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EDITORIAL COMMENT

Expanding Success of Mitral Transcatheter Edge-to-Edge Repair in Real-World Patients

And More Questions to Answer*

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Transcatheter edge-to-edge repair of the mitral valve (M-TEER) has become a mature, guideline-recommended interventional method for the treatment of secondary mitral regurgitation (SMR). These recommendations are based on the results of the randomized COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trial and other, mainly European large-scale registries.[1,2] With the updated American College of Cardiology/American Heart Association guideline recommendations,[3] the use of M-TEER is expanding rapidly in the United States into real-world SMR populations, which may differ from the randomized, highly selected COAPT

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patient population. As such, COAPT-PAS (COAPT Post-Approval Study), published in this issue of the *Journal of the American College of Cardiology,* is a prospective, single-arm, real-world surveillance study of the first 5,000 patients who underwent M-TEER for SMR after U.S. Food and Drug Administration approval of the MitraClip (Abbott Vascular) device in the United States.[4] This study represents the largest prospective collection of procedural and clinical outcomes in SMR patients so far.

Several findings from this study presented by Goel et al[4] are notable. First, in contrast to the original COAPT trial, which tested the first generation of the MitraClip device, patients in COAPT-PAS were treated, in the vast majority of cases (98%), with third and fourth generation devices, which may be associated with improved outcomes.[5] However, reduction of MR appeared to be comparable between COAPT-PAS and the original COAPT trial. The second important finding is the low and comparable rate of major adverse events at the 1-year follow-up (FU), confirming the safety of M-TEER in this high-risk patient population. Furthermore, the value of the presented study stems from its comprehensive comparison to the results of the original COAPT and MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) trials.[6] For those comparisons, the study focuses on patient inclusion and exclusion criteria of the 2 trials, forming subcohorts within COAPT-PAS that would resemble the interventional arm of each randomized trial. As such, the population of both randomized trials (COAPT and MITRA-FR) do not seem to be well representative of real-world patients. Only roughly 20% of COAPT-PAS patients would have been eligible for the COAPT/MITRA-FR trial—or, in other words, the original COAPT/MITRA-FR trial patients are clearly a minority in the real-world spectrum of patients with severe SMR. Patients in COAPT-PAS, among other parameters, more frequently had severe tricuspid regurgitation (TR), had more challenging mitral valve anatomies (for example, leaflet calcification), had more comorbidities, and were more often female as

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compared to both randomized trials. The last fact is relevant because it shows that the problem of underrepresentation or undertreatment of female patients in cardiovascular studies could be ameliorated under real-world conditions.

When compared to the guideline-directed medical therapy (GDMT) control groups of COAPT and MITRA-FR, the main benefit of M-TEER in COAPT-PAS patients was evidenced by low heart failure hospitalization (HFH) rates at the 1-year FU. The differences in 1-year all-cause mortality were small, which might be explained by the relatively short and incomplete 1-year FU. (The FU rate in COAPT-PAS was only 53%.) Accordingly, it will be of interest to see if a longer and complete FU of the real-world COAPT-PAS study population will show differences in mortality and HFH rates when compared to the original COAPT and MITRA-FR study populations.

As discussed in numerous publications, the diverging results between the original COAPT and MITRA-FR studies are a conundrum. Whether procedural success rates, different medication regimens, proportionality of SMR, or the concomitant presence of right heart failure can explain the results and, especially, the neutral outcome in MITRA-FR is debatable. Post hoc analyses of both trials aimed at testing different hypotheses, but none could conclusively explain the discrepancies in outcomes so far.[7-10] Also, COAPT-PAS cannot fully solve this conundrum but suggests that the major differences in outcomes are based on patient selection criteria. This hypothesis is also supported by substudies from MITRA-FR and an analysis of the European Registry of Transcatheter Repair for Secondary Mitral Regurgitation (EuroSMR) cohort by Koell et al.[2,11] Undisputed is the efficacy of M-TEER in reducing MR and the symptomatic benefit, which is also confirmed in COAPT-PAS. Because M-TEER has now been established in real-world practice in North America and Europe, the research focus should move to a further optimization of this pillar of heart failure therapy.

Therefore, future research efforts in the field of transcatheter SMR treatment should solve the following questions.

- Should M-TEER be applied earlier? Moderate SMR is associated with impaired quality of life but also reduced survival. Therefore, it could be reasonable to treat patients in earlier stages of heart failure with moderate or moderate-to-severe SMR to avoid future progression of SMR with its impact on prognosis. This hypothesis is tested by the currently ongoing EVOLVE-MR (Transcatheter Mitral Valve Repair for the Treatment of Mitral Valve Regurgitation in Heart Failure [NCT03891823]) trial, which will assess quality of life over 24 months in patients treated with M-TEER vs medical therapy.
- Can we accept residual moderate MR after M-TEER in SMR patients? In patients with primary MR undergoing M-TEER, residual mild MR was associated with improved outcomes when compared with a residual mild-to-moderate MR. This observation was not seen in the original COAPT cohort,[12] which might be explained by small sample sizes. Accordingly, it will be of great interest to see if less residual MR in the larger real-world COAPT-PAS population will be associated with improved outcomes. This would also provide some insights into whether transcatheter mitral valve replacement (TMVR) might play a future role in this patient population—especially, when future transseptal TMVR devices will become available that completely abolish SMR.
- What requirements of GDMT should patients fulfill to qualify for M-TEER? In COAPT-PAS, the requirements for GDMT were less rigidly controlled than in the original COAPT trial, but the survival and HFH outcomes appear to be comparable. Furthermore, the EuroSMR registry demonstrated that GDMT up-titration after M-TEER is feasible in a significant proportion of patients, which is associated with improved survival rates.[13] Thus, it remains to be evaluated if M-TEER should only be considered in fully GDMT up-titrated patients or if an earlier M-TEER treatment with a postprocedural up-titration might be equally effective or even associated with improved outcomes.
- Is there a need to treat concomitant TR? Concomitant TR is associated with mortality in heart failure patients. In COAPT-PAS, 16% of patients had concomitant severe TR, and 50% of patients presented with moderate or severe TR. With the increasing experience in tricuspid TEER, there is an obvious need to evaluate whether an additional treatment of TR will improve outcomes in these heart failure patients.
- Can we better predict outcomes after M-TEER in SMR patients? The majority of currently used risk scores for MR are based on surgical experiences and evaluate the early survival outcomes after surgery. Because of the excellent safety of M-TEER procedures, early outcomes are usually of less

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concern, but the overall mortality rates of around 20% and even >50% at 1 and 5 years after M-TEER in SMR patients raise the question of which patients will profit or will not profit from such procedures.[14] Thus, there is a significant need to develop and validate dedicated risk prediction models for M-TEER outcomes in SMR patients that will help the heart teams in selecting the right patient for such procedures.

In summary, the results of COAPT-PAS and other real-word registries have unambiguously shown that: 1) M-TEER is safe; 2) M-TEER effectively reduces MR; and 3) M-TEER is associated with improved outcomes outside of randomized trials. Transcatheter edge-to-edge therapy for SMR is now a guideline-recommended therapeutic option for heart failure patients with SMR, but many more questions remain to be answered to accompany the successful expansion of M-TEER in real-world daily practice and to further optimize outcomes in this vulnerable patient population.

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