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EDITORIAL COMMENT

Crossover in COAPT

Does This Extend the Reach of TMVr for Treating Functional MR?*

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The global public health burden of heart failure is staggering and remains a leading cause of death and hospitalizations despite guideline-directed medical therapy (GDMT) and advanced therapies, including implantable cardioverter-defibrillators, cardiac resynchronization therapy (CRT), ventricular assist devices, or transplantation (1). Mitral regurgitation (MR) is a common heart valve disorder worldwide. The leading mechanism responsible for MR is functional (74%) rather than degenerative (21%), with the former carrying a poor prognosis and low rates of surgical intervention (2). Functional MR results from progressive left ventricular (LV) dysfunction or atrial enlargement (i.e., atrial mitral regurgitation). Approximately 40% of patients with heart failure have concomitant moderate or severe MR. Treatment for functional MR entails maximizing GDMT to reduce LV volume/pressure and/or considering CRT to halt the vicious cycle between progressive left-sided chamber enlargement and MR severity. Isolated mitral valve surgery for functional MR is rarely pursued due to a higher peri-operative mortality and recurrent MR (3). Thus, a unique intersection exists between heart failure and functional MR, due to the excessive morbidity and mortality of heart failure, coupled with a high prevalence of MR and a paucity of effective surgical options. This constellation is the driving force for the emergence of transcatheter therapies for mitral valve intervention in patients with heart failure.

In 2018, the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial was published (4), which led to the U.S. Food and Drug Administration's approval of the MitraClip (Abbott, Santa Clara, California) transcatheter mitral valve repair (TMVr) system for treatment of functional MR. In COAPT, symptomatic (New York Heart Association functional classes II, III, or ambulatory IV) patients with heart failure (n = 614) with LV dysfunction (ejection fraction 20% to 50% and LV end-systolic diameter ≤70 mm) with moderate-to-severe (3+) or severe (4+) MR, despite maximally tolerated GDMT and CRT (if appropriate), were randomized in an open-label fashion to GDMT (n = 312) alone versus GDMT plus the MitraClip (n = 302) (4). The primary efficacy endpoint of all heart failure hospitalizations was significantly lower in patients who received the MitraClip plus GDMT compared with those who received GDMT alone at 24 months, with low rates of device-related complications at 12 months. The MitraClip significantly reduced all-cause mortality at 24 months compared with GDMT alone. In addition, functional capacity, quality of life, and MR severity were all significantly improved with the MitraClip.

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In this issue of the *Journal*, Mack et al. (5) report the 3-year follow-up results of the COAPT trial, including the pre-specified crossover findings. At 36 months, loss to follow-up was similar between the MitraClip plus GDMT (7.6%) and GDMT alone (12.6%) groups. The longer term outcomes at 36 months

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mirrored the 24-month outcomes. The MitraClip plus GDMT group had significantly lower rates of heart failure hospitalizations (35.5% per patient-year vs. 68.8% per patient-year; hazard ratio [HR]: 0.49; $p < 0.0001$; number needed to treat [NNT] = 3.0), all-cause hospitalizations, all-cause mortality (42.8% vs. 55.5%; HR: 0.67; $p = 0.001$; NNT = 7.9), death from heart failure, and need for ventricular assist device or heart transplantation. In addition, MR severity, quality of life, and functional capacity significantly improved with the MitraClip plus GDMT compared with GMDT alone. The durability of the MitraClip was sustained through 36 months. The absolute benefit of the MitraClip at 36 months over GDMT alone for the composite endpoint of all-cause mortality and heart failure hospitalization (59% vs. 88%; HR: 0.48; $p < 0.0001$; NNT = 3.4) was larger compared with the 24-month outcomes (45% vs. 67%; HR: 0.56; $p < 0.0001$; NNT = 4.5) because the Kaplan-Meier curves were separated further by 36 months.

