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Editorial

Editorial: Real World Transcatheter Edge to Edge Repair Eligibility in HF Patients: Finding the *Opportunity*

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Transcatheter edge-to-edge repair (TEER) in patients with secondary mitral regurgitation (MR) demonstrated reductions in heart failure hospitalizations, cardiovascular and all-cause mortality in the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial, thus leading to Food and Drug Administration (FDA) approval of the MitraClip device (Abbot, Menlo Park, CA) in 2019.[1] Approval criteria for TEER in secondary MR mirror the COAPT inclusion criteria, specifically moderate-to-severe or severe secondary (or functional) MR (MR $\geq$ Grade III per American Society of Echocardiography criteria) in patients with a left ventricular ejection fraction $\geq$ 20% and $\leq$50% and a left ventricular end-systolic dimension $\leq$ 70 mm whose symptoms and MR severity persist despite maximally tolerated guideline-directed medical therapy (GDMT) as determined by a multidisciplinary heart team. Since FDA approval, utilization of the technology has steadily increased; however, questions have been raised as to the number of potential heart failure patients that meet the strict COAPT criteria and thus are eligible for TEER therapy.

In this issue of Structural Heart, Ambrosy et al.[2] present original research on TEER Eligibility and Potential Benefit in a Contemporary Cohort with Heart Failure using a dataset of patients within a large health care system in Northern California. Patients were selected by identifying those with a diagnosis of heart failure from 2013-2013 using discharge diagnoses and International Classification of Diseases, 9th Edition codes. The primary data source for clinical details, including medical therapy, was the electronic health record. Echocardiographic data was obtained by analyzing echocardiogram reports using specific queries to obtain data on ejection fraction, left ventricular dimensions, and MR severity. FDA approval criteria for TEER were then applied to create two cohorts: those that would meet criteria for TEER (FDA+) and those that would not (FDA-). A total of 50,841 patients with a heart failure diagnosis were identified, among whom 2461 individuals (4.8%) were eligible for TEER (FDA+). The FDA+ cohort was more likely to have had a heart failure hospitalization in the previous year and had a higher prevalence of atrial fibrillation or flutter. Echocardiographic parameters differed significantly between the two groups with the FDA+ group having a lower ejection fraction (35 vs. 55%, $p < 0.001$) and a more dilated left ventricle and left atrium. The outcomes in the FDA+ cohort were significantly worse than those in the FDA-, with higher rates of HF hospitalization and all-cause mortality per 100 patient-years.

The authors should be commended for this work in identifying those patients who meet current FDA eligibility for TEER in secondary MR. They have convincingly shown, in this large real-world cohort, that FDA approval criteria identify a higher-risk group of patients with worse outcomes that could potentially benefit from TEER therapy. The glaring result and true message, however, is the low percentage (4.8%) of patients that meet criteria for therapy. This result is similar to another study of community heart failure patients in Canada that identified only 1% of patients who would be eligible for TEER therapy using the COAPT inclusion criteria.[3] This has raised an important question for the cardiology community: despite the important impact on patient outcomes, how can we use TEER therapy in heart failure if it is only applicable to 5% of the population?

Victory comes from finding opportunities in problems.

Sun Tzu.

Perhaps the better question is, *where is the opportunity to use TEER therapy in this population to improve outcomes in a larger proportion of heart failure patients?* Much can be learned by examining the patients in the FDA cohort and understanding why these patients did not meet FDA approval criteria.

Firstly, a significant number of patients in this study did not have appropriate MR severity, with 47,371 patients having less than moderate-severe or severe MR. Importantly, an additional 778 patients

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did meet the criteria for MR severity but were not included for reasons that are unclear, a lost opportunity for treatment. In addition, 19.3% of patients (n = 9352) in the FDA cohort had missing data for left ventricular dimensions and were therefore excluded. This highlights an important challenge in using such echo criteria for patient selection, as the absence of data prevents patients from being considered for treatment. The *opportunity* to improve may lie in novel approaches using artificial intelligence (AI) to assist image acquisition during transthoracic echocardiography. AI has the potential to improve valve assessments through the development of programs that guide image acquisition. In addition, AI-driven automated image analysis to provide selected measurements such as left ventricular dimensions could greatly increase quantitative assessments, accuracy, and reproducibility.[4] The future may lie in such algorithms also assessing TEER suitability on transesophageal echocardiography and potential device success.

