Transcatheter Mitral Valve Replacement: Current Challenges and Future Perspective

Is transcatheter mitral valve replacement a better solution for mitral regurgitation than transcatheter repair techniques?

BY PAVEL OVERTCHOUK, MD; JUAN F. GRANADA, MD; AND THOMAS MODINE, MD, PHD, MBA

Mitral regurgitation (MR) prevalence increases with age. Isolated MR has been estimated to be present in between 0.5% to 3% of the Western population who are 65 to 74 years old and in > 3% of the Western population who are 75 years or older; similar to aortic stenosis, it is responsible for increased mortality risk.[1-3] Surgical intervention on the mitral valve accounts for 5% to 10% of all surgical procedures.[4] Despite the fact that interventional treatment remains the cornerstone of mitral valve disease therapy, intervention for MR is still an unmet need.[5] The perceived invasiveness of open surgery and an insufficient consideration of MR to genuinely impact patient survival and symptoms might constitute some reasons for this unmet need, hence they are possible targets for research.

TRANSCATHETER MITRAL VALVE REPAIR

The MitraClip device (Abbott Structural Heart) was the first transcatheter mitral valve (TMV) developed with the aim to percutaneously reproduce the surgical Alfieri technique.[6,7] The recently published COAPT and MITRA-FR trials enrolled patients with severe secondary MR, moderate left ventricular dysfunction, and suitable anatomy for implantation. In the COAPT trial, a benefit was seen with MitraClip at 2 years in the form of reduced long-term mortality (29.1% vs 46.1% for the intervention and control groups, respectively; hazard ratio [HR], 0.62; 95% confidence interval [CI], 0.46–0.82; $P < .001$) and rehospitalization for heart failure (35.7% vs 56.7% for the intervention and control groups, respectively; HR, 0.53; 95% CI, 0.40–0.70; $P < .001$).[8]

In the MITRA-FR trial, the rate of mortality at 1 year was 24.3% and 22.4% for the intervention and control groups, respectively; the rate of rehospitalization for heart failure was 48.7% and 47.4% for the intervention and control groups, respectively.[9] Put together, COAPT and MITRA-FR showed that compassionate use of MitraClip does not save patient lives, nor does it reduce the risk of rehospitalization. However, selected patients with secondary severe MR associated with moderate left ventricular dysfunction and suitable anatomy for implantation could still benefit from MitraClip use.

The results of the RESHAPE-HF2 (NCT02444338; comparison against medical therapy) and MATTERHORN (NCT02371512; comparison against mitral surgery) trials might provide further insight into the appropriate use of MitraClip for the treatment of secondary MR. However, it is worth noting that despite extensive preoperative echocardiographic screening in COAPT, more than one clip was necessary in > 60% of patients (and three clips or more in 8% of cases) to achieve satisfactory reduction of MR.[8] This underscores the device's lack of efficacy in achieving persistent low-grade MR

after the intervention. Implanting an excessive number of clips can yield a significant increase in transmitral gradient, which has been reported to be associated with worse outcomes.[10] It is worth remembering that the Alfieri technique was described for primary MR, and one of the reasons it was abandoned was the high rate of recurrence and reoperation (10% at 5 years in the original cohort).[6]

The popularity of surgical mitral valve repair at the beginning of the century encouraged the development of numerous percutaneous mitral valve "plasty" devices (Table 1).[11,12] After MitraClip, the valvular plasty device armamentarium was later expanded by the development of percutaneous annuloplasty (Cardioband, Edwards Lifesciences) and chordoplasty (NeoChord, NeoChord, Inc.; Harpoon, Edwards Lifesciences) systems.[13-15] A difficult learning curve and a lack of efficiency in resolving MR are among the main limitations of these devices, and they could be viewed as inherited from the surgical repair techniques that inspired them.[13] Combining transcatheter repair techniques has been proposed to mitigate the lack of efficacy on MR resolution; however, this poses the question of increased complication risk and cost.[16,17] Perhaps valve replacement could provide a better option.

