Chapter

Transcatheter Mitral Valve Replacement: Evolution and Future Development

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Abstract

We will review transcatheter mitral valve replacement (TMVR) and discuss this evolving cutting edge procedure in terms of types (valve in valve, valve in ring and valve in mitral annular calcification MAC), clinical indications, pre-procedural planning and value of pre-procedural imaging including computed tomography role, technical challenges encountered in these procedures, potential complications for each type of TMVR, and potential strategies to mitigate and avoid such complications, We will review the currently available devices dedicated for mitral valve replacement, with a summary of their preliminary data and early outcome results. We will also discuss knowledge gaps and ideas for future research.

Keywords: Transcatheter mitral valve replacement, valve in valve, valve in ring, valve in mitral annular calcification

1. Introduction

Valvular heart disease affects >100 million patients worldwide, which is estimated to increase further with the aging population and a subsequent increase in degenerative valve disease [1]. Based on analysis of the Society of Thoracic Surgery (STS) National Database, there are >40,000 mitral valve replacements being performed annually in the United States (US), with shift from mechanical to bioprosthetic valve replacements [1]. It is known that redo mitral valve surgery is associated with higher mortality compared to first mitral surgery; with 30-day mortality ranging from 6% for elective second mitral valve surgery and 17.8% for emergency surgery [2]. The risk of a third or fourth surgery is even higher; with 30-day mortality reaching up to 44% in urgent surgery [3]. As such, Transcatheter mitral valve replacement (TMVR) using aortic balloon-expandable transcatheter heart valves (THV) has been increasingly performed for patients with severe mitral valve disease who are not candidates for surgery [4]; as it emerged as a less invasive alternative option for these patients with relatively lower mortality than the predicted STS predicted rates of mortality [4]. Moreover, dedicated devices for TMVR have been developed and some are currently being studied [5–10]. Results of the clinical outcomes of TMVR are promising, but anatomical differences between mitral bioprosthetic valves, annuloplasty rings, and severely calcified mitral annulus are associated with specific procedural challenges for TMVR procedures [1, 4].

2. Types of TMVR

There are three main types of TMVR: 1) valve-in-valve (ViV) for severe mitral valve disease due to degenerated mitral bioprosthetic valves, 2) valve-in-ring (ViR) for failed surgical repairs with annuloplasty rings, and 3) valve-in-mitral annular calcifications (ViMAC) for native mitral valve disease with severe MAC who are poor surgical candidates [1]. Mitral ViV for high surgical risk patients was approved by the Food and Drug Administration (FDA) in the United States (US) in 2017, while mitral ViR and ViMAC remain off-label at this current time [4]. The role of TMVR in native mitral valve disease, whether MR or mitral stenosis, is currently being studied using various device types and designs. We will discuss these separately under the dedicated TMVR device section.

3. Scientific evidence supporting TMVR

The scientific evidence supporting TMVR is based on observational data, mostly from registries, in North America and Europe [1, 4–15], summarized in **Table 1**. Several studies showed data on outcomes of mitral ViV, ViR, ViMAC from single or multi-center registries; with consistent results demonstrating overall better outcomes for mitral ViV procedures compared to mitral ViR and ViMAC [1, 4–15].

The role of mitral ViV, ViR, and ViMAC has been evaluated in a prospective early feasibility clinical trial, the MITRAL trial (Mitral Implantation of Transcatheter Valves, NCT 02370511), which is the first prospective study assessing outcomes of TMVR in all of the three separate subtypes. The results of the trial have been recently published [16–18].

Author, year published	Number of patients	Major outcomes
Guerrero et al. [11]	64 patients with ViMAC	• Technical success was 72% • 30-day all-cause mortality was 29.7% • 84% of the survivors with follow-up data available were in New York Heart Association (NYHA) class I or II at 30 days
Yoon et al. [13]	248, 176 patients undergoing ViV, 72 patients undergoing ViR	• ViR had lower technical success (83.3% vs. 96.0%; p = 0.001) due to more frequent second valve implantation (11.1% vs. 2.8%; p = 0.008) • ViR had higher 1-year all-cause mortality rate (28.7% vs. 12.6%; log-rank test, p = 0.01).
Eleid et al. [14]	87 patients (ViV = 60, ViR = 15, ViMAC = 12)	• Procedural success was 97% in ViV, and 74% in ViR and ViMAC. • 30-day survival free of death and cardiovascular surgery was 95% in ViV and 78% in ViR and ViMAC • 1-year survival free of death and cardiovascular surgery was 86% in the ViV compared with 68% in ViR and ViMAC
Guerrero et al. [5]	106 patients with MAC	• 30-day and 1-year all-cause mortality was 25% and 53.7%, respectively. • Most patients who survived 30 days were alive at 1 year and majority were in NYHA functional class I or II

