

Transcatheter Valve Implantation for Calcific Mitral Stenosis

TMVR with aortic THV devices might evolve into an acceptable alternative for selected patients with severe mitral annular calcification.

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Mitral annular calcification (MAC) is a chronic degenerative process of the mitral valve ring associated with risk factors for atherosclerosis. Data from the Framingham Heart Study showed that patients with MAC are elderly, often female, have multiple comorbidities, and are at higher risk of cardiovascular disease, cardiovascular death, and all-cause mortality.¹⁻³ The surgical risk for mitral valve replacement is very high due to the comorbidities and technical challenges related to calcium burden, with potential serious complications including rupture of the posterior wall of the left ventricle.^{4,5} Many patients with severe valvular dysfunction and severe MAC are not offered standard mitral valve surgery due to their high surgical risk. Transcatheter mitral valve replacement (TMVR) has been performed in this patient population with the compassionate use of aortic transcatheter heart valves (THVs) in the mitral position.

INITIAL EXPERIENCE WITH TMVR IN MAC

The first successful TMVR (beating-heart procedure) in a native mitral valve with severe MAC was reported by Hasan et al using a Sapien XT valve (Edwards Lifesciences) via a surgical transapical approach.⁶ A report by Sinning et al also describes a successful implantation of a Sapien XT valve in a native mitral valve via a transapical approach.⁷ Both procedures were performed in patients with severe calcific mitral stenosis and MAC who were not candidates for mitral

valve surgery. Ferrari et al reported the first transcatheter implantation of a Sapien XT valve in a native mitral valve via a transatrial approach (on-pump fibrillating heart).⁸ A 29-mm Sapien XT valve was implanted successfully under direct visualization via transatrial approach in a patient with a previously placed CoreValve device (Medtronic) in the aortic position. The Sapien XT valve was fixed to the mitral annulus with three sutures.

Guerrero et al reported the first-in-human percutaneous implantation of a balloon-expandable transcatheter valve in a native mitral valve.⁹ A 26-mm Sapien valve (Edwards Lifesciences) was used to treat a patient with severe calcific mitral stenosis who was not a candidate for standard mitral valve surgery, nor a candidate for surgical transapical access given his extremely high surgical risk. The guidewire was externalized through a sheath percutaneously placed in the left ventricle via apical needle puncture to improve coaxiality and support during transseptal valve deployment. Fassa et al reported the first transcatheter implantation of a Sapien XT valve in a native mitral valve using a percutaneous transseptal approach without externalizing the wire through the left ventricle, which is the least invasive approach.¹⁰ Himbert et al reported a series of four patients with severe MAC treated with the use of a Sapien XT valve. Two patients had severe mitral stenosis, and two had severe mitral regurgitation (MR). The Sapien XT valve was implanted via a transseptal approach in all patients.¹¹

Several other reports detail the use of newer aortic THV technologies, such as the Lotus (Boston Scientific Corporation) and Direct Flow valves (Direct Flow Medical), in the mitral position for severe MAC.^{12,13} There continues to be a growing interest for TMVR in patients with MAC.

TMVR IN MAC MULTICENTER GLOBAL REGISTRY

Although the initial case reports were encouraging regarding the technical feasibility of TMVR, the safety and efficacy of this procedure as well as the incidence of unreported complications were unknown. The TMVR in MAC Global Registry was created to collect outcomes data of similar procedures performed worldwide to better understand its safety and efficacy in a larger patient population. The registry was initiated in October 2013. Centers around the world with experience in TMVR using balloon-expandable valves in patients with MAC were invited to participate.

The outcomes of the first 64 patients from 32 centers in North America, Europe, and South America who underwent TMVR with the compassionate use of a balloon-expandable THV between September 2012 and July 2015 were recently published by Guerrero et al.¹⁴ The mean age of the patients was 73 ± 13 years, 66% were women, and they had multiple comorbidities, including previous aortic valve replacement (54.8%). The mean Society of Thoracic Surgery score was 14.4 ± 9.5 , and left ventricular ejection fraction was preserved in most patients ($59.5\% \pm 11.3\%$). The primary mitral valve pathology was stenosis in 93.5%, and 6.5% primarily had MR. Mean mitral valve gradient (MVG) in patients with stenosis was 11.4 ± 4.4 mm Hg, and mean mitral valve area (MVA) was 1.18 ± 0.51 cm². Most patients were in New York Heart Association (NYHA) class III or IV (91.9%).

