

Early Experience With Transcatheter Mitral Valve Replacement

The current status of this novel technique to treat patients with severe mitral disease who are not candidates for surgery.

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Transcatheter mitral valve replacement has recently emerged as one of the new frontiers in the field of structural interventions. Although transcatheter aortic valve replacement (TAVR) is a well-established treatment option for patients with symptomatic severe calcific aortic stenosis who are considered high surgical risk, and it might perhaps prove effective for intermediate-risk patients in the near future, the experience with transcatheter mitral valve replacement is at a very early stage.

There have been important limitations for the development of this technology, including the complexity of the mitral valve anatomy. This anatomy involves a saddle oval shape, a subvalvular apparatus, interaction with the left ventricular outflow tract (LVOT) and aortic valve, and a large size requiring a larger prosthesis (and therefore, a larger catheter for implantation), which limits the delivery modality to a transapical approach in most cases. However, this approach has become standard given the complex anchoring mechanisms and the requirement for correctly orienting transcatheter mitral valves. The wide variety of mitral pathology, from stenosis to multiple mechanisms of regurgitation, also adds to the difficulties of valve design. Furthermore, the patient population requiring this treatment option usually involves high-risk substrates due to multiple comorbidities that may affect the overall outcome.

Despite these limitations, there have been a few successful cases reported worldwide with different technologies. Several devices specifically designed for the mitral valve are being evaluated, and commercially available devices for

aortic and pulmonic valve replacement have been used in the mitral position as well. This article summarizes this early experience, including the successes and failures that have been reported thus far.

FAILED MITRAL BIOPROSTHESES

The initial experience with transcatheter mitral valve replacement occurred in patients with failed surgical mitral bioprostheses or mitral rings. Repeat cardiac surgery in these patients is associated with significant morbidity and mortality, and therefore, a less-invasive approach was an attractive alternative in selected cases. The first patients were treated using the balloon-expandable Sapien and Sapien XT valves (Edwards Lifesciences) in this clinical scenario, with good short- and midterm clinical outcomes. However, the first successful cases were implanted surgically via a transapical approach, as the initial attempts at transcatheter replacement via transseptal and transatrial access routes failed.¹⁻³

A multicenter registry report by Webb et al described their early experience of the first seven cases.⁴ The first two attempts in humans were unsuccessful. The first case was attempted using a percutaneous transseptal approach. The transcatheter valve embolized in the left ventricle due to a noncoaxial and too-ventricular position. The procedure was converted to open heart surgery, and the patient died from multisystem failure the next day. In the second patient, an open transatrial approach was attempted. Stable and coaxial positioning of the delivery system could not be accomplished, and the procedure was converted to a transapical approach requiring bilateral thoracotomy.

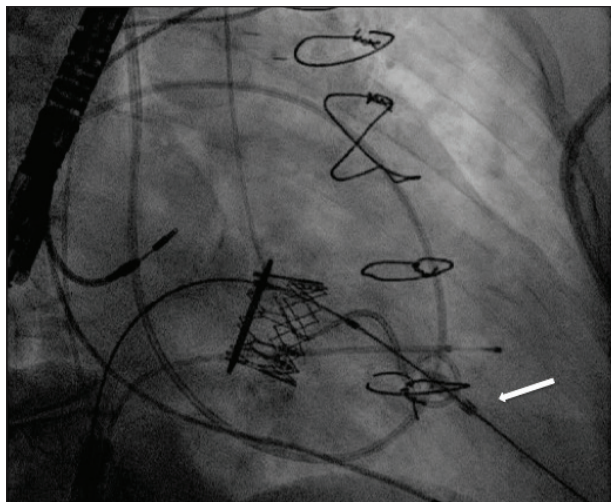


Figure 1. Mitral valve-in-valve procedure with a modified antegrade approach. A 26-mm Sapien XT valve was deployed in a 29-mm Hancock valve (Medtronic) via antegrade approach with a wire externalized through a 6-F sheath that was percutaneously placed in the left ventricle (arrow). The percutaneous ventricular access was successfully closed with an Amplatzer Duct Occluder II device (St. Jude Medical).