Author, year published	Number of patients	Major outcomes
Urena et al. [12]	91 patients (ViV 37.3%, ViR in 33.0%, and ViMAC in 29.7%)	• mortality rate at 30 days was 7.7% without significant differences between groups • The cumulative rates of all-cause mortality at 1-year and 2-year follow-up were 21.0% and 35.7%, respectively, with higher late mortality in patients with MAC.
Yoon et al. [1]	521 patients (322 ViV, 141 ViR, and 58 ViMAC)	• ViMAC was associated with higher all-cause mortality in comparison to ViR and ViV at follow up of 30 days (34.5% vs. 9.9% vs. 6.2%; log-rank P < 0.001) and 1 year (62.8% vs. 30.6% vs. 14.0%; log-rank P < 0.001).
Werner et al. [15]	7 patients (3 ViV, 1 ViR, 3 ViMAC)	• clinical success with functional improvement of at least one NYHA class was achieved in all patients with in-hospital mortality rate of 14% (1/7) • After hospital discharge, no death occurred, and clinical improvement remained stable at 1 year
Guerrero et al. [4]	903 patients (680 ViV, 123 ViR, 100 ViMAC)	• Technical and procedural success were higher in ViV. • In-hospital mortality (ViV = 6.3%, ViR = 9%, ViMAC = 18%; *P* = 0.004) and 30-day mortality (ViV = 8.1%, ViR = 11.5%, ViMAC = 21.8%; *P* = 0.003) were higher in ViMAC.

Table 1.
Summary of observational TMVR studies with their major outcomes.

In the MITRAL trial, in which 30 patients undergoing transseptal mitral ViV were enrolled between July 2016 and October 2017, technical success was achieved in 100% of cases with 30-day all-cause mortality of 3.3%, which remained unchanged at 1 year. At 1-year follow-up, the vast majority of patients were in New York Heart Association (NYHA) functional class I or II [16].

Similarly, in the MITRAL trial assessing patients undergoing transeptal mitral ViR, 30 patients were studied with results showing technical success of 66.7% (driven primarily by need for a second valve in 6 patients), all-cause mortality of 6.7% at 30 days and 23.3% at 1 year. Similar to ViV study, the vast majority of patients were in NYHA class I or II at 1 year [17].

MITRAL trial assessed ViMAC by prospectively enrolling 31 patients and was challenged by a high proportion of patients with threatened left ventricular outflow tract (LVOT) obstruction. As such mitigation strategies were devise in the form of alcohol septal ablation and trans-atrial valve implantation accompanied by anterior leaflet resection. As such as high proportion of patients received trans-atrial TMVR (48.4%), while transseptal access was used in 48.4%, and transapical access 3.2%. Technical success was achieved in 74.2% of cases, overall 16.7% (trans-atrial, 21.4%; transseptal, 6.7%; transapical, 100% [n 1/4 1]; p = 0.33) all-cause mortality rate at 30 days and 34.5% (trans-atrial, 38.5%; transseptal, 26.7%; p = 0.69) mortality at 1 year. Similar to ViV and ViR study, the vast majority of patients were in NYHA class I or II at 1 year [18]. Importantly, this trial introduced preemptive alcohol septal ablation as a mitigation strategy to prevent LVOT obstruction [18].

