Status of Transcatheter Mitral Valve Replacement

An emerging frontier with unique anatomic, technical, and clinical challenges.

BY NISHTHA SODHI, MD, AND ALAN ZAJARIAS, MD

The first-in-human, balloon-expandable transcatheter aortic valve replacement (TAVR) was performed by Dr. Alan Cribier in 2002. Since then, TAVR technology has transformed the management of aortic valve disease and may soon be a viable treatment modality for patients regardless of their predicted surgical risk. In contrast to the aortic valve, transcatheter therapies for the mitral valve face several anatomic, technical, and clinical challenges that vary depending on disease etiology. Unique anatomic aspects of the mitral valve include a large asymmetric "D" shape, annular and leaflet remodeling, lack of a well-defined rigid annulus to anchor the replacement valve, presence of a complex subvalvular apparatus with chordae and papillary muscles, and a dynamic relationship with the left ventricle creating geometric changes during the cardiac cycle.[1,2] Technical considerations regarding the interaction of the mitral prosthesis with the left ventricular outflow tract (LVOT) and the aortic valve are also critical. Finally, clinical characteristics of these currently high-risk and inoperable patients with multiple comorbidities make the postprocedural course difficult, particularly if the patient has concomitant advanced cardiomyopathy. Nevertheless, through multiple technologies and renditions, transcatheter mitral valve replacement (TMVR) is progressing.

TMVR FOR DEGENERATIVE AND FUNCTIONAL MITRAL REGURGITATION

Because several TMVR systems are currently being investigated for clinical use, this article focuses on the systems with the most clinical experience to date (Table 1).

CardiAQ

The first transcatheter mitral valve implanted in a human was the CardiAQ device (Edwards Lifesciences) in 2012, which is composed of porcine pericardium leaflets mounted on a self-expanding nitinol stent with atrial and ventricular flanges that clamp the mitral annulus and leaflets/chordae.[3] The frame is covered by a polyester fabric skirt to minimize the risk of paraprosthetic leak, and the valve is positioned supra-annular to minimize LVOT obstruction. It is deployed via a transapical or transseptal technique. After access and positioning are established, the LV anchors are released by turning the retraction wheel to initiate leaflet capture. The valve is expanded and once positioning is confirmed, the valve is released.

To date, the device has successfully been deployed in 12 of 13 patients (92.3%) who have received the valve (periprocedural mortality, 15.4%; all-cause 30-day mortality, 53.8%).[4] In early 2017, Edwards paused enrollment in the clinical trial in order to reevaluate the device design. Enrollment was reinitiated in 2018 with transseptal access being the sole delivery mode.

Intrepid

The Intrepid valve (Medtronic) has an outer stent frame with cleats for fixation and a flexible atrial brim to facilitate visualization under echocardiography. The circular inner stent houses a 27-mm trileaflet bovine pericardial valve.[5] The outer frame is available in three sizes (43, 46, and 50 mm), and the valve is deployed transpically via a 35-F system. Unique aspects of the Intrepid valve include cleat technology allowing for fixation of the prosthesis with the subannular apparatus to minimize embolization, no rotational alignment required, and a valve height < 18 mm to reduce the chance of LVOT obstruction.[6] The overall cork-like effect is produced by radial forces along the valve stent.[4] After transapical access, the system is advanced across the mitral valve that is then expanded until the brim is completely deployed with contact in the surrounding struc-

tures. Under echocardiographic guidance, the valve is positioned and then released under rapid ventricular pacing.

The first Intrepid valve was implanted in September 2014. The Intrepid pilot study has since enrolled 50 high-risk patients (Society of Thoracic Surgeons [STS] score, 6.4% ± 5.5%) with severe mitral regurgitation (MR) (functional [n = 21], 78%). Technical success was achieved in 92.6% of cases (30-day mortality, 24%; 8-month follow-up, 26%).[7]

The APOLLO trial is the only ongoing pivotal randomized trial; high-risk patients will be randomized on a 1:1 basis to either the Intrepid TMVR device or to surgical mitral valve replacement. High-risk/inoperable patients in the single-arm group will receive the Intrepid TMVR device. The primary outcome is the composite of all-cause mortality, disabling stroke, reoperation or reintervention, and cardiovascular hospitalization at 1 year, with results expected in 2021.[8]

Tendyne

The Tendyne valve (Tendyne Holdings, Inc, a subsidiary of Abbott Vascular) is a self-expanding nitinol frame with an outer stent form that is D-shaped to conform to the saddle-shaped mitral annulus and an inner stent frame that houses a trileaflet porcine pericardial valve. There is also an adjustable tether to anchor the valve to the LV apex, serving to counteract axial forces and apply both a proximal and distal constraint.[4] After transapical access, the delivery system is advanced through the mitral valve into the left atrium. Partial expansion is completed and the rotational alignment is corrected to ensure the D-shaped outer stent is correctly oriented. The valve is deployed, and then the apical pad is threaded over the tether using a tension tool to adjust the tether length.