Procedural Results

Edwards valves were used in 95.3% of the cases (Sapien in 7.8%, Sapien XT in 59.4%, Sapien 3 in 28.1%), and the Inovare valve (Braile Biomedical) was used in 4.7%. Transapical and transeptal approaches were used in the majority of cases, 45.3% and 40.6%, respectively. An

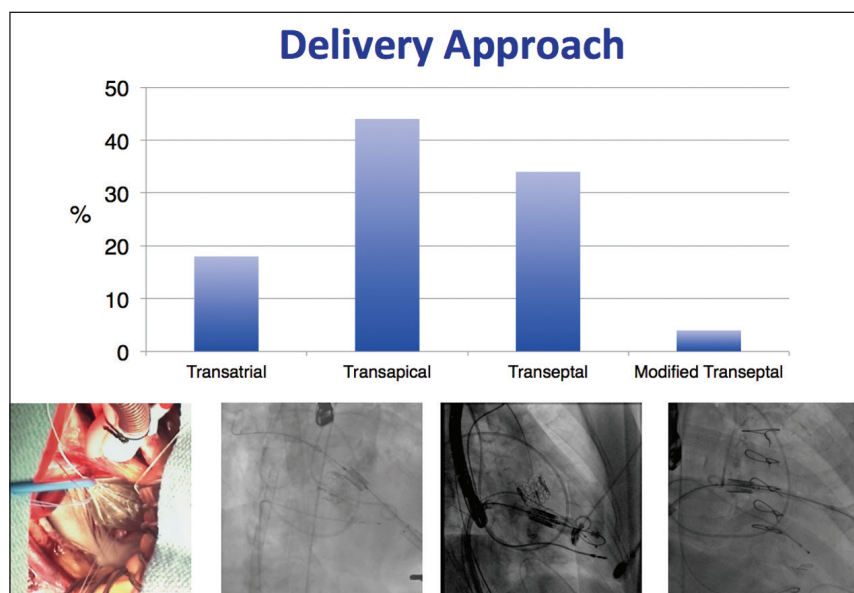


Figure 1. Delivery approaches used for TMVR in the global registry.

open surgical transatrial approach was used to deliver the THV under direct visualization in 14.1% of the cases. Two to three sutures were used in the majority of cases to help secure the stent frame to the annulus (Figure 1). Technical success according to the Mitral Valve Academic Research Consortium criteria was achieved in 46 of the 64 patients (72%), primarily limited by the need for a second THV in 11 (17.2%) patients. At the end of the procedure, the mean MVG was 4 ± 2.2 mm Hg, the mean MVA was 2.2 ± 0.95 cm², and paravalvular regurgitation was mild or absent in all patients. Six patients (9.3%) had severe left ventricular outflow tract (LVOT) obstruction with hemodynamic compromise after valve deployment (average peak LVOT gradient, 72 mm Hg). Four valves embolized to the left atrium (6.25%), all during the index procedure. There were no cases of annular rupture or perforation reported.

Thirty-Day Outcomes

The 30-day mortality was 29.7% (cardiovascular, 12.5%; noncardiac, 17.2%). Thirty-day follow-up echocardiographic data were available for 22 patients. Mean MVG was $5.9 (\pm 2.1)$ mm Hg with a mean MVA of $2.3 (\pm 0.8)$ cm². Eighteen patients (81.8%) had zero to trace MR, and four (18.2%) had mild MR; moderate to severe MR was not seen. The mean LVOT gradient was $15 (\pm 17.8)$ mm Hg. Most survivors reported significant improvement in symptoms. At 30 days, 29 of the 37 patients (78%) with 30-day clinical follow-up data were NYHA class I or II (Figure 2).

Outcomes Relative to Experience

An update of the outcomes in this registry was recently presented by Guerrero et al in a late-breaking trials session at EuroPCR 2016.¹⁵ This update included an analysis of outcomes of 104 patients divided in tertiles in chronological order according to the date of the procedure. Most complications occurred in the first tertile of the patients, and improved outcomes were observed in the second and third tertiles of the experience. The technical success in the first tertile was 62.5%, improved to 84.4% in the second tertile, and was 80% in the third tertile. The 30-day mortality was 37.5% in the first tertile, decreased to 21.9% in the second tertile, and decreased to 15% in the last tertile (Table 1). Although there is a steep learning curve for this procedure, these results are encouraging and suggest that sharing knowledge with other operators may help improve outcomes.