4. Procedural planning

Successful TMVR depends on accurate sizing of the mitral annulus and avoidance of LVOT obstruction. In the absence of a validated standard method for mitral annulus sizing at the present time, operators have extrapolated from transcatheter aortic valve replacement (TAVR) experience and used a variety of sizing approaches including echocardiography, 3-dimensional (3D) transesophageal echocardiography, cardiac CT, and balloon sizing techniques [10]. Cardiac CT is the most accepted imaging modality for annulus sizing. In general, pre-procedural imaging constitutes of contrast-enhanced CT to identify critical cardiac structures and anatomy, including sizing of the mitral annulus, which is the basal-most structure of the mitral leaflets [19]. In addition to annular sizing, CT also provides essential information for pre-procedural planning, including the amount and distribution of calcifications, as well as predictors of LVOT obstruction; the left ventricular cavity size, anterior leaflet length, aorto-mitral angulation, septal hypertrophy, among other features. CT is also helpful in identifying the trajectory and site of access, whether transapical or transseptal [10, 19].

Data utilizing 2-dimensional (2D) echo imaging correlated acute angulation of the mitral aorta-outflow-angle (mAOA) with higher risk of LVOT obstruction compared with that of more obtuse mAOA. However, risk of LVOT obstruction is not solely based on mAOA; this is because LVOT is a 3D anatomical structure and mAOA on 2D echo images may not provide the comprehensive assessment needed. CT overcomes this limitation as it provides a 3D assessment. Both the prosthetic valve and the anterior displacement of anterior mitral leaflet can result in severe LVOT obstruction. Additionally, utilization of computer-aided designs and 3-D printed models allows us to test devices in patient-specific anatomy and at different angulations and depths with estimation of risk for LVOT obstruction [19].

LVOT obstruction is a fatal complication; thus, pre-procedural planning in an attempt to predict neo-LVOT provides a key step in the success of TMVR procedure. In a multicenter study of 38 patients undergoing TMVR using balloon-expandable valves for severe mitral valve dysfunction because of degenerative surgical mitral ring, bio-prosthesis, or severe native mitral stenosis from severe mitral annular calcification, the investigators defined LVOT obstruction as increase of 10 mmHg or more in LVOT peak gradient following TMVR and found that 7 of the 38 patients had LVOT obstruction, with CT neo-LVOT surface area correlating well with measurements after TMVR [20]. Yoon and colleagues in their study of 194 patients undergoing TMVR found that LVOT obstruction was associated with higher procedural mortality compared with patients without LVOT obstruction (34.6% vs. 2.4%; $p < 0.001$) [21].

5. Technical considerations

The first few TMVR procedures were performed using a surgical transapical [6, 7] or open trans-atrial [8, 9] approach, but subsequent reports described successful implantation with a completely percutaneous trans-femoral transseptal approach [10–12]. Transseptal access has been the default access in ViV and ViR in the MITRAL trial, while both transseptal and trans-atrial access have been equally used in ViMAC [16–18]. All-cause 30-day mortality in ViMAC was 16.7% (trans-atrial, 21.4%; transseptal, 6.7%; transapical, 100% [n = 1]; p 0.33) and 1-year mortality was 34.5% (trans-atrial, 38.5%; transseptal, 26.7%; p = 0.69) [18]. These mortality rates are relatively higher than other transeptal or transapical procedures; as studies have shown that the 30-day and 1-year mortality rates were 3.6% and 23.2% for

patients undergoing transseptal transcatheter edge-to-edge repair using MitraClip for secondary mitral regurgitation, and the 30-day and 1-year mortality rates were 8.4% and 25.4% for transapical TAVR [22, 23].

Because the mitral annulus is larger in size compared to aortic valve annulus, TMVR requires larger devices, including prosthesis and delivery systems [10]. Mitral annular calcifications are less common compared with aortic valve calcifications, and their presence may condition the implant of a transcatheter mitral prosthesis. For this purpose, the role of TMVR in presence of considerable annular calcification is less clear, as shown in the MAC (mitral annular calcification) Global Registry, which demonstrated that TMVR was feasible in MAC but associated with relatively high early and midterm mortality at 1 year, although patients who survived at 1-year follow-up had sustained improvement of symptoms [4, 5]. Similarly, the MITRAL trial showed relatively high 1-year mortality in ViMAC patients, but transeptal ViMAC showed promising results with 30-day mortality lower than the predicted STS score, however mortality rates in this population remains higher than other transeptal procedures, including transcatheter edge-to-edge repair using MitraClip [1, 2, 18].