The first case was performed in October 2014 as part of the Tendyne global feasibility trial. Thirty patients (average STS score, 7.3% ± 5.7%), with 3 to 4+ MR, underwent transapical TMVR for secondary (n = 23, 77%), primary (n = 3), or mixed (n = 4) pathology. Successful device implantation was achieved in 28 patients (93%), and successful device implantation free of cardiovascular mortality, stroke, and device malfunction at 30 days was 86.6%. At 30 days, echocardiography showed no residual MR (n = 26) and mild MR (n = 1), with 75% of patients reporting New York Heart Association class I or II symptoms at follow-up.[9]

Tiara

The Tiara valve (Neovasc Inc.) is a D-shaped self-expanding trileaflet bovine pericardial valve in a nitinol frame. The atrial portion has a full skirt to assist in valve seating, and there are three ventricular anchors (two anterior, one posterior) for fixation to the free margins of the native leaflets as part of a leaflet engagement design.[4] After transpical access is established and the delivery system is positioned across the mitral valve, the atrial portion of the prosthesis is unsheathed, oriented, and aligned with the D-shaped mitral annulus. The delivery system is then retracted to secure the atrial positioning and the ventricular anchors are released to secure the ventricular portion of the prosthesis.[3] The first cases were performed in Vancouver, Canada in January 2014. To date, the Tiara valve has successfully been implanted in 16 of 19 patients (84.2%), with three instances of valve embolization requiring cardiac surgery (periprocedural mortality, 0%; all-cause 30-day mortality, 15.8%). An early feasibility study is currently enrolling patients.[10]

Caisson

The Caisson TMVR (LivaNova PLC) has a two-stage deployment system with an external anchor that grips under the mitral valve annulus. The valve is composed of a self-expanding nitinol frame with a trileaflet porcine pericardial valve that is housed in the anchor. It utilizes a transseptal 31-F delivery system. Thus far, 19 patients have been treated worldwide, with 15 of 19 implants successfully deployed.[11]

MValve/Lotus

The MValve system (MValve Technologies Ltd.) is essentially a docking device designed to house other transcatheter valves. MValve in conjunction with the Lotus transcatheter heart valve (Boston Scientific Corporation) is currently part of an early feasibility study with 30 patients.[4]

Gate Tricuspid Atrioventricular Valved Stent

The first-in-human implantation of the Gate stent (NaviGate Cardiac Structures Inc.) was performed in October 2015. The valve consists of a nitinol stent frame with a cone-like design with several annular anchoring winglets.

HighLife Two-Component TMVR System

The HighLife two-component TMVR system (HighLife Medical, Inc.) has a subannular implant ring and a prosthetic valve placed inside the ring. Thus far, six patients have been treated with the device worldwide.

Sapien M3

The Sapien M3 valve (Edwards Lifesciences), designed for the aortic valve, was recently reconceptualized to include a sealing skirt and the ability to be housed in an anchoring dock. It is composed of a docking system that

TABLE 1. TRANSCATHETER MITRAL VALVE REPLACEMENT PLATFORMS

Device	First-in-Human Implantation	Valve Positioning	Anchoring Design	Delivery System Size and Access
CardiAQ	2012	Supra-annular with intra-annular sealing skirt	Mitral annulus capture with native leaflet entanglement	Transapical and transseptal, 33 F
Intrepid	2014	Intra-annular	Radial forces and subannular cleats	Transapical, 35 F
Tendyne	2014	Intra-annular	Adjustable apical tether	Transapical, 36 F; fully recapturable system after complete deployment
Tiara	2014	Intra-annular	Fibrous trigone capture with native leaflet entanglement	Transapical, 32 F
Caisson	2016	Supra-annular	External anchor; mitral annulus capture with engagement at subannular fibrous groove	Transapical
MValve/Lotus	2015	Universal dock system	External anchor; mitral annulus capture	Transapical, 32 F; fully retrievable
Gate Tricuspid Atrioventricular Valved Stent	2015	–	Annular winglets	Transapical, transatrial, or transfemoral, 30 F
HighLife Two-Component TMVR System	2017	–	External anchor; mitral annulus capture	Transapical, 32 F; fully retrievable
Sapien M3	2018	Intra-annular	Docking system	Transseptal, 20 F

holds the native leaflets together and creates a landing zone for a separate balloon-expandable valve.