The most significant limitation to achieving FDA approval criteria for TEER in this study was the absence of adequate GDMT, which excluded 22,978 patients or 45% of the entire study cohort. This is not a novel finding in the heart failure population. A population-based retrospective cohort study using the Discharge Abstract Database and the National Prescription Drug Utilization Information System datasets from the Canadian Institute for Health Information was used to evaluate the utilization of GDMT in patients following an index hospitalization for heart failure in the 6 months postdischarge. A total of 66,372 patients with HF and reduced ejection fraction and 65 years of age and older were identified. Adequacy of GDMT was evaluated by monitoring therapy combinations, optimal dosing (proportion receiving >50% of the target dose for these inhibitors and blockers, and any dose of mineralocorticoid receptor antagonist), and maximal and last dose assessed. The results were sobering. In this cohort, 7.2% (n = 4768) were on no therapy, 25.9% (n = 17,184) were on monotherapy, 46.6% (n = 30,912) were on dual therapy, and 20.4% (n = 13,508) were on triple therapy. Only 13.2% (n = 8747) and 8.3% (n = 5484) achieved optimal GDMT based on the maximum dose and the last dispensed dose, respectively.[5] These results are similar to those from The Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure (GUIDE-IT) trial, a multicenter randomized trial of NT-proBNP-guided treatment of heart failure. In this trial, the rate of optimized GDMT was low, with only 15.5% of patients achieving optimal GDMT at 6 months. Reasons for failing to achieve GDMT in this trial included the clinician's assessment that patients were "clinically stable" or "already at maximally tolerated therapy.[6]

Given the limitations of achieving GDMT in HF patients with secondary MR prior to TEER, perhaps the *opportunity* lies in adopting a strategy of combined therapy rather than the current sequential approach. In fact, a retrospective analysis from the EuroSMR registry demonstrated that the use of TEER for patients with secondary MR resulted in significant up-titration of GDMT in 38% of patients. The proportion of patients receiving angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor-neprilysin inhibitors, beta-blockers, and mineralocorticoid receptor antagonists was 78%, 89%, and 62% before M-TEER and 84%, 91%, and 66% 6 months after M-TEER (all $p < 0.001$). GDMT up-titration resulted in a lower risk of all-cause death (adjusted hazard ratio: 0.62; 95% confidence interval [CI]: 0.41-0.93; P ¼ 0.020) and of all-cause death or HF hospitalization (adjusted hazard ratio: 0.54; 95% CI: 0.38-0.76; $p < 0.001$) compared to patients without up-titration. Success of TEER and the degree of MR reduction between baseline and 6-month follow-up were also independent predictors of GDMT up-titration after TEER (adjusted odds ratio: 1.71; 95% CI: 1.08-2.71; P ¼ 0.022).[7]

Finally, for those patients unable to achieve GDMT, a small study performed in Israel suggests that the presence or absence of GDMT may be less important than the success of TEER and MR reduction. This retrospective study of 168 patients with secondary MR undergoing TEER was divided into two groups: those receiving GDMT, n = 116 (69%) at the time of TEER, and those not receiving GDMT, n = 52 (31%). There were no other significant demographic or clinical differences between the groups or differences in procedural success and complications. At 1 year, mortality was identical in the two groups (15 vs. 15%; relative risk 1.06, CI 0.43-2.63, $p = 0.90$) suggesting that there was no significant impact of the presence or absence of GDMT.[8]

In conclusion, Ambrosy et al. present an important message regarding the population of heart failure patients currently eligible for TEER based on the FDA approval criteria. The current problem is discovering ways to identify patients who may benefit and perhaps thinking outside the box of the current approval criteria. There is much to learn and more progress to make. Victory for these patients requires finding the *opportunity* to improve our current practice.

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