6. Procedural complications

6.1 ViV

Complications in ViV are considered relatively low, with reported LV perforation 0.4%, LVOT obstruction 0.7% and conversion to surgery in 1.3% [1, 4]. Post-procedure mitral valve function was excellent with a median mean mitral valve gradient of 4 mm Hg and residual mitral regurgitation grade of 1+ or less in 98.1%. A second valve was needed in a relatively small proportion of mitral ViV patients (1.5%) and was associated with higher mortality at 30 days. The reasons or mechanisms for which this was associated with higher mortality (residual mitral regurgitation, thrombosis, renal failure) are not known at this time [4].

6.2 VIR

Generally speaking, studies have shown that ViR TMVR is associated with worse outcomes compared with ViV, but better outcomes compared with ViMAC procedures [1, 4, 10, 16–18]; ViR is a more complex procedure than ViV due to the different types of rings (rigid versus nonrigid, complete versus incomplete) and different shapes, which are usually not round predisposing to residual paravalvular leak [1, 4]. There are 3 main challenges in ViR cases: valve anchoring, LVOTO and paravalvular leak. Yoon et al. showed that ViR had a significantly lower technical success rate compared with the ViV group (83.3% vs. 96.0%; $p = 0.001$) due to more frequent second valve implantation (11.1% vs. 2.8%; $p = 0.008$) [1]. Moreover, the investigators found that residual mitral regurgitation moderate or higher at 30 days was more frequent in patients with flexible rings compared with those with semi-rigid rings (44.4% vs. 10.8%, $p = 0.02$) [1]. A study showed that the 30-day mortality was 11.5% in ViR patients with median STS PROM score of 9.3% [4]. The reasons for higher mortality in mitral ViR are probably multifactorial; potentially related to higher procedural complication rates including LVOT obstruction, higher valve embolization rate, residual mitral regurgitation and need for reintervention including conversion to surgery, as well as different baseline characteristics including a lower baseline left ventricular ejection fraction [4]. In fact, the ViR group also had the highest rate of device embolization at 30 days 3.6% compared with mitral ViV 0.2% and ViMAC 1.6% [4].

Guerrero et al. showed 4.9% rate of LVOT obstruction in ViR, which was lower than the 8% in the VIVID registry; this could be related to increased experience in patient selection and risk-reduction strategies. Overall, mitral ViR is observed to have higher rates of LVOTO as compared to ViV, possibly due to the presence of a preserved anterior mitral leaflet. In most ViV cases, the anterior leaflet is no longer present making LVOT obstruction less likely [4].

Guerrero et al. also demonstrated that when comparing outcomes by types of rings (complete versus incomplete, rigid versus nonrigid), there was a larger mitral valve area in incomplete rings versus complete rings [4]. However, there was no statistically significant difference in median mean mitral valve gradients and clinical outcomes between the groups based on the type of ring [4].

6.3 ViMAC

Studies have shown that ViMAC procedures were associated with the lowest technical success and the highest in-hospital and 30-mortality compared with mitral ViR and ViV [1, 4]. Similar to ViR, ViMAC has significant challenges to anchoring, paravalvular leak and LVOTO. The reasons are multifactorial, including presence of multiple comorbidities and technical challenges including the complexity of the mitral valve anatomy; as the native mitral valve is a saddle oval shape being treated with a round transcatheter valve which may lead to paravalvular leak at commissures, non-uniform calcium distribution, and relatively small sized ventricles accompanied by threatened LVOTO [1, 4, 10]. Therefore, there is a frequent need for LVOT modification taking the form of three options: LAMPOON, Alcohol septal ablations or surgical resection of the anterior leaflet.

LVOT obstruction is considered the Achilles' heel of TMVR, especially in ViMAC. It has limited treatment options and was the strongest predictor of 30-day and 1-year mortality in the TMVR in MAC Global Registry [4, 5, 10]. Studies have shown that LVOT obstruction rate in ViMAC procedures is at least 10% [1, 4, 5, 10]. One factor that could contribute to different rates of LVOT obstruction observed among registries may be the different definitions used, such as LVOT obstruction with hemodynamic compromise versus increase in mean LVOT gradient of ≥10 mm Hg from baseline. Another important factor may be improved screening process with cardiac computed tomography to predict LVOT obstruction and strategies to prevent it [1, 4]. Potential predictors of LVOT obstruction are the angle of the mitral valve in relation to the LVOT long axis, the presence of small LV cavity, bulging or severe hypertrophy of the basal interventricular septum, long anterior mitral valve leaflets, dynamic alterations as the pushing of the native anterior leaflet toward the LVOT, prosthesis protrusion and device flaring [4, 5, 10, 19–21].

