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EDITORIAL COMMENT

Mitral TEER With Fourth-Generation Devices

A New Era of Possibilities?*

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Innovation is not an event, it's a process.
—Jerry Cahn

Innovation is not always about creating something new. Indeed, enhancements of an existing technology can potentially yield a significant impact on a scale comparable to that of the original invention. This is evident in the life journey of coronary stents (eg, drug coating), transcatheter aortic valves (eg, external skirts), and atrial appendage closure devices (eg, close cell design). Therefore, biomedical device companies allocate substantial resources to optimize their implants, leading to newer iterations with enhanced features to improve clinical outcomes every few years. This iterative process is at variance with the usual 1-time approval of pharmaceutical agents, which poses several challenges for industry, clinicians, and regulators. One challenge is to design and conduct clinical studies to ensure the safety and efficacy of the newer-generation devices. Although randomized trials remain the gold standard for generating evidence, their application in evaluating iterative device changes is limited by their prohibitive cost. In addition, such trials carry the risk of obsolescence because of the time required for trial completion and the rapid and continuous device refinement. It has become customary to use postmarket (usually industry-sponsored) registries to assess the safety and efficacy of updated device versions. The quality of the evidence obtained from these registries varies according to the use of imaging core laboratories and clinical event adjudication committees, the duration of follow-up, and the extent of missing data.

The original MitraClip (Abbott), which was implanted first by Condado 20 years ago, was regarded as a transformational technology because of its high safety profile leading to Food and Drug Administration approval in 2013. Notwithstanding, the first-generation device was intricate and associated with limitations that questioned the practicality and scalability of mitral transcatheter edge-to-edge repair (TEER). In addition, the rigorous anatomical criteria required for a successful TEER excluded many patients who could have potentially benefited from the procedure. However, the device has since undergone several iterations allowing it to stand the test of time and expand its reach to >100,000 patients globally. In parallel, there was an expansion in the evidence based on the results of randomized trials of TEER that informed recommendations in the latest European Society of Cardiology and American College of Cardiology/American Heart Association guidelines for the management of valvular heart disease. The latest iteration (G4) of the MitraClip device features several notable improvements over its predecessor, such as 2 wider clip sizes (NTW and XTW, 6 vs 4 mm width), independent leaflet grasping, and improved arm designs to reduce leaflet stress. With these added features, MitraClip G4 promised to simplify the TEER procedure, improve its efficacy, and provide operators with the ability to address challenging anatomies. The EXPAND G4 registry is a postmarket registry designed to provide insights into the impact of this latest MitraClip iteration on the outcomes of mitral TEER.

In this issue of *JACC: Cardiovascular Interventions*, Rogers et al[1] and von Bardeleben et al[2] leveraged the

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EXPAND G4 registry to assess the safety, efficacy, and the extend treatment potential of the G4 MitraClip system. The registry enrolled 1,164 patients who underwent TEER G4 MitraClip interventions at 60 centers in 10 countries between March 2021 and February 2022. The study included "subjects scheduled to receive the MitraClip per the current approved indications for use, and who consent for the study." There were no prespecified clinical or anatomical exclusion criteria. Patients with primary mitral regurgitation (PMR) or secondary mitral regurgitation (SMR) were eligible for the study. Device(s) selection was left to the operator's discretion, although general recommendations to match the clip type with the patient's valve anatomy were provided. The outcomes assessed included safety endpoints (30-day major adverse events [MAEs]: all-cause death, myocardial infarction, stroke, or nonelective surgery for device-related complications), efficacy endpoints (acute procedural success [device implant and ≤2+ mitral regurgitation [MR] on discharge] and degree of MR reduction at 30 days), and patient-reported outcomes (NYHA functional class and Kansas City Cardiomyopathy Questionnaire [KCCQ] summary scores). Additionally, a post hoc analysis was performed to assess the performance of G4 MitraClip in 2 categories of "expanded" indications: 1) TEER in anatomies traditionally deemed unsuitable for TEER because of either a risk of inducing mitral stenosis (RoS) (severe annular or leaflet calcifications, prior annuloplasty, or valve area <3.5 cm^2) or a risk of inadequate MR reduction (RoIR) (Barlow's disease, bileaflet flail/prolapse, significant secondary jet, severe leaflet degeneration with large gaps, minimal leaflet tissue, or significant cleft/scallop) and 2) TEER for moderate mitral regurgitation (MMR). An independent core laboratory adjudicated baseline, discharge, and 30-day echocardiographic data according to the American Society of Echocardiography guidelines. Five-year follow-up is planned for all patients, but the current reports are limited to 30-day outcomes.