TRANSCATHETER MITRAL VALVE REPLACEMENT EXPERIENCE

Mitral repair is favored over replacement for open surgical treatment of MR in the international guidelines. However, this recommendation is based on observational data.[18] Recent randomized data showed that replacement nearly eliminates the risk of long-term recurrence of moderate or severe MR at 2 years (58.8% after repair vs 3.8% after replacement).[19] By avoiding the morbidity of open mitral surgery and effectively preventing recurrence of MR, TMV replacement could provide the best option (Table 2).

The first-in-human TMV replacement was performed in 2012 with the CardiAQ valve (Edwards Lifesciences).[20] Since then, TMV replacement feasibility studies have been published on the Intrepid (Medtronic) and Tendyne (Abbott Structural Heart) devices, which were implanted transapically in patients at very high surgical risk. Thirty-day mortality was high (seven out of 50 patients in the Intrepid study and one out of 30 patients in the Tendyne study), but elimination of significant MR was constant.[21,22] Following the example of the PARTNER and SURTAVI trials on transcatheter aortic valve implantation (TAVI), the first trials comparing TMV replacement with the Intrepid and Tendyne devices to open surgery are already underway (APOLLO, NCT03242642; SUMMIT, NCT03433274).

The principal limitation of these systems is their transapical delivery. Transapical delivery is a major limitation of TMV replacement compared to transseptally deployed TMV repair systems such as MitraClip. Experience with TAVI showed that the transapical approach is associated with higher bleeding risk, as well as residual left ventricular apex dysfunction.[23,24]

Developing transseptally implantable devices will take time. The transition from the current 32- to 45-F transapical delivery catheters to transseptal-compatible delivery systems will require engineering modifications in size, valve design, and delivery methods. Perhaps adapting existing TAVI technology could be more efficient. Webb et al recently published their experience with the transseptally implanted Sapien M3 transcatheter heart valve (THV; Edwards Lifesciences).[25] The balloon-expandable Sapien M3 THV and its delivery system are a direct adaptation of the Sapien 3 TAVI system, and Edwards took advantage of the decade-long experience in TAVI development. In the reported experience, Sapien M3 was implanted in 10 patients who presented with primary and/or secondary MR. The technical success rate was 90%, with no stroke or death at 30-day follow-up. Numerous other transapical and transseptal TMV replacement safety and feasibility single-arm studies are also underway (TIARA-I, NCT02276547; HighLife, NCT02974881; RELIEF, NCT02722551).

Another challenge for TMV replacement device developers is the absence of a solid anatomic structure to anchor the THV in the mitral annulus. The valve calcification that rendered the implantation of TAVI devices stable in stenotic aortic valves is less frequent in mitral valves. However, even in patients with mitral annular calcification (MAC), technical success when using TAVI devices (valve-in-MAC procedures) was only 62.1%.[26] Previously surgically implanted bioprostheses and annuloplasty rings with recurrent regurgitation can also provide a rigid anatomic structure for THV implantation. In those patients, valve-in-valve (ViV) and valve-in-ring (ViR) procedures (TMV replacement with TAVI devices in degenerated mitral bioprostheses or failed annuloplasty rings, respectively) yielded better results than valve-in-MAC procedures, with approximately 95% and 81% technical success rates, respectively.[26] More development and research are warranted to address the unmet need for severe MAC and degenerated mitral rings.

CHALLENGES AND FUTURE FOCUS

Patient selection is challenging. Traditionally used surgical risk estimators, such as the Society of Thoracic Surgeons risk score, fail to account for frailty, hostile chest, and anatomic compatibility with TMV intervention devices. Beyond ruling out an indication for open

TABLE 1. TMV REPAIR DEVICES IMPLANTED IN CLINICAL COHORTS

Percutaneous Plasty Device	Study	Approach	Successful Implantation	30-Day Mortality	30-Day MR 2+ or More
MitraClip	EVEREST II trial[5]	Transseptal	178/178	2/178	41/178
Pascal (Edwards Lifesciences)	Praz et al[12]	Transseptal	18/23	3/23	7/19
NeoChord	TACT trial,[14] Colli et al[31]	Transapical	89/93	1/92	30/92
Harpoon	TRACER trial[15]	Transapical	28/30	0/30	3/27
Cardioband	Messika-Zeitoun[32]	Transseptal	58/60	2/60	18/58

Abbreviations: MR, mitral regurgitation; TMV, transcatheter mitral valve.