The patient died on postoperative day 45. Due to the problems encountered with the transseptal and transatrial approaches, the subsequent cases were performed via a transapical approach and were successful. The most recent report by this group describes the outcomes of 23 consecutive patients with a failed mitral bioprosthesis who were successfully treated with transcatheter valve replacement via a transapical approach.⁵ The device success rate was 100%. There was no intraprocedural or 30-day mortality. At a median follow-up of 753 days, the survival rate was 90.4%, with the longest follow-up at 1,448 days. Clinical improvement in heart failure symptoms to New York Heart Association (NYHA) class I/II was observed in all but one patient (95.6%) at last follow-up.

Other centers have reported favorable outcomes in a few cases of transcatheter mitral valve replacement via a transseptal approach using the Sapien XT valve^{6,7} and the Melody valve (Medtronic),^{8,9} but the vast majority of the published cases have employed a transapical approach.^{3,5,10-12} Dvir et al reported the outcomes of 70 patients included in the global valve-in-valve registry (11.4% valve in ring, 88.6% valve in valve). All patients were treated with the Sapien valve (23 mm in 22.9%, 26 mm in 58.6%, and 29 mm in 18.6%). Transapical access was used in 85.7%, transseptal in 10%, and transatrial in 4.3%. Device malposition occurred in 4.3%. The 30-day all-cause mortality rate was 10.3%, and 82.3% were NYHA functional class I or II at 30 days.¹³

Recently, outcomes with the transseptal approach have been better than initially reported. Bouleti et al reported a series of 17 patients (six bioprostheses and 11 valve-in-ring procedures) who underwent transcatheter mitral valve replacement using a transvenous transseptal approach. The technical success was 82%, and there was one procedural death and one valve embolization. At a mean follow-up of 22 months, there were four deaths (three from a cardiac cause), and 75% of the survivors were NYHA class $\leq$ II.¹⁴ This approach may offer a less-invasive alternative to patients who are not candidates for a surgical transapical approach. In collaboration with Dr. William O'Neill and his team at Henry Ford Hospital, we have found similar good outcomes using a modified transseptal approach with a guidewire externalized via a sheath percutaneously placed in the left ventricle (Figure 1).

Due to a growing body of evidence indicating favorable outcomes, the Sapien XT transcatheter valve received CE Mark approval in February 2014 for use in aortic and mitral valve-in-valve procedures to treat patients with failed bioprostheses who were at extremely high surgical risk.

FAILED MITRAL VALVE REPAIR WITH ANNULOPLASTY RINGS

Valve-in-ring procedures are technically more challenging because the rings do not provide the scaffold support that a bioprosthesis does, nor do they serve as a reliable landing zone. There are different types of rings, varying in shape and degree rigidity, and this needs to be taken into consideration as well. Despite these limitations, several single-case reports have described successful implantation of the Sapien XT valve in a mitral ring using a variety of approaches, including a percutaneous antegrade approach,¹⁵⁻¹⁸ a transapical approach,^{19,20} and an off-pump transatrial approach through an anterolateral mini-thoracotomy.^{20,21} The largest series of 17 patients reported by Descoutures et al also describes favorable outcomes using the Sapien XT valve, with a technical success rate of 89% using the transapical approach and 87% with the transseptal approach.²² Overall, there were two early postoperative deaths related to heart failure. All survivors were in NYHA class II at discharge. The mean follow-up was 13 ± 5 months, with a survival rate of 72% (12/17). No patient had more than mild paravalvular regurgitation with small paravalvular jets. Three patients had LVOT gradients of 15 to 17 mm Hg due to displacement of the subvalvular apparatus toward the outflow tract.

Successful implantations of the Melody valve in mitral rings using transapical and antegrade approaches have been reported as well.^{23,24} Transcatheter mitral valve-in-ring implantation is also feasible in the presence of a

transcatheter valve in the aortic position. Ladeiras et al reported a successful transapical TAVR followed by a transapical transcatheter mitral valve-in-ring implantation during the same procedure to treat a patient with severe aortic stenosis and failed ring with severe mitral stenosis (MS).²⁵ The Sapien XT valve was used to treat both valves. This report is very valuable because it provides evidence that transcatheter aortic and mitral valve replacement can be successfully performed in the same procedure.