Several key attributes of the registry require additional attention. First, missing echocardiograms or those deemed nonevaluable (by the core laboratory) were common, but their frequency varied depending on the data element adjudicated. For example, the number of patients with missing or nonevaluable baseline echocardiographic data was 171 (15.2%) when assessing the etiology of MR and 425 (36.5%) when classifying anatomies into TEER suitable vs unsuitable. Second, there was a large proportion of patients who had less than severe MR at baseline, acknowledging that MR assessment may be variable depending on loading conditions. Per site reporting, nearly one-third of patients had moderate or less MR at baseline. Although the proportion of patients with adjudicated severe MR at baseline is not explicitly reported, only 505 patients had 3+ MR before TEER by the core laboratory assessment, suggesting that the prevalence of ≤ MMR at baseline was higher (40%-50%). It is also important to note that the echocardiographic core lab assessment was performed retrospectively and had no impact on patient enrollment in the study. Third, this is a single-arm registry (ie, without a comparator arm). However, the authors frequently drew comparisons between the early results from EXPAND G4 and those of EXPAND (MitraClip® EXPAND Study of the Next Generation of MitraClip® Devices), a registry that involved patients treated with third-generation MitraClip devices.[3,4] With these considerations regarding the strengths and limitations of the EXPAND G4 registry, the interpretation of the study findings can be better appreciated.

The first analysis by von Bardeleben et al[2] included 1,164 patients, 1,044 (91%) of whom completed the 30-day follow-up. Most patients had SMR (58.4%), and 13.5% had complex mitral anatomy. The number of clips implanted was 1.4 ± 0.6, with 65% of patients treated with a single device. Wider-arm clips (NTW and XTW) were more frequently used (87.8%), whereas the use of independent leaflet grasping was uncommon (19%). The median device and procedure times were 35 and 77 minutes, respectively. Acute procedural success was achieved in 96.2%, and 30-day MAEs occurred in 2.7%. Device-related complications were rare, with 1.1% of patients experiencing single leaflet device attachment (SLDA). MR reduction to ≤2+ and ≤1+ was accomplished in 98% and 91% of patients, respectively. Importantly, the proportion of patients in NYHA functional class I/II increased from 31% at baseline to 83% at 30 days, and the summary KCCQ score increased by +18 points (from 52 to 70). These outcomes were comparable between patients with PMR and those with SMR.

The second analysis by Rogers et al[1] included 739 patients who had adequate echocardiographic data to classify their mitral valve anatomies into TEER suitable (n = 303) or TEER unsuitable (RoS [n = 56], RoIR [n = 54], and MMR [n = 326]) based on previously published heart valve consortium consensus criteria.[5] Acute procedural success was comparable in the 4 cohorts (96.9%, 92.2%, 94.4%, and 97.9%, respectively) with low MAE rates (<3%). The post-TEER residual MR grade was ≤1+ in 90.8%, 97.4%, 75.0%, and 93.1% and ≤2+ in 99.6%, 97.4%, 93.5%, and 93.1% of patients in the following respective groups: TEER

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suitable, ROS, RoIR, and MMR. In the RoS group, the postprocedure transmitral gradient modestly increased from 3.3 ± 1.6 mm Hg to 4.5 ± 1.6 mm Hg at 30 days. The improvement in quality of life metrics (KCCQ score and NYHA functional class) was consistent among the 4 groups. The authors concluded that the fourth-generation MitraClip system is safe, is effective in reducing MR and improving symptoms, and can treat mitral anatomies previously deemed unsuitable for TEER. These conclusions deserve further discussion.