7. Strategies to mitigate procedural complications

Cardiac computed tomography to measure the expected neo-LVOT area to assess the risk of TMVR-induced LVOT obstruction identifying patients at risk facilitates implementation of measures to decrease such risk including preemptive alcohol septal ablation, percutaneous laceration of the anterior mitral leaflet, surgical excision of the anterior mitral leaflet during trans-atrial TMVR or deciding not to perform the procedure at all [1, 4, 10, 24, 25].

Several strategies to prevent or treat LVOT obstruction caused by TMVR have been developed and studied. These strategies include: 1) preemptive alcohol septal ablation in patients at risk for TMVR-induced LVOT obstruction who have favorable anatomy for alcohol ablation as shown in the MITRAL trial [18], 2) percutaneous

laceration of the anterior leaflet to decrease the risk of TMVR-induced LVOT obstruction in TMVR procedures (The LAMPOON trial; Laceration of the Anterior Mitral Leaflet to Prevent Outflow Obstruction During TMVR) [24, 25], 3) possibly trans-atrial surgical access for TMVR in severe MAC, as evaluated by the SITRAL Trial (Surgical Implantation of Transcatheter Valves) [1, 4, 24, 25].

8. Dedicated TMVR devices

In addition to the balloon expandable valves which were initially designed for the aortic valve and have been used in mitral valve interventions, several valve designs dedicated to the mitral valve have been developed and studied in several studies with a relatively small number of patients, with some promising results [10]. These dedicated mitral valves are summarized in **Figure 1** and **Table 2**.

The CardiAQ (Edwards Lifesciences Inc) valve is a nitinol self-expanding tri-leaflet valve, composed of bovine pericardial tissue, which was the first dedicated device for TMVR in 2012 in high-risk patients with severe MR. This was followed by the second generation of the valve, which was used for the first time in 2014 [26]. The new redesigned version was renamed as the EVOQUE valve. It offers both a transapical and transfemoral-transseptal approach. The EVOQUE valve offered enhanced maneuverability and depth control, and lower ventricular projection to avoid LVOT obstruction. Currently, the Edwards EVOQUE TMVR Early Feasibility Study (NCT02718001) is recruiting and will assess feasibility at 30 days. The RELIEF (Reduction or Elimination of Mitral Regurgitation in Degenerative or Functional Mitral Regurgitation With the CardiAQ-Edwards™ Transcatheter Mitral Valve, NCT02722551) trial was stopped by the Edwards Company for further design validation. From the preliminary results presented, 13 patients have been treated with technical success of 92% and high mortality rate of 45% at 30 days [10, 27].

The Tiara (Neovasc Inc., Canada) valve is a bioprosthetic valve; it constitutes of bovine pericardial tissue, which is mounted inside a nitinol frame. It is self-expanding and has a relatively large atrial skirt, which decreases the risk of paravalvular leaks. The first implant of Tiara valve was performed in Vancouver in 2014. The two major studies of the Tiara valves, TIARA-I (Early Feasibility Study of the