TRANSCATHETER HEART VALVE IMPLANTATION IN NATIVE MITRAL VALVES

Implantation of transcatheter heart valves in native mitral valves is significantly more challenging than mitral valve-in-valve and valve-in-ring procedures due to the previously mentioned limitations. In mitral valve-in-valve implantation, there is a scaffold that the operator can use to anchor the new prosthesis and use as a landing zone. In addition, anterior displacement of the anterior mitral valve leaflet during transcatheter mitral valve replacement contributes to LVOT obstruction; however, when transcatheter mitral valve replacement is performed after a previous surgical valve replacement, the risk of LVOT obstruction caused by displacement of the anterior mitral valve leaflet is lower, as it was removed during the initial surgery.

The type of transcatheter mitral valve design chosen is pathology dependent. In patients with mitral regurgitation, a self-expanding nitinol frame with an anchoring system has been used in most cases, whereas with severe calcific mitral stenosis (as with calcific aortic stenosis), balloon-expandable valves have been used. Most of the reported cases were performed with the Sapien or Sapien XT valves, which are designed for calcific aortic stenosis.

MITRAL REGURGITATION

The CardiAQ Valve

The CardiAQ valve (CardiAQ Valve Technologies, Inc.) was the first transcatheter valve percutaneously implanted in a native mitral valve in humans. The first generation was made of porcine pericardium mounted on a self-expandable nitinol stent (Figure 2A). The first procedure was performed in Denmark on an 85-year-old man with severe 4+ mitral regurgitation (MR) who was not a surgical candidate. The procedure was successful via a transseptal approach with circulatory support, reducing the severity of MR to 1+. Despite proper functioning of the valve, the patient died on postprocedure day 3 due to multiorgan failure. There were no structural valvular abnormalities noted on autopsy.²⁶

The second generation of the CardiAQ can be delivered via a transapical or transfemoral approach. Sondergaard et al reported their experience with the first three patients

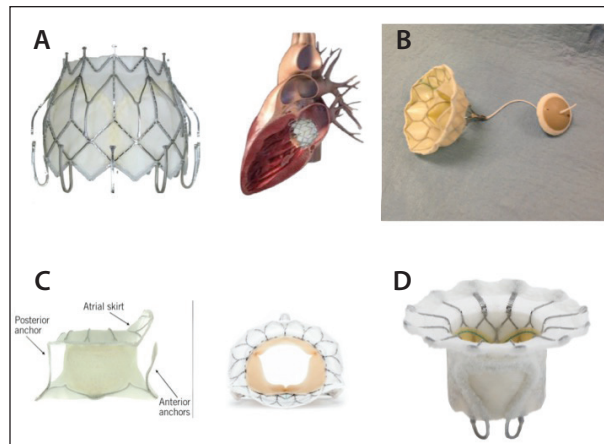


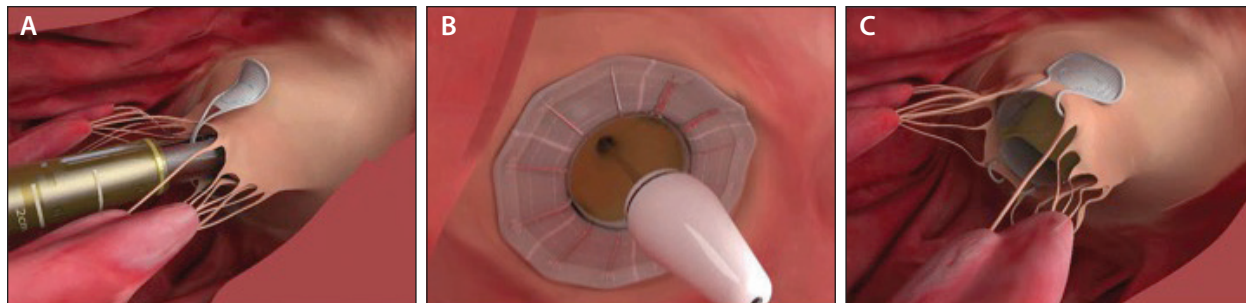
Figure 2. The first-generation CardiAQ valve (A), Tendyne valve (B), Tiara valve (C), Fortis valve (D).