First, affirming the safety of the G4 system is paramount given the higher frequency of device-related complications (namely, SLDA) that were observed upon transitioning from the G2 to the G3 MitraClip.[6] Fortunately, the MitraClip G4 in this registry maintained a superb safety profile with MAEs <3%, 30-day mortality of 1.3%, and an SLDA rate of 1.1%. Importantly, the low complication rate was consistent even among patients with challenging mitral anatomies. Second, the impressive MR reduction (≤1+ in 91.0% and ≤2+ in 98.0%) with consistent results across various pathologies coupled with the considerable improvement in patient-reported outcomes support the notion that mitral TEER has matured to rival surgical results. Opponents of such conclusions would point out that PMR patients were under-represented and that a large proportion of patients had MMR at baseline. However, subgroup analyses in patients with PMR vs SMR and among those with ≤2+ vs ≥3+ MR at baseline yielded similar efficacy of TEER across all groups. Collectively, these results add to the growing and reproducible evidence supporting the utility of TEER in various clinical scenarios and mitral valve anatomies, although the long-term durability remains an area of concern that requires further investigation.[4,7-13] Third, a key question the registry was designed to address is whether the addition of the G4 MitraClip system would further broaden the scope of TEER. The EXPAND G4 did indeed document that patients with challenging anatomies (ie, at risk for RoS and RoIR) were effectively treated with the G4 system. However, caution needs to be exercised considering the small number of patients with these disease phenotypes (110 total) and the lack of long-term follow-up data. Moreover, it is uncertain whether the observed results were solely caused by the added features in the G4 system because a similar analysis has not been conducted on prior generation devices.

The more intriguing data in our opinion come from the analysis of TEER efficacy in patients with MMR. This analysis, made possible by the unintended inclusion of a large proportion of patients with MMR in EXPAND G4, showed significant improvements in KCCQ score and NYHA functional class in these patients after TEER. If confirmed in further studies and supported by echocardiographic evidence of left ventricular remodeling, this could significantly broaden the pool of patients who may benefit from TEER. However, we should interpret these data with prudence considering the non-negligible limitations of the registry and the historical lessons learned from the conflicting data on MMR management in the cardiac surgery literature.[14,15] Decades ago, the question of whether treating MMR improves clinical outcomes was proposed by cardiac surgeons who were interested to know if they should address MMR at the time of coronary bypass grafting. In this context, numerous observational studies consistently showed a benefit of surgical repair of MMR, but a dedicated trial (the Cardiothoracic Surgical Trials Network study) later showed no beneficial effect of surgery on clinical outcomes or left ventricular remodeling.[15] Hence, expanding the use of TEER to patients with MMR should await dedicated prospective trials (eg, EVOLVE-MR [Transcatheter Mitral Valve Repair for the Treatment of Mitral Valve Regurgitation In Heart Failure; NCT03891823). Nonetheless, the findings by Rogers et al[1] should trigger a healthy debate on our approach to MMR. Is a resting echocardiogram adequate to adequately grade MR? Do we need to expand the use of stress echocardiography, cardiac magnetic resonance, or invasive hemodynamic testing in the evaluation of this highly dynamic disease?[16-18]

The studies by von Bardeleben et al[2] and Rogers et al[1] should be considered in the context of the rapidly evolving landscape of transcatheter mitral valve interventions. Recently, a randomized clinical trial comparing MitraClip with the recently introduced PASCAL (CLASP 2D) clasping system (Edwards Lifescience) reported similar echocardiographic and clinical outcomes.[11] However, the follow-up duration was short, and the comparison was limited to patients with simple pathologies suitable for TEER, which could have camouflaged potential differences between the devices. Long-term data on PASCAL and other emerging TEER devices (including future-generation MitraClip) would contribute further to the continued maturation of the mitral TEER field. Additionally, over the past decade, novel transcatheter mitral valve replacement (TMVR) systems have emerged leading to speculation that they may soon replace TEER. Nonetheless, despite its potential

benefits, TMVR has been challenged by its demanding techniques and strict anatomical requirements. Therefore, for the foreseeable future, TMVR is expected to be a complementary approach to treating MR, particularly in anatomies that are not suitable for TEER. As TEER approaches its 10th commercial-approval anniversary, it is not only maintaining its position but also expanding and breaking new boundaries.

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