

Percutaneous Mitral Valve Replacement

An overview of the transcatheter valve replacement therapies for treating mitral regurgitation.

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Mitral regurgitation (MR) is the most common form of valvular heart disease, particularly in the aging population, with a prevalence over 10% in people older than 75 years.¹ Surgical repair/replacement is the standard of care for the treatment of severe primary MR. Patients with heart failure and functional MR should receive optimal medical treatment, and surgery may be considered as a therapeutic option in the presence of severe continued symptoms unresponsive to medical therapy.²

Data from the Euro Heart Survey revealed that nearly 50% of patients with symptomatic severe MR are not referred for surgery.³ Older patients with additional comorbidities, MR of nonischemic etiology, or low left ventricular ejection fraction (LVEF) are more likely to be denied for surgery.^{3,4} A large, single-center, retrospective study showed that more than half of patients with severe MR and heart failure were medically managed.⁴ Untreated severe MR in patients with heart failure is associated with mortality rates as high as 20% and 50% at 1- and 5-year follow-up, respectively, and the vast majority of patients have at least one hospitalization for heart failure decompensation within the 5 years after the diagnosis.⁴ Therefore, the development of less-invasive transcatheter techniques for treating MR has generated high clinical interest in the last few years.

To date, the MitraClip system (Abbott Vascular) is the most widely used therapy for transcatheter intervention in MR and has been in clinical use since 2003.⁵ The EVEREST I and II trials established the feasibility, safety, and efficacy of the MitraClip system in reducing the severity of MR.⁶⁻⁸ Subgroup analyses from EVEREST II indicated that surgery was superior to MitraClip therapy for treating degenerative MR but not in patients with functional MR. Also, older patients and those

with reduced LVEF had similar clinical outcomes with surgery and MitraClip therapy. In addition to MitraClip, other devices targeting the mitral annulus (direct or indirect annuloplasty devices) have also been evaluated in the field of transcatheter MR repair.⁹

Transcatheter mitral valve replacement (TMVR) is growing as another alternative to percutaneous mitral repair for treating MR. However, the development of TMVR has been much slower than that of transcatheter aortic valve replacement, mainly due to the increased anatomical challenges of the mitral valve in addition to the heterogeneity of mitral valve disease.⁵ Also, the mitral valve annulus, which serves as the landing zone for the transcatheter valve prosthesis, has a complex dynamic anatomy of large dimensions and does not provide a rigid structure in which a valve can be placed.^{10,11} Despite all of these difficulties, TMVR may offer some advantages over percutaneous mitral repair therapies, including a higher degree of predictability in the reduction of MR severity and the potential applicability to a greater proportion of patients, particularly if TMVR evolves toward a fully percutaneous procedure with multiple transcatheter valve prototypes and sizes.

In this article, we report the current TMVR technologies for treating MR in native noncalcified valves. The information was obtained from the available literature. The valves that are presented are not approved for sale in any country and have been implanted either through compassionate clinical use or feasibility trials.

FORTIS TRANSCATHETER MITRAL VALVE

The Fortis valve (Edwards Lifesciences) comprises a self-expanding nitinol frame, trileaflet bovine pericardial tissue, an atrial flange, and opposing paddles that capture the native mitral leaflets and secure them to the frame, forming the primary attachment mechanism

Courtesy of Edwards Lifesciences.



Figure 1. The Fortis transcatheter mitral valve, which includes the atrial flange, the ventricular side (or valve body), and two paddles.

(Figure 1). The 29-mm Fortis valve is implanted through a transapical approach using a dedicated delivery system that is 42 F in outer diameter. The valve is suitable for patients with native annular diameter distance at a A2-P2 level between 30 and 44 mm.¹²

The valve is implanted under general anesthesia in an operating room using transesophageal and fluoroscopic guidance. The approach consists of a small left lateral thoracotomy and a direct puncture of the ventricular apex. The mitral valve is then crossed with a balloon catheter to ensure that the wire is free from the mitral subvalvular apparatus. A J-tip guidewire is then positioned into the right superior pulmonary vein and exchanged for an extra-stiff J-tip guidewire. Once the extra-stiff wire is in place, the delivery system with the crimped valve is advanced over the wire into the mid-ventricular cavity. At this point, the paddles are partially exposed, and the correct orientation of the valve is confirmed under echocardiographic guidance. After confirming the correct orientation, the paddles are fully exposed and opened in preparation for leaflet capture. The system is advanced to capture the leaflets, and the atrial flange is released. The valve is then released by unsheathing the ventricular portion (Figure 1).