treated. These patients were elderly and had severe MR with New York Heart Association class IV symptoms. Two patients had functional MR due to cardiomyopathy with an ejection fraction (EF) < 40%, and one had chordal rupture. The procedure was successful via a transapical approach. One patient died on postoperative day 9 due to pneumonia. The other two recovered and were discharged home. Follow-up transesophageal echocardiography on days 1, 30, and 60 revealed the stable position of the valve with proper function and minimal LVOT gradient.²⁷

The Tendyne Valve

The Tendyne valve (Tendyne Holdings, Inc.) is made of porcine pericardium mounted on a nitinol frame, is fully retrievable, and is anchored with an apical tether (Figure 2B). The first implantation was performed in February 2013 in a 57-year-old man with severe degenerative MR, and the second was implanted in a 55-year-old woman with severe MR due to combined rheumatic and degenerative etiology. Both patients were scheduled to undergo surgical mitral valve replacement and gave consent to undergo transcatheter implantation of a Tendyne valve to evaluate its performance, followed by removal of the Tendyne prosthesis and traditional mitral valve replacement. The valves were deployed via a transapical approach. The procedures were successful. One patient had 1+ paravalvular regurgitation due to difficulty achieving proper positioning of the valve. The patient's hemodynamics nevertheless improved. After complete evaluation of the valve's position and function, the patients underwent conventional mitral valve replacement, during which, the Tendyne prosthesis was explanted. No damage to the mitral valve apparatus or leaflets was noted.²⁸

In December 2014, Tendyne announced the results of the first three long-term implantations performed at



Courtesy of Edwards Lifesciences.

Figure 3. Important steps in Fortis valve implantation. Leaflet capture: the paddles are seen outside both leaflets. Closing the paddles results in trapping the leaflets between the paddles and the body of the valve (A). Release of the atrial flange is achieved by pushing the nose cone forward (B). Valve deployment: once the paddles are closed and the atrial flange released, the valve is deployed by unsheathing the ventricular body (C).

Royal Brompton Hospital in London, England, under a compassionate-use basis.²⁹ The first procedure was performed in a 68-year-old woman with severe functional MR who was not a surgical candidate. The subsequent patients were 85 and 87 years old with severe degenerative MR and were also not candidates for conventional mitral valve surgery. The procedures were performed using a transapical approach and were successful. All patients were discharged home.

The Tiara Valve

The Tiara valve (Neovasc Inc.) is a bovine pericardial valve mounted on a self-expandable nitinol stent. It has a “D” shape to better adapt to the shape of the mitral annulus and decrease the risk of LVOT obstruction. It has ventricular anchoring structures that attach to the fibrous trigone and the posterior shelf of the annulus to prevent embolization (Figure 2C). It is implanted via a transapical approach using a 32-F delivery system.

The first two implantations in humans were performed in January and February 2014 at St. Paul’s Hospital in Vancouver, British Columbia, Canada. The patients were 73 and 61 years old with severe functional MR and left ventricular EFs of 15% and 25%, respectively. They were not candidates for conventional surgery. The valves were successfully implanted via a transapical approach. The prosthesis had normal function with only trace paravalvular MR, the mean mitral valve gradients were 2 and 3 mm Hg, and no LVOT obstruction was noted. The patients recovered well from the procedure. Follow-up echocardiography at 4 weeks demonstrated proper functioning of the prosthesis. However, the first patient died from progressive heart failure 69 days after the procedure. The second patient improved clinically; his baseline NYHA class IV symptoms decreased to class II at 5-month follow-up.³⁰

The Fortis Valve

The Fortis valve (Edwards Lifesciences) is a bovine pericardial valve mounted on a self-expandable nitinol frame covered with a fabric skirt to minimize paravalvular regurgitation and facilitate tissue ingrowth. It has two paddles attached to the central body that capture the mitral valve leaflets to anchor the valve and prevent embolization. It has an atrial flange made of nitinol struts covered with the same fabric as the center body (Figure 2D), and it is delivered via a transapical approach.