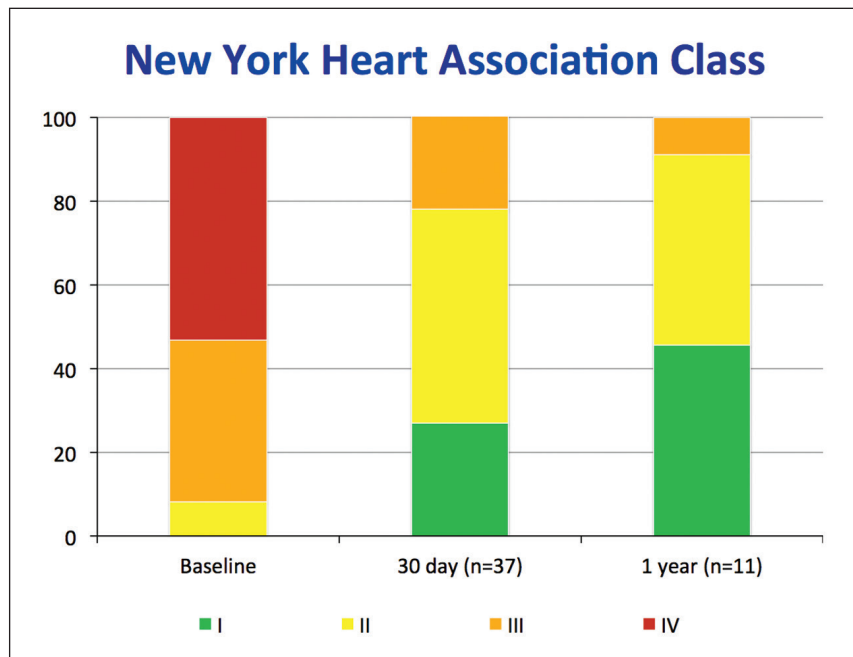


Figure 2. NYHA class at baseline and after TMVR.

ROLE OF CARDIAC IMAGING

Only few patients treated in the early experience were not evaluated with cardiac CT. Cardiac CT has been the most accepted method for annulus sizing, and it may also

TABLE 1. CLINICAL OUTCOMES RELATIVE TO EXPERIENCE

Outcome	First Tertile (n = 32) n (%)	Second Tertile (n = 32) n (%)	Third Tertile (n = 40) n (%)
Technical success*	20 (62.5%)	27 (84.4%)	32 (80%)
30-day mortality	12 (37.5%)	7 (21.9%)	6 (15%)
Complications			
Valve embolization	3 (9.3%)	1 (3.1%)	0
LVOTO	4 (12.5%)	2 (6.2%)	5 (12.5%)
Need for a second valve	7 (21.9%)	3 (9.3%)	2 (5%)
Cardiac perforation	2 (6.25%)	0	0
Conversion to open surgery	4 (12.5%)	0	0

Abbreviations: LVOTO, left ventricular outflow tract obstruction; MVARC, Mitral Valve Academic Research Consortium.

*By MVARC criteria.

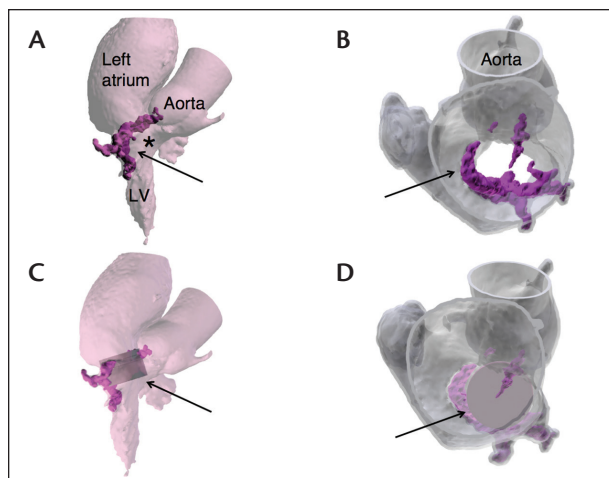


Figure 3. Computer-aided design images show the amount and distribution of calcium (arrows) and LVOT space (asterisk) (A, B). A 29-mm cylinder is used to simulate a 29-mm balloon-expandable valve at the 80/20 position (80% ventricular and 20% atrial) (C, D). LV, left ventricle.

provide essential information for preprocedural planning. It helps evaluate the amount and distribution of calcium in an attempt to predict valve anchoring and features that may assist in predicting LVOT obstruction, including the aortomitral angle, anterior leaflet length, size of the left ventricular cavity, presence of septal hypertrophy, and the change in the residual LVOT space after valve implantation using simulation modeling (Figures 3 and 4).¹⁶ Cardiac CT is also helpful in planning the site and trajectory of transapical or transseptal access.