TABLE 2. TMV REPLACEMENT DEVICES IMPLANTED IN CLINICAL COHORTS

THV	Study	Approach	Successful Implantation	30-Day Mortality	30-Day Moderate or Severe MR
Tendyne	Sorajja et al[33]	Transapical	96/100	6/100	1/94
Intrepid	Bapat et al[21]	Transapical (transseptal under development)	48/50	7/50	0/42
Sapien M3	Webb et al[25]	Transseptal	9/10	0/10	1/10
Tiara (Neovasc Inc.)	Verheye et al[34]	Transapical	7/8	0/7	0/7
HighLife (HighLife Medical, Inc.)	Barbanti et al[35]	Transapical	2/2	1/2	1/1

Abbreviations: MR, mitral regurgitation; THV, transcatheter heart valve; TMV, transcatheter mitral valve.

surgery in the context of the heart team discussion, the insight provided by surgical risk estimators is limited. Besides operability, TMV interventions require preoperative feasibility screening to verify mitral anatomy compatibility and pathway practicability. Finally, the possibility to reintervene will be crucial as long as device durability remains uncertain. TMV repair devices (such as MitraClip) can be combined with annuloplasty devices (such as Cardioband); although subsequent transcatheter replacement would be impossible, ViV transcatheter replacement would be feasible.

TMV replacement is not without risks. One of the most feared complications is left ventricular outflow tract (LVOT) obstruction because of its major impact on procedural mortality. In a study by Yoon et al, patients with LVOT obstruction had a higher rate of mortality than patients without LVOT obstruction (34.6% vs 2.4%; $P < .001$).[27] Preoperative CT plays an important role in the eligibility screening of patients with three-dimensional reconstructions and the simulation of potential interaction between patient anatomy and future mitral THV. A threshold of simulated neo-LVOT area ≤ 1.7 cm^2 on CT has been proposed. However, further research is warranted as the provided threshold seems optimizable because it was obtained in a valve-in-MAC, ViV, or ViR population treated with a TAVI device.[27] Various factors have been identified that contribute to LVOT obstruction, specifically device protrusion into the left ventricle, anterior leaflet displacement, and narrow aortomitral angle.[28,29]

Patients treated with TMV replacement are younger than those treated with TAVI because mitral valve disease affects younger patients.[30] Also, the younger the patients, the higher the risk of structural valve deterioration. Structural valve deterioration is more frequent in patients with bioprostheses in the mitral position than in the aortic position, which may be due to higher closing pressure. All of these concurrent factors will rapidly render the issue of bioprosthesis durability an important focus for TMV replacement devices.

Heart prostheses implanted percutaneously differ from those implanted surgically and require proper antithrombotic management. As numerous randomized trials are currently investigating several antithrombotic options to avoid aortic THV thrombosis, this is likely to become even more important for the mitral prostheses because the mitral position is at higher thrombotic risk than the aortic.[36] International guide-

lines have yet to address this issue, and future research will need to investigate the important question of whether anticoagulation should be preferred to antiplatelet treatment and how long the treatment should be continued in the absence of concurrent indications for anticoagulation, such as atrial fibrillation.

Long-term follow-up of TMV replacement prostheses is warranted, and the current published literature is insufficient. However, if TMV replacement challenges are met with appropriate development and research, it could possibly provide a better solution than transcatheter repair techniques. ■

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Pavel Overtchouk, MD
Department of Cardiology
University Hospital of Bern
Bern, Switzerland
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Juan F. Granada, MD
Columbia University Medical Center
NewYork-Presbyterian Hospital
Cardiovascular Research Foundation
New York, New York
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Thomas Modine, MD, PhD, MBA
Jiao Tong University
Shanghai, China
Heart Valve Center, Institut Cœur Poumon
CHRU Lille
Lille, France
t1modine@yahoo.fr
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