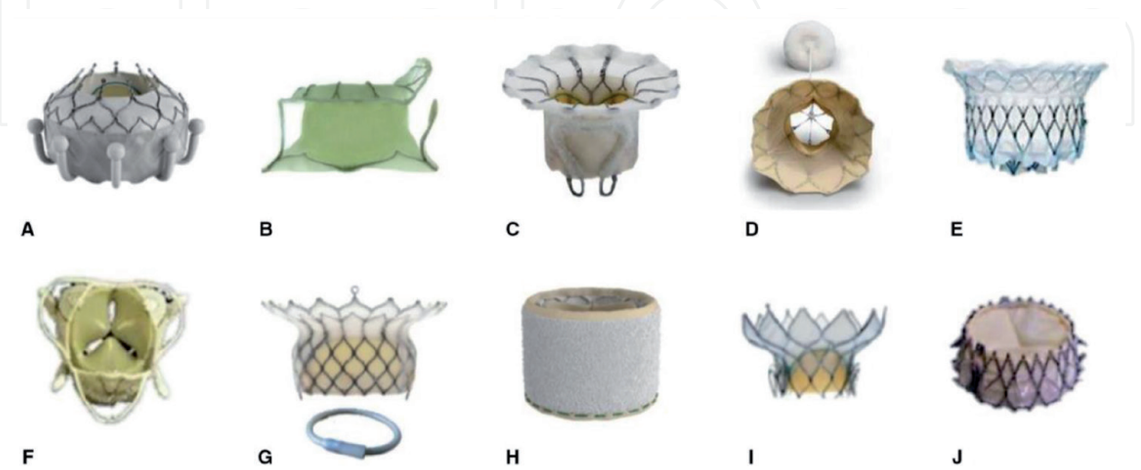

Figure 1.
Current transcatheter mitral valve replacement devices. **A**, *CardiAQ/EVOQUE (Edwards Lifesciences Inc).* **B**, *Tiara (Neovasc Inc., Canada).* **C**, *FORTIS (Edwards Lifesciences Inc).* **D**, *Tendyne (Abbott Inc).* **E**, *intrepid (Medtronic Inc).* **F**, *caisson (LivaNova, UK).* **G**, *HighLife bioprosthesis and sub-annular implant (HighLife SAS, France).* **H**, *SAPIEN M3 (Edwards Lifesciences Inc).* **I**, *Cardiovalve (Cardiovalve, Israel).* **J**, *Navi-gate (NaviGate cardiac structures, Inc., CA). Obtained with permission from Testa et al. publication [10].*

Device name	Brief description	Number of patients	Primary outcomes
CardiAQ-EVOQUE (Edwards Lifesciences Inc)	• Nitinol self-expanding tri-leaflet valve, composed of bovine pericardial tissue • Transapical/transseptal • EVOQUE valve: new redesigned version of the valve	13	Technical success, 92% Mortality at 30 days, 45%
Tiara (Neovasc Inc., Canada)	• Nitinol self-expanding tri-leaflet valve of bovine pericardial tissue • Transapical	30	Technical success, 90% Mortality at 30 d, 10%
FORTIS (Edwards Lifesciences Inc)	• Nitinol self-expanding tri-leaflet valve of bovine pericardial tissue • Transapical	13	Technical success, 76.9% Mortality at 30 d, 38.5%
Tendyne (Abbott Inc)	• Self-expanding tri-leaflet valve of porcine pericardial tissue, mounted on nitinol double-frame stent • Transapical	100	Technical success, 96% Mortality at 30 d, 6%
Intrepid (Medtronic Inc)	• Nitinol self-expanding tri-leaflet valve of bovine pericardial tissue • Transapical (transseptal approach under development)	50	Technical success, 96% Mortality at 30 d, 14%
Caisson (LivaNova, UK)	• Nitinol self-expanding tri-leaflet valve of porcine pericardial tissue, with a D-shaped anchor • Transseptal	NA	NA
HighLife (HighLife SAS, France)	• Two separate components: nitinol alloy-based self-expanding frame with a tri-leaflet valve of bovine pericardium tissue and a sub-annular implant • Transapical/trans-atrial (transseptal approach under development)	Anecdotal cases	Promising results in anecdotal cases
SAPIEN M3 (Edwards Lifesciences Inc)	• Nitinol docking system and a modified SAPIEN 3 valve • Transseptal	15	Technical success, 86.7% Mortality at 30 d, 0%
Cardiovalve (Cardiovalve, Israel)	• Dual nitinol frame with a tri-leaflet bovine pericardium valve • Transseptal	5	Technical success, 100% Mortality at 30 d, 60%
Cephea (Cephea Valve Technologies)	• Self-expanding double-disk and tri-leaflet bovine pericardium tissue • Transseptal/trans-atrial	Preclinical models First-in-human cases	Promising results in reported cases
AltaValve (4C Medical Technologies Inc)	• Self-expanding supra-annular device, with a bovine tissue valve mounted into a spherical nitinol frame • Transapical	Preclinical models Anecdotal first-in-human case (n = 1)	Promising results in models and reported case

Device name	Brief description	Number of patients	Primary outcomes
NaviGate (NaviGate Cardiac Structures Inc)	• Nitinol self-expandable system with several annular winglets • Transapical	Case report	Promising result in reported cases.