The 30-day follow-up results of the first 13 patients treated with the Fortis device were recently reported.¹³ Procedural success was achieved in 10 patients (76.9%). Two patients were converted to surgery, one because chordal entanglement of the balloon catheter precluding valve implantation and the other due to valve malposition. Another patient died 4 days



Courtesy of Edwards Lifesciences.

Figure 2. CardiAQ-Edwards transcatheter mitral valve system.

after the procedure because of partial migration of the device due to incomplete leaflet capture. Four (30.8%) patients died during index hospitalization. Postprocedural echocardiography demonstrated a mean transmitral gradient of 3 ± 1 mm Hg, with trace or no MR in eight patients and mild MR in one patient. An additional patient died 2 weeks after the procedure due to probable valve thrombosis.

The 6-month follow-up from the first three patients treated at the Quebec Heart and Lung Institute was recently published.¹⁴ The New York Heart Association (NYHA) functional class, Duke Activity Status Index functional status, distance walked in the 6-minute walk test, and quality of life improved in all patients at 3-month follow-up, and the functional status improvement persisted at 6 months.

In late 2015, Edwards Lifesciences decided to temporarily stop the Fortis program because of evidence of valve thrombosis.

CARDIAQ-EDWARDS TRANSCATHETER MITRAL VALVE SYSTEM

The CardiAQ-Edwards transcatheter mitral valve (Edwards Lifesciences) is a self-expanding nitinol valve with a trileaflet bovine pericardial tissue (the leaflets of the first generation of this device were made with porcine pericardium). The valve can be implanted through the transapical or transseptal approach. The attachment mechanism is composed of left ventricular anchors that engage the native mitral leaflets and annulus and preserve the subvalvular apparatus. The symmetric design requires no rotational alignment. The frame is covered with a polyester fabric skirt to reduce the risk of paraprosthetic leaks (Figure 2). The delivery catheter has a maximal diameter of 33 F.¹⁵

The procedure is performed under transesophageal echocardiographic and fluoroscopic/angiographic guidance. The transeptal procedure can be summarized in six steps¹⁵: (1) the creation of an arteriovenous loop with an exchange nitinol wire after a transeptal puncture is performed; (2) the transeptal delivery system is advanced across the septum, and after crossing the mitral valve, a ventriculogram is obtained to reassess the mitral plane and correct the height of the system by feeding/retracting the venous wire; (3) the left ventricular anchors are released by turning the retraction wheel; (4) the posterior mitral leaflets are captured by rotating the retraction wheel slowly to expand the diameter of the prosthesis, and the capture is confirmed by transesophageal echocardiography; (5) the valve is released after unlocking and rotating the release wheel; and (6) the system is centered within the bioprosthesis, and the tapered tip is retracted until flush with the capsule.

The procedure for transapical valve implantation can also be summarized in six steps¹⁵: (1) the left ventricle is accessed through the fifth or sixth intercostal space, and after ventricular apical puncture, a 0.035-inch guidewire is placed across the mitral valve, and a balloon is passed over the wire and is free of the subvalvular apparatus; (2) the transapical delivery system is inserted over the wire, and the mitral valve is crossed until ventricle anchors are at the level of the mitral valve; (3) the capsule wheel is retracted, and the ventricular anchors are released; (4) the prosthesis position is adjusted until the ventricular anchors are 1 cm below the mitral valve, the valve is expanded to capture the mitral leaflets, and subsequently, the capture is confirmed by transesophageal echocardiography; (5) the tapered tip is advanced by rotating the control wheel, and when the atrial anchors are above the annulus, the bioprosthesis is released from the delivery system; and (6) the system is removed by centering it within the bioprosthesis and retracting the tapered tip until flush with the capsule.