Bapat et al recently reported the results of the first five implantations in humans (Figure 3). All patients had severe functional MR, were not candidates for conventional mitral valve surgery, and were implanted on a compassionate use basis. The procedures were successful. The first patient had an EF of 15% to 20%. After a slow recovery due to persistent heart failure, the patient was discharged on postoperative day 15. The 30-day follow-up echocardiogram revealed minimal MR. The patient was rehospitalized on day 37 with decompensated heart failure and died on day 76 despite maximal medical treatment. The second patient developed renal failure on day 1, followed by pulmonary edema requiring mechanical ventilation on day 2. The echocardiogram revealed increased MR and a displaced posterior paddle with the valve partially embolized to the left atrium. The patient died on day 4. The autopsy confirmed loss of capture of the posterior leaflet and partial embolization of the prosthesis to the left atrium. The third patient had no complications and was discharged on day 6. At 30-day follow-up, the patient showed improvement in the 6-minute walk test (from 135 m to 215 m) and adequate functioning of the prosthesis. The patient continues to slowly improve. The fourth patient had an uneventful procedure and was discharged on day 9 but was readmitted on day 15 with heart failure decompensation and systemic inflammatory response syndrome. Reduced leaflet mobility of the prosthesis was noted on

echocardiography with high gradients. Antibiotics and heparin were initiated, but the patient rapidly deteriorated and died on day 15. An autopsy was not performed due to the family's wishes. The fifth patient had an uneventful procedure, was discharged on day 6, and continues to improve clinically.

Despite poor outcomes in some patients who underwent treatment with the Fortis valve, the two patients with good outcomes may provide proof of the concept that transcatheter mitral valve replacement may be an option for nonsurgical candidates. However, the patient selection process is important to avoid poor outcomes associated with progressive end-stage heart failure, as observed with the first patient.³¹

It is unclear at this early stage if the initial poor outcomes were related to the device itself, the procedure, the learning curve, or simply because this technology was used in extremely sick patients who had no other options. Careful patient selection will be important to avoid poor outcomes associated with progressive end-stage heart failure.

CALCIFIC MITRAL STENOSIS

The first successful balloon-expandable transcatheter valve implantation in a native mitral valve in a human was reported by Hasan et al using a Sapien XT valve via a surgical transapical approach.³² A report by Sinning et al also describes a successful implantation of a Sapien XT valve in a native mitral valve with a transapical approach.³³ Both procedures were performed in patients with severe calcific MS who were not candidates for mitral valve surgery due to high surgical risk. Long-term follow-up of these patients has not been published. Wilbring et al reported a transcatheter implantation of a Sapien XT valve in a native mitral valve with suboptimal results.²⁰ The initial plan was to proceed with surgical mitral valve replacement. Intraoperatively, the annulus was found to be extremely calcified, making surgical implantation impossible. A 29-mm Sapien XT valve was implanted under direct visualization with initial good results. An echocardiogram the following day revealed incipient valve dislocation and paravalvular leak. This was successfully treated via surgery with a running 3–1 polypropylene suture to an atrial cuff. The valve function remained adequate, but the patient died on postoperative day 41 from a massive upper gastrointestinal bleed.

The transapical approach is preferred by many operators who are comfortable with this method for TAVR. However, not all patients may be candidates for a surgical transapical access due to their risk factors. Therefore, an even less-invasive approach may be needed for some patients. A percutaneous method is preferred in these

