. De Bonis M, Lapenna E, Barili F, Nisi T, Calabrese M, Pappalardo F, et al. Long-term results of mitral repair in patients with severe left ventricular dysfunction and secondary mitral regurgitation: does the technique matter? Eur J Cardiothorac Surg. 2016;50(5):882-9. doi:10.1093/ejcts/ezw139.

10. Votta E, Maisano F, Soncini M, Redaelli A, Monteverci FM, Alfiere O. 3-D computational analysis of the stress distribution on the leaflets after edge-to-edge repair of mitral regurgitation. J Heart Valve Dis. 2002;11(6):810-22.

11. Obadia JF, Messika-Zeitoun D, Leurent G, Jung B, Bonnet G, Pirio U, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation. N Engl J Med. 2018;379(24):2297-306. doi:10.1056/NEJMoA1805374.

12. Jung B, Armoiry X, Vahanian A, Boutitie F, Mewton N, Trochu JN, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation: outcomes at 2 years. Eur J Heart Fail. 2019;21(12):1619-27. doi:10.1002/ejhf.1616.

13. Stone GW, Lindenedf J, Abraham WT, Kar S, Lim DS, Mitchell JM, et al. Transcatheter mitral-valve repair in patients with heart failure. N Engl J Med. 2018;379(24):2307-18. doi:10.1056/NEJMoa1806640.

14. Grayburn PA, Sannino A, Packer M. Proportionate and disproportionate functional mitral regurgitation: a new conceptual framework that reconciles the results of the MITRA-FR and COAPT trials. JACC Cardiovasc Imaging. 2019;12(2):353-62. doi:10.1016/j.jcmg.2018.11.006.

15. Packer M, Grayburn PA. New evidence supporting a novel conceptual framework for distinguishing proportionate and disproportionate functional mitral regurgitation. JAMA Cardiol. 2020;5(4):469-75. doi:10.1001/jamacardio.2019.5971.

16. Lindenedf J, Abraham WT, Grayburn PA, Kar S, Asch FM, Lim DS, et al. Association of effective regurgitation orifice area to left ventricular end-diastolic volume ratio with transcatheter mitral valve repair outcomes: a secondary analysis of the COAPT trial. JAMA Cardiol. 2021;6(4):427-36. doi:10.1001/jamacardio.2020.7200.

17. Adamo M, Cani DS, Gavaizzato M, Taramasso M, Lupi L, Fiorelli F, et al. Impact of disproportionate secondary mitral regurgitation in patients undergoing edge-to-edge percutaneous mitral valve repair. EuroIntervent. 2020;16(5):413-20. doi:10.1093/ei/DJL-D-19-01114.

18. Hagendorff A, Knebel H, Heifen A, Stoebe S, Donsent T, Falk V. Disproportionate mitral regurgitation: another myth? A critical appraisal of echocardiographic assessment of functional mitral regurgitation. Int J Cardiovasc Imaging. 2021;37(1):183-96. doi:10.1007/s10554-020-01975-6.

19. Doms JF, Bouwmeester S, Debonnaire P, Nasser R, Voigt JJ, Schoborg MA, et al. Transcatheter edge-to-edge repair in proportionate versus disproportionate functional mitral regurgitation. J Am Soc Echocardiogr. 2022;35(1):105-15.e6. doi:10.1016/j.echo.2021.08.002.

20. Obadja JF, Jung B, Messika-Zeitoun D. The disproportionate success of the disproportionate concept. J Thorac Cardiovasc Surg. 2022;163(1):e7-e8. doi:10.1016/j.jtcvs.2020.06.114.

21. Timek TA. Reply: Proportioning our beliefs to the evidence. J Thorac Cardiovasc Surg. 2022;163(1):e8-9. doi:10.1016/j.jtcvs.2020.07.098.