The first-in-human implantation of the first-generation CardiAQ mitral valve prosthesis was performed in 2012 in Copenhagen via a transeptal approach.¹⁶ Since then, another four cases have been reported, including three patients treated with transapical access and one patient treated with the transeptal approach.¹⁵⁻¹⁹ In the first patient treated with the first-generation device, the valve was successfully implanted, but the patient died 3 days after the procedure because of multiorgan failure.²⁰ The first fully percutaneous transeptal implantation with the second-generation valve was performed successfully with no periprocedural complications. The patient was NYHA class I at 30-day follow-up, and the



Figure 3. Tiara transcatheter mitral valve system.

prosthesis functioned well.¹⁷ The three patients who were treated via a transapical approach underwent a successful procedure with accurate prosthesis positioning. Two patients were discharged home, and echocardiography performed at 1, 30, and 60 days showed good valve function. One patient died 9 days after the procedure due to pneumonia.

A phase 1 early feasibility study with the transeptal and transapical delivery systems is currently enrolling in the United States, and the RELIEF study will evaluate the procedural safety and valve prosthesis performance in 200 patients in Europe and Canada.²¹

TIARA MITRAL VALVE SYSTEM

The Tiara valve (Neovasc Inc.) consists of a nitinol self-expanding frame and trileaflet bovine pericardium. The valve is designed to fit the D-shaped mitral annulus. The atrial portion helps to seat the prosthesis onto the atrial portion of the mitral annulus, and the ventricular anchoring structures are designed to secure the valve into the fibrous trigones and the posterior part of the annulus (Figure 3). The valve is loaded into a 32-F delivery sheath and is implanted through a transapical approach. The valve is available in a single 35-mm size.²²

The procedure is performed under general anesthesia with transesophageal echocardiographic and fluoroscopic guidance. The left ventricle apex is exposed through a small left mini-thoracotomy, and after apical puncture, a 0.035-inch J-tip wire is introduced across the mitral valve into the left atrium. The Tiara delivery system is introduced directly and across the mitral valve. The atrial portion of the prosthesis is unsheathed and oriented and aligned with the D-shaped mitral annulus to allow for proper fit. The delivery system is then

Courtesy of Neovasc Inc.

Mitral valve anatomy is a major challenge, and thus the development of TMVR and experience with the technology is in its early phases.

pulled back to seat the atrial part of the valve. The ventricular anchoring mechanisms are released to secure and release the prosthetic valve.²³

The first two cases of human Tiara valve implantation were performed in Vancouver in 2014.²⁴ Postprocedural echocardiograms obtained at 48 hours and at 1- and 2-month follow-up demonstrated good valve function and no significant residual MR. The first patient died due to congestive heart failure and chronic renal failure 69 days after the procedure. The second patient remained well at 5 months after the procedure.²² The short-term results of another six patients (eight in total) who underwent Tiara valve implantation have been reported.²³ In seven of the eight cases, the Tiara valve was successfully implanted, and one patient required conversion to surgical valve replacement due to valve malposition. The predischARGE and 30-day echocardiograms showed no evidence of residual MR in all cases.²³

An early feasibility trial (TIARA-I) including a total of 30 patients is currently enrolling.²⁵

TENDYNE BIOPROSTHETIC MITRAL VALVE SYSTEM

The Tendyne bioprosthetic mitral valve system (Tendyne Holdings, Inc.) is a new version of the Lutter valve and consists of a trileaflet valve of porcine pericardium, two self-expanding nitinol stents, an adjustable tether, and an apical fixation/sealing pad. The inner stent is one size and circular to maintain an effective orifice area $> 3 \text{ cm}^2$, and the outer stent is D-shaped to conform to the shape of the mitral annulus. Atrial flanges provide the atrial sealing and anchoring, and a left ventricular apical tethering system with an apical pad reduces paravalvular leak and assists with apical closure (Figure 4). The valve is implanted by means of a transapical approach with a 34-F sheath in patients with an intercommissural diameter of 34 to 50 mm.²⁶