A unique design of the COAPT trial was the prespecified analysis of patients randomized to GDMT alone who were allowed to crossover and undergo TMVr using the MitraClip at 24 months. Of the 312 patients randomized to GDMT alone, 44% were eligible for crossover at 24 months (n = 138), and 38% received the MitraClip between 24 and 26 months (53 of 138 patients). Death occurred in 73% of the 169 patients who were not eligible for crossover at 24 months. Five patients crossed over to the MitraClip before 24 months, bringing the total number of crossover patients to 58 or 19% of the GDMT alone population. MR was significantly reduced in patients who crossed over to the MitraClip. An important limitation to the study was the inherent survivor bias that was present in the patients who crossed over to receiving the MitraClip, but the investigators appropriately used time-dependent survival analyses to overcome the limitations of survivorship (i.e., a form of selection bias). When the crossover patients were landmarked at the time of TMVr treatment (median follow-up: 7.7 months), rates of heart failure hospitalizations and a composite of all-cause mortality or heart failure hospitalizations mirrored the landmarked Kaplan-Meier curves of the patients originally randomized to GDMT plus the MitraClip. In addition, a time-dependent multivariable analysis revealed that crossing over to MitraClip was independently associated with freedom from death or heart failure hospitalization. All-cause mortality did not appear to be different between groups (i.e., GDMT plus the MitraClip, GDMT alone, and GDMT crossovers), but the mortality benefit of the MitraClip was not observed until 24 months in the original COAPT publication (4). Despite certain limitations of the crossover design in COAPT, namely, a 1-sided crossover (i.e., GDMT alone to the MitraClip) and the implications of survivor bias, the results were quite meaningful. This analysis demonstrated that TMVr reduces death and heart failure hospitalizations in medically optimized patients even after being deferred for transcatheter therapy for 24 months. Moreover, the overall benefit of TMVr at 36 months was likely more substantial because 38% of the patients who received GDMT alone underwent TMVr in the intention-to-treat analysis.

The results of the COAPT trial (4) were scrutinized due to the dissimilar findings from the MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) trial results, which did not demonstrate any benefit of the MitraClip versus medical therapy alone in patients with heart failure with severe functional MR (6,7). The marked differences in trial results between COAPT and MITRA-FR have sparked significant debate and speculation regarding trial size, patient selection, anatomical and/or echocardiographic differences, operator experience, medical optimization, and hypotheses to account for the apparently contradictory trial results (8,9). The RESHAPE-HF-2 (Randomized Study of the MitraClip Device in Heart Failure Patients With Clinically Significant Functional Mitral Regurgitation; NCT02444338) trial, which compared the MitraClip to medical therapy, and the MATTERHORN (Multicenter, Randomized, Controlled Study to Assess Mitral Valve Reconstruction for Advanced Insufficiency of Function or Ischemic Origin; NCT02371512) trial, which compared MitraClip and surgery, should provide additional insights on TMVr for treating functional MR.

Currently, mitral valve leaflet approximation is the leading approach used for TMVr for functional MR using either the MitraClip or PASCAL (Edwards Lifesciences, Irvine, California) systems; the latter received a Conformité Européenne mark for treating degenerative and functional MR in 2019 and is currently being studied in the CLASP IID/IIF (Edwards PASCAL Transcatheter Valve Repair System Pivotal Clinical Trial; NCT03706833) study. The growth of transcatheter solutions for treating mitral valve disease that mimic surgical approaches to address the complex anatomical and pathological maladies of the mitral valve will continue to change the landscape of treatments options available to patients with MR.

How do we view the latest results of the COAPT trial? The longer-term follow-up results further support the use of TMVr in selected patients with heart

failure with LV dysfunction and moderate-to-severe or worse functional MR. Because of the contrasting results of MITRA-FR, it is crucial that patients selected for TMVr model patients in the COAPT trial. The crossover analysis highlights that patients still benefit from TMVr despite delaying therapy for 2 years. The future of TMVr for patients with heart failure with functional MR remains promising, and this technology should be an important consideration in the management of these patients going forward.

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REFERENCES

1. Ambrosy AP, Fonarow GC, Butler J, et al. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. J Am Coll Cardiol 2014;63:1123–33.

2. Goel SS, Navkaranbir Bajaj N, Aggarwal B, et al. Prevalence and outcomes of unoperated patients with severe symptomatic mitral regurgitation and heart failure: comprehensive analysis to determine the potential role of MitraClip for this unmet need. J Am Coll Cardiol 2014;63:185–6.

3. Asgar AW, Mack MJ, Stone GW. Secondary mitral regurgitation in heart failure: pathophysiology, prognosis, and therapeutic considerations. J Am Coll Cardiol 2015;65:1231–48.

4. Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter mitral-valve repair in patients with heart failure. N Engl J Med 2018;379:2307–18.

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. Obadia JF, Messika-Zeitoun D, Leurent G, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation. N Engl J Med 2018;379:2297–306.

7. 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.

8. Tang GHL, Verma S, Bhatt DL. Two randomized clinical trials on the treatment of secondary mitral regurgitation-contradictory or complementary? JAMA Cardiol 2019;4:311–3.

9. 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. J Am Coll Cardiol Img 2019;1:353–62.

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