22. McDonald M, Virani S, Chan M, Ducharme A, Ezekowitz JA, Giannetti N, et al. CCS/CHFS heart failure guidelines update: defining a new pharmacologic standard of care for heart failure with reduced ejection fraction. Can J Cardiol. 2021;37(4):S31-46. doi:10.1061/CIRCULATIONAHA.121.01.017.

23. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP 3rd, Gentile F, 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. Circulation. 2021;143(5):e35-e71. Erratum in: Circulation. 2021;143(5):e228. Erratum in: Circulation. 2021;143(10):e784. doi:10.1161/CIRCULATIONAHA.120.045991.

24. Vahanian A, Beyersdorf A, Praz F, Milojivic M, Baldus S, Baurersachs J, et al. 2021 ESC/EACTS guidelines for the management of valvular heart disease: Eur Heart J. 2022;43(7):561-632. Erratum in: Eur Heart J. 2022; doi:10.1093/ehjheart/ehab395.

25. Lancellotti P, Moura L, Pierard LA, Agricola E, Popescu BA, Tribouilloy C, et al. Association of effective regurgitation orifice area to left ventricular end-diastolic volume ratio with transcatheter mitral valve repair outcomes: a secondary analysis of the COAPT trial. JAMA Cardiol. 2021;6(4):427-36. doi:10.1056/NEJMoa1806640.

26. Goldstein D, Moskowitz AJ, Gelijns AC, Ailawadi G, Parides MK, Perrault LP, et al. Two-year outcomes of surgical treatment of severe ischemic mitral regurgitation. N Engl J Med. 2016;374(4):344-53. doi:10.1056/NEJMoa1512913.

27. Lancellotti P, Moura L, Pierard LA, Agricola E, Popescu BA, Tribouilloy C, et al. European association of echocardiography recommendations for the assessment of valvular regurgitation. Part 2: mitral and tricuspid re-
gurgitation (native valve disease). Eur J Echocardiogr. 2010;11(4):307-32. doi:10.1093/ejechocard/jep031.

29. Timek TA, Malinowski M, Hooker RL, Parker JL, Willekes CL, Murphy ET, et al. Long-term outcomes of etiology specific annuloplasty ring repair of ischemic mitral regurgitation. Ann Cardiothorac Surg. 2021;10(1):141-8. doi:10.21037/acs-2020-mv-fs-0166.

30. Filsoufi F, Castillo JG, Rahmanian PB, Carpentier A, Adams DH. Anuloplastia remodeladora mediante un anillo específico para la reparación de la regurgitación mitral isquémica de tipo IIIb. Rev Esp Cardiol. 2007;60(11):1151-8. Spanish.

31. Kaneko T, Hirji S, Zaid S, Lange R, Kempfert J, Conradi I, et al. Mitral valve surgery after transcatheter edge-to-edge repair: mid-term outcomes from the Cutting-Edge international registry. JACC Cardiovasc Interv. 2021;14(18):2010-21. doi:10.1016/j.jcin.2021.07.029.

32. Chikwe J, O’Gara P, Frenes S, Sundt TM 3rd, Habib RH, Gammie J, et al. Mitral surgery after transcatheter edge-to-edge repair: society of thoracic surgeons database analysis. J Am Coll Cardiol. 2021;78(1):1-9. doi:10.1016/j.jacc.2021.04.062.

33. Mack M, Carroll JD, Thourani V, Vemulapalli S, Squiers J, Manandhar P, et al. Transcatheter mitral valve therapy in the United States: a report from the STS/ACC TVT registry. Ann Thorac Surg. 2022;113(1):337-65. doi:10.1016/j.athoracsur.2021.07.030.

34. Sugiura A, Kavsur R, Spieker M, Iliadis C, Goto T, Öztürk C, et al. Recurrent mitral regurgitation after mitraclip: predictive factors, morphology, and clinical implication. Circ Cardiovasc Interv. 2022;15(3):e010895. doi:10.1161/CIRCINTERVENTIONS.121.010895.

This is an open-access article distributed under the terms of the Creative Commons Attribution License.

Brazilian Journal of Cardiovascular Surgery