EARLY EXPERIENCE WITH TMVR

These initial TMVR experiences with first-in-human and early feasibility studies demonstrate a reasonable procedural technical success rate (average, 88%).[4] Most platforms are transapical and reserved for high-risk to inoperable patients who often have advanced and irreversible cardiomyopathy. Thus, we must be cognizant and cautious of early study outcomes, particularly because the results are not likely to be so strikingly favorable as in early TAVR trials.

Unresolved challenges that still need to be overcome include LVOT obstruction with hemodynamic compromise after valve deployment (due to either anterior leaflet displacement or the ventricular aspect of the valve stent obstructing outflow), embolization/failure of the anchor of the bioprosthesis, bleeding, tamponade, vascular complications, perivalvular leaks, stroke, coronary compression, and myocardial infarction.[12] Development toward a completely percutaneous approach via transfemoral venous transseptal access with smaller device profiles will help to address some of these issues. A transseptal approach may also provide an access route that may not have a negative effect on postoperative LV function in patients who have significant LV dysfunction preoperatively.

Patient selection is critical for a successful procedure. We must be mindful that the chronic volume-overloaded ventricle (as seen in MR) responds differently to the chronic pressure-loaded ventricle (as seen in aortic stenosis) when the valve pathology is treated. The vast etiologies of MR also make it more difficult to predict which patient will have a survival advantage or symptomatic benefit from TMVR until a more applicable manner of identifying patients with MR who have contractile reserve is identified. The postoperative course, particularly in patients with advanced cardiomyopathy as is often currently the case in these patients, can be challenging as the left and right ventricle adjust to the new hemodynamic conditions. These difficulties may support a shift toward timing with earlier intervention, before irreversible remodeling, in patients with MR. The data obtained from the ongoing trials will be useful in answering these important considerations.

TRANSCATHETER MITRAL VALVE-IN-VALVE AND VALVE-IN-RING PROCEDURES

Favorable results from the STS/American College of Cardiology Transcatheter Valve Therapy Registry led to US Food and Drug Administration approval of the Sapien 3 valve (Edwards Lifesciences) for mitral valve-in-valve therapy in June 2017. The preexisting circular frame provided by a surgical bioprosthesis is used as an anchor and landing zone for transcatheter implantation of an aortic valve in the mitral position via transapical or transseptal access. Given the success of transcatheter mitral valve-in-valve (TMVIV) therapy, attention has expanded to applying the same strategy to valve-in-ring and valve-in-mitral annular calcification cases. The VIVID (Valve-in-Valve International Data) Registry showed the potential of this therapy in prohibitive surgical risk patients.[13] The MITRAL trial is a prospective multicenter trial that evaluated the safety and feasibility of transcatheter mitral valve regurgitation with the Sapien 3 valve in three patient populations: (1) native valves with severe mitral annular calcification, (2) failed surgical rings, and (3) failed surgical bioprostheses in patients at high risk for surgical complications.[14] The Mitral Valve-in-Valve Registry of the PARTNER 3 trial will enroll patients with degenerated bioprosthetic valves in the mitral position who are at least at intermediate risk for surgical complications.

Preprocedural planning in determining an access route for TMVIV and transcatheter mitral valve-in-ring with the Sapien 3 valve involves obtaining the surgical notes to document manipulation of the interatrial septum or other factors that may influence route selection. CT and echocardiographic analysis of the interatrial septum for thickness, calcification, and any potential technical issues with a transseptal puncture is key. If no septal anatomic challenges are identified, a transseptal antegrade approach is favored. Transseptal puncture is performed low and posterior when the patient is under general anesthesia. Subsequent balloon septostomy with a 12- or 14-mm balloon is performed to facilitate valve delivery. The middle marker of the Sapien valve is positioned 3 to 5 mm atrially in relation to the sewing ring or centered in the previous ring. Slow deployment is performed with rapid ventricular pacing. The final position of the Sapien prosthesis should be at the level of the ventricular post of the valve.[15]

In most cases, the iatrogenic atrial septal defect is small enough, with only a mild degree of bidirectional shunting, and eventually resolves. However, if evidence of acute hypoxemia and significant right-to-left shunting occurs immediately intraoperatively, an Amplatzer septal occluder (Abbott Vascular [formerly St. Jude Medical]) can be employed to close the defect.