PROSPECTIVE CLINICAL TRIALS

The results from the multicenter global registry are encouraging, but more data are needed to determine better patient selection, methods for annulus sizing, proper valve size selection, and prevention and treatment of complications, including embolization and LVOT obstruction. For that reason, the MITRAL (Mitral Implantation of Transcatheter Valves) trial was recently initiated. The MITRAL trial is a physician-sponsored, US Food and Drug Administration–approved, investigational device exemption trial aiming to evaluate the safety and feasibility of the Sapien XT and Sapien 3 in

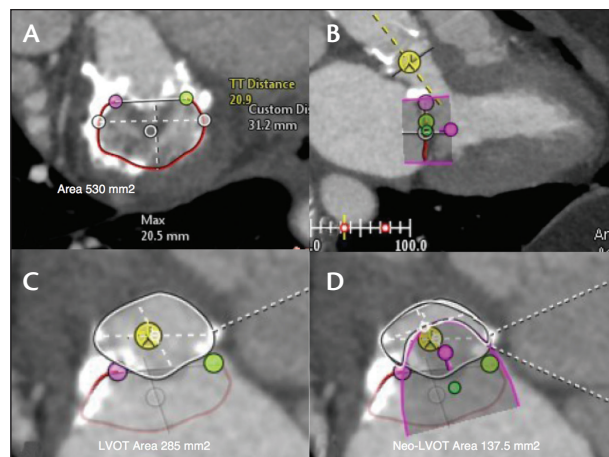


Figure 4. Cardiac CT-based measurement of the calcified mitral annulus using 3Mensio Structural Mitral Workflow version 8.0 (Pie Medical Imaging) (A). A cylinder in pink is used to simulate a 26-mm balloon-expandable valve (B). The white circle represents the measured LVOT area (C). The white circle represents the estimated Neo-LVOT area after implantation of a 26-mm balloon-expandable valve (D).

patients with severe native mitral disease and severe MAC who are not candidates for standard surgical mitral valve replacement (NCT02370511) (the trial is partially funded by a research grant from Edwards Lifesciences). There are three arms in the MITRAL study: a valve-in-MAC arm, a valve-in-ring arm, and a valve-in-valve (Figure 5). Enrollment started in February 2015 and is currently ongoing at 10 participating sites. We anticipate that this trial may help provide further insights to improve overall clinical outcomes.

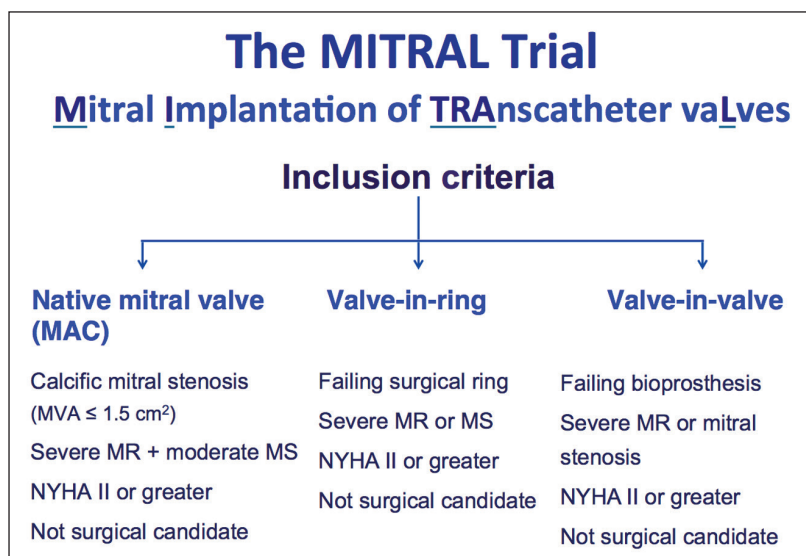


Figure 5. Inclusion criteria for the MITRAL trial.

CONCLUSION

TMVR with aortic THV devices might evolve into an acceptable alternative for selected patients with severe MAC who are not candidates for conventional mitral valve surgery. However, this field is at a very early stage. Preliminary data from a global multicenter registry are encouraging, but data from a prospective clinical trial are needed. We invite physicians to enroll patients in the MITRAL trial. Details can be found at <https://clinicaltrials.gov/ct2/show/NCT02370511>. ■

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