Table 2.
Summary of dedicated TAMR devices and primary outcomes of available early feasibility studies.

Neovasc Tiara Mitral Valve System) (NCT02276547) and the latest TIARA-II (Tiara Transcatheter Mitral Valve Replacement Study), are actively enrolling patients, with promising preliminary results in 71 patients, mostly in functional MR (61%), showing 94% technical success rate, with a mortality rate of 11.3% at 30 days [28, 29].

The FORTIS (Edwards Lifesciences Inc) valve is a self-expanding bioprosthetic valve of bovine pericardial tissue. The first FORTIS implant was performed in 2014. Preliminary results demonstrated outcomes of 13 patients with procedural success of 76.9%. In the early experience, the study was put on hold due to reported valve thrombosis [30].

The Tendyne MV system (Abbott Inc) is a self-expanding porcine pericardial valve, which is mounted on a nitinol stent. It is implanted using the transapical approach and the device is anchored to the annulus using apical tethers. The first Tendyne MV implant was performed in 2014. The Feasibility Study of the Tendyne Mitral Valve System for Use in Subjects With Mitral Annular Calcification (NCT03539458) of the first 100 patients showed that the technical success rate was 97% with no periprocedural mortality and 30-day mortality rate of 6% [31]. Most patients (98.8%) had non-significant MR at 30 days [31]. Importantly, the SUMMIT (Clinical Trial to Evaluate the Safety and Effectiveness of Using the Tendyne Mitral Valve System for the Treatment of Symptomatic Mitral Regurgitation; NCT03433274) is an ongoing multi-center clinical trial randomizing patients to TMVR using the Tendyne valve versus conventional mitral valve surgery, with goal to enroll 1010 patients and expected completion year in 2026.

The Intrepid (Medtronic Inc) valve is a bovine pericardial valve fixed onto a self-expanding nitinol frame. The valve is implanted via transapical access in the majority of cases, but a transseptal approach is being developed. The first implant was performed in 2014. An initial pilot study enrolled 50 high-risk patients with MR and reported 96% success rate, 14% 30-day mortality rate and trivial-trace or mild residual MR at 30 days in all patients [32]. The multicenter randomized APOLLO (Transcatheter Mitral Valve Replacement With the Medtronic Intrepid TMVR System in Patients With Severe Symptomatic Mitral Regurgitation; NCT03242642) trial is still ongoing with patients randomized in a 1:1 fashion to the Intrepid valve versus conventional mitral valve surgery. Outcomes will be evaluated at 30 days, 6 months, and 1 year, with up to 5 years follow-up duration, and estimated study completion date in 2025 [10].

The HighLife (HighLife SAS, France) valve is a 2-component system. The prosthetic valve is implanted in the mitral position and has an anchoring system placed by the trans-arterial retrograde approach in the sub-annular position [10]. Anecdotal initial cases are reported showing acceptable results of the valve [33]. A feasibility trial (NCT02974881) is still active.

The SAPIEN M3 (Edwards Lifesciences Inc) valve is a modified SAPIEN 3 valve. It is implanted using the transseptal approach. It uses nitinol docking system, which allows anchoring of device [10]. From the initial results of feasibility study in 15 patients, technical success was achieved in 86.7%, MR reduction was achieved in

93.3% and no mortality was reported at 30 days [34]. The ENCIRCLE trial is an ongoing study designed to assess the outcomes of the SAPIEN M3 device in 400 patients (NCT04153292).

The Cardiovalve (Cardiovalve, Israel) valve is a bovine pericardial valve mounted on dual nitinol. It is usually implanted using the transseptal approach. The system allows multi-steerable catheter utilization, which provides better control of the device [10]. The AHEAD (European Feasibility Study of the Cardiovalve Transfemoral Mitral Valve System; NCT03339115) study is designed to assess the outcomes of Cardiovalve system in MR. The first 5 cases showed 100% of technical success with significant reduction of MR and absent or non-significant paravalvular leak [35].