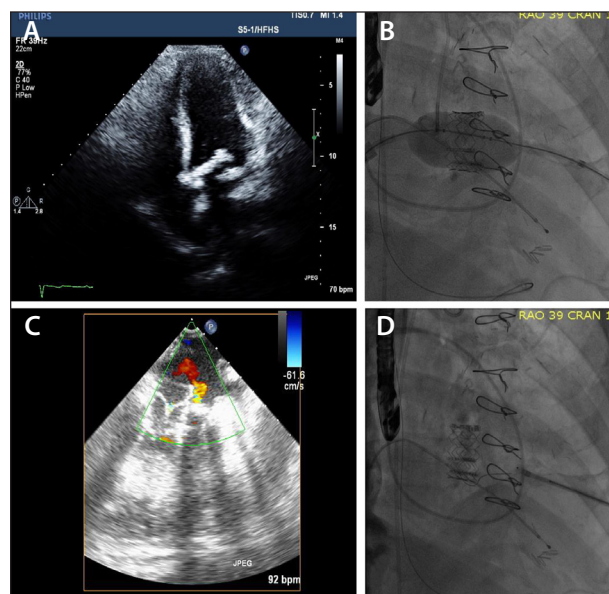


Figure 4. Echocardiography at baseline demonstrates a severely calcified mitral valve (A). Fluoroscopy of a Sapien valve being implanted in a native mitral valve via a modified antegrade approach with the guidewire externalized through a sheath that was percutaneously placed in the left ventricle (B). Transesophageal echocardiography confirms proper positioning of the Sapien valve in the mitral annulus with only trace to mild paravalvular regurgitation (C). Fluoroscopy of the percutaneous ventricular access being closed with a 4-mm Amplatzer muscular VSD occluder (St. Jude Medical) (D). Reprinted from Guerrero M, Greenbaum A, O'Neill W. First in human percutaneous implantation of a balloon expandable transcatheter heart valve in a severely stenosed native mitral valve. *Catheter Cardiovasc Interv.* 2014;15:83:E287–291.³⁴

situations. However, the typical transvenous antegrade approach may not provide an adequate coaxial position and support during valve deployment and may result in valve embolization.⁴ To improve coaxiality during transeptal deployment, the guidewire may be externalized through the left ventricle.

We reported the first-in-human percutaneous implantation of a balloon-expandable transcatheter valve in a native mitral valve.³⁴ We used a 26-mm Sapien valve to treat a patient with severe calcific MS who was not a candidate for mitral valve surgery or surgical transapical access given his extremely high surgical risk. Due to the need to improve the coaxiality and support of the traditional antegrade approach, we decided to externalize the guidewire through a sheath that was percutaneously placed in the left ventricle (Figure 4). This approach is less invasive than the surgical transapical approach and could be considered

for truly inoperable patients when coaxiality cannot be achieved with the traditional antegrade approach. The procedure was successful, and the valve had adequate function with only trivial paravalvular regurgitation. However, the patient died on postoperative day 10 from noncardiac causes including renal failure, suspected sepsis, and multiorgan failure.

Fassa et al reported a successful transcatheter implantation of a Sapien XT valve in a native mitral valve using the traditional antegrade approach, which is the least-invasive approach.³⁵ Himbert et al recently reported a series of four patients treated with Sapien XT via a transvenous transseptal approach with good results.³⁶ The combined experience of these cases suggests that transcatheter implantation of balloon-expandable valves in severe calcific mitral valve disease is feasible in carefully selected patients. However, there have been important complications including valve embolization, LVOT obstruction, and catheter-induced ventricular perforation with the transseptal approach. These complications have not been reported in the literature.

We are currently working on a global multicenter registry to collect and report all of our outcomes. Interestingly, significant paravalvular leak has not been a frequent problem. Perhaps the native leaflets seal the gap between the round stent frame and the oval native annulus during systole, preventing significant paravalvular regurgitation. There is a growing interest in the use of this technology for this patient population. However, more data are needed to determine methods for annulus sizing, proper valve size selection, prevention and treatment of complications including embolization and LVOT obstruction, and the best delivery method. For that reason, the MITRAL (Mitral Implantation of Transcatheter Valves Native Mitral Stenosis) trial was recently initiated. This is a physician-sponsored, US Food and Drug Administration–approved investigational device exemption trial aiming to evaluate the safety and feasibility of using the Sapien XT valve in severe calcific native mitral stenosis. Enrollment started in February 2015 and is currently ongoing at six participating sites in the United States. We are optimistic that this trial will generate important knowledge that can be used to improve the patient selection process and therefore achieve better outcomes. The details of this trial can be found at www.clinicaltrials.org (NCT02370511).

CONCLUSION

Transcatheter mitral valve replacement might evolve into an acceptable alternative for patients with severe mitral regurgitation or calcific stenosis of native mitral valves who are not candidates for conventional mitral valve surgery. However, this field is at a very early stage,

and progress will be significantly slower than the development of TAVR due to the complexity of the mitral valve anatomy and its pathology. We have learned important lessons during this early experience, and many challenges exist with the currently available technology. New valve designs and delivery methods may improve technical success. Optimizing the patient selection process by using multimodality imaging tools to accurately measure the annulus size and evaluate the risk of LVOT obstruction is essential to minimizing complications. Similarly, carefully selecting candidates and avoiding patients at the end of their disease process when treatment is futile might also improve the overall outcomes. ■

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