CONCLUSION

In developing transcatheter technologies for the mitral valve, we have been forced to understand unique anatomic, technical, design, and clinical challenges. The dynamic relationship of the mitral valve, the subvalvular apparatus, and the left ventricle demonstrates that this valvular pathology, unlike the aortic valve, is not just about the valve itself. In the coming years, as we match design, engineering, and preprocedural imaging to these unique heterogeneous aspects of mitral pathophysiology, we will continue to make advances in the emerging frontier of TMVR. ■

1. Guerrero ME, Salinger MH, Levisay JP, Feldman T. Transcatheter mitral valve replacement therapies. American College of Cardiology. http://www.acc.org/latest-in-cardiology/articles/2017/04/28/09/32/transcatheter-mitral-valve-replacement-therapies. Accessed May 5, 2018.
2. Krishnaswamy A, Mick S, Navia J, et al. Transcatheter mitral valve replacement: a frontier in cardiac intervention. Clev Clin J Med. 2017;83(suppl 2):S10-S17.
3. Sondergaard L, De Backer O, Franzen OW, et al. First-in-human case of transfemoral CardiAQ mitral valve implantation. Circ Cardiovasc Interventions. 2015;8:e002135.
4. Regueiro A, Granada JF, Dagenais F, Rodes-Cabau J. Transcatheter mitral valve replacement: insights from early clinical experience and future challenges. J Am Coll Cardiol. 2017;69:2175-2192.
5. Moore BM, Ng B, Naum C, et al. Transcatheter mitral valve replacement with a novel dual stent bioprosthesis. Circ Cardiovasc Interv. 2017;10:e004841.
6. Stanazai Q, Alkhouli M. The intrepid adventure of early transcatheter mitral valve replacement. J Thorac Dis. 2018;10(suppl 9):S999-S1002.
7. Bapat V, Rajagopal V, Meduri C, et al. Early experience with new transcatheter mitral valve replacement. J Am Coll Cardiol. 2018;71:12-21.
8. Transcatheter mitral valve replacement with the Medtronic Intrepid TMVR system in patients with severe symptomatic mitral regurgitation (APOLLO). Clinicaltrials.gov website. https://clinicaltrials.gov/ct2/show/NCT03242642. Accessed May 3, 2018.
9. Muller DWM, RS Farivar, Jasz P, et al. Transcatheter mitral valve replacement for patients with symptomatic mitral regurgitation: a global feasibility trial. J Am Coll Cardiol. 2017;69:381-391.
10. Evans AS, Weiner M, Patel PA, et al. The year in cardiothoracic and vascular anesthesia: selected highlights from 2017. J Cardiothorac Vasc Anesth. 2018;32:1-13.
11. Williams M. Transfemoral TMVR: Caisson transcatheter mitral valve replacement. Presented at: TVT 2018; June 20–22, 2018; Chicago, IL.
12. Eleid MF, Whisenant BK, Cabalka AK, et al. Early outcomes of percutaneous transvenous transseptal transcatheter valve implantation in failed bioprosthetic mitral valves, ring annuloplasty, and severe mitral annular calcification. JACC Cardiovasc Interv. 2016;10:1932-1942.
13. Yoon HS, Whisenant BK, Bleiziffer S, et al. Transcatheter mitral valve replacement for degenerated bioprosthetic valves and failed annuloplasty rings. J Am Coll Cardiol. 2017;70:1121-1131.
14. Guerrero M, Dvir M, Himbert D, et al. Transcatheter mitral valve replacement in native mitral valve disease with severe calcification: results from the first multicenter global registry. JACC Cardiovasc Interv. 2016;9:1361-1371.
15. Sarkar K, Reardon MJ, Little SH, et al. Transcatheter mitral valve replacement for native and failed bioprosthetic mitral valves. Methodist DeBakey Cardiovasc J. 2017;13:142-151.

Nishtha Sodhi, MD
Structural Heart Disease Fellow
Barnes Jewish Hospital of Washington University
St. Louis, Missouri
nishthasodhi@gmail.com
Disclosures: None.

Alan Zajarias, MD
Associate Professor of Medicine
Director Structural Heart Disease Fellowship Program
Barnes Jewish Hospital of Washington University
St. Louis, Missouri
azajarias@wustl.edu
Disclosures: None.