The procedure can be summarized in four steps²⁶: (1) initiate the procedure using a standard transapical approach through a left mini-thoracotomy and left ventricle access with a 34-F delivery sheath; (2) a

balloon-tipped catheter is advanced over a guidewire into the left atrium, the delivery system is advanced in the sheath, and the valve is brought into the left atrium and positioned above the mitral annulus and allowed to expand until 80% of the valve is in the left atrium; (3) the D-shaped Tendyne outer stent is oriented so that the straight side is aligned with the aortomitral continuity, the valve is retracted into the mitral annulus; and (4) the apical pad is inserted in position over the tether, and a tension gauge tool is used to adjust the tether tension from the valve to the ventricular apex under transesophageal echocardiographic guidance. The apical pad is secured and assists with closure of the apex.

The first-in-human implantations were performed in Paraguay in 2013. Two patients undergoing mitral valve replacement first received a Tendyne valve implant and were monitored for 2 hours after implantation. Improvement in MR severity and reduction in left atrial pressures were observed.²⁷ Three patients were treated in the United Kingdom, and all patients had an uneventful procedure without in-hospital complications. There was no MR or trivial MR and no significant transmitral gradient in all three patients.

In September 2015, Abbott Vascular announced the acquisition of Tendyne Holdings. An early feasibility trial is currently enrolling. The multicenter, single-arm study will include 110 patients, and the estimated primary completion date will be in May 2018.²⁸

INTREPID TWELVE TRANSCATHETER MITRAL VALVE REPLACEMENT

The Intrepid Twelve valve (Twelve, Inc.) has also been implanted in humans; however, to date, there are

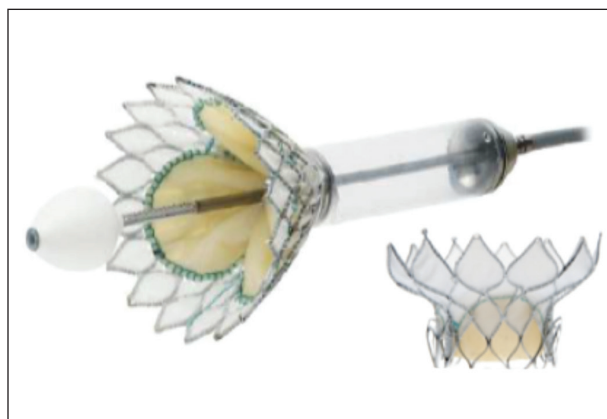


Figure 4. Tendyne bioprosthetic mitral valve system. Reproduced from Tobis JM, Abudayyeh I. Percutaneous mitral valve repair devices beyond MitraClip. *Cardiac Interv Today*. 2015;9:28–32.

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no publications describing the details of the valve or the procedural outcomes. In August 2015, Medtronic announced the agreement to acquire Twelve, Inc.

TMVR DEVICES UNDER PRECLINICAL EVALUATION

There are several transcatheter mitral replacement systems at different stages of preclinical development, including the AccuFit TMVR (Sino Medical Sciences Technology, Inc.), Caisson TMR (Caisson Interventional, LLC), Cephea (Cephea Valve Technologies), Direct Flow Medical transcatheter mitral valve (Direct Flow Medical, Inc.), Highlife Medical MVR (Highlife Medical), EndoValve (Micro Interventional Devices), Gorman TMV (Gorman Cardiovascular Research Group), MitralHeal (MitralHeal Ltd.), MitrAssist valve (MitrAssist Ltd.), MValve (MValve Technologies Ltd.), Navigate TMVR (Navigate Cardiac Structures Inc.), Saturn TMVR (HT Consultant), Tresillo (Transcatheter Technologies GmbH), and Cardiovalve (Valtech Cardio, Ltd.).

CONCLUSION

Mitral valve anatomy is a major challenge, and thus the development of TMVR and experience with the technology is in its early phases. First-in-human experiences have shown the feasibility of TMVR with different valve platforms, mainly implanted through a transapical approach. Further studies are needed to provide definitive data on the safety and preliminary efficacy of these procedures. The potential role of TMVR compared to percutaneous mitral valve repair for the treatment of patients with severe MR at high or prohibitive surgical risk will need to be elucidated in future trials. ■

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