The Cephea (Cephea Valve Technologies) system is a repositionable and recapturable frame valve and usually implanted using the transseptal approach. The frame structure allows adequate anchoring independent of the sub-valvular structures. The valve was tested in preclinical models with good performance at 90 days [36]. In addition, early experience with the Cephea device has been reported in 3 patients after the first in-human case with 100% technical success [37, 38]. After a median 6-month follow-up, valve function, echocardiographic parameters and patients' functional status were all favorable [38].

The AltaValve (4C Medical Technologies Inc) is a supra-annular device, which constitutes of bovine tissue mounted onto a nitinol frame. It is a self-expanding valve and implanted using the transseptal or transapical approach. Animal studies showed good performance, and a first-in-human case was performed in Canada in 2018, with satisfactory results [10, 39].

The NaviGate (NaviGate Cardiac Structures Inc) valve is a self-expanding valve and constitutes of a nitinol stent frame and multiple annular winglets, to allow anchoring of the device in the mitral annular position. The valve is implanted using transapical approach. The first in-human valve implant was performed in 2015 in Chile [40]. After an initial interest of this valve in mitral valve position, the device was implanted in the tricuspid position for tricuspid regurgitation using transcatheter interventions with trans-jugular or trans-atrial approach [41].

9. Knowledge gaps and ideas for future research

With the recent advances in TMVR in the most recent years, there remain knowledge gaps and challenges in order to understand the disease and correlate clinical outcomes with this evolving technology. MR is often coexistent with other comorbidities, including valvular disease, such as tricuspid regurgitation, severe pulmonary hypertension, and atrial fibrillation, with significant and independent morbidity and mortality rates [4]. The role of these co-existing factors in this setting is not well-known and should be evaluated in future research.

Studies have shown that TMVR is associated with higher rates of paravalvular leak compared to TAVR; this could be attributed to reduced anatomical support, asymmetrical annulus or asymmetric leaflets in mitral valve compared to aortic valve [4, 10]. Additionally, post-dilation of mitral prosthetic valve could potentially be challenging and risky; due to the close proximity of the mitral valve to the left circumflex artery, the conduction system and the aortic valve. In addition, efforts to avoid damage to sub-valvular structures should be pursued [4, 10]. Future improvement of the dedicated TMVR-specific device design should address these anatomical issues. As we discussed in the previous section, different transcatheter devices have been designed for the treatment of MR (and, in some cases, for off-label treatment of mitral stenosis). Most of the TMVR technologies are still under clinical

investigation. Thus, data about their rates of structural deterioration and durability is limited [10].

At the present time, clinical outcomes we have are based on data of mainly the first and second generation prosthetic valves. Outcomes may potentially improve with newer generation devices, improvement in the process of patient selection, operators' experience and innovations in procedural techniques [4]. Newer generation valves with repositionable and retrievable ability could be of benefit in certain patients. For example, the Lotus valve (Boston Scientific, Marlborough, Massachusetts) and Direct Flow (Direct Flow Medical Inc. Santa Rosa, California) valves have been successfully implanted in patients with severe MAC, however the outcomes of these valves should be assessed in future randomized clinical trials utilizing larger number of patients [11].

In conclusion, we have seen several advances in TMVR in the past decade with promising results. However, there remain challenges that need to be evaluated in future studies in order to optimize our procedural success, device evolution, and clinical outcomes to make this new cutting-edge technology available for high-risk patients.

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References

[1] Yoon SH, Whisenant BK, Bleiziffer S, Delgado V, Dhoble A, Schofer N, Eschenbach L, Bansal E, Murdoch DJ, Ancona Met al.. Outcomes of transcatheter mitral valve replacement for degenerated bioprostheses, failed annuloplasty rings, and mitral annular calcification.**Eur Heart J**. 2019; 40:441-451. doi: 10.1093/eurheartj/ehy590. https://pubmed.ncbi.nlm.nih.gov/30357365/

[2] Jamieson WR, Burr LH, Miyagishima RT, Janusz MT, Fradet GJ, Lichtenstein SV, Ling H. Reoperation for bioprosthetic mitral structural failure: risk assessment. Circulation. 2003 Sep 9;108 Suppl 1:II98-102. doi: 10.1161/01.cir.0000089184.46999.f4. PMID: 12970216.

[3] Expósito V, García-Camarero T, Bernal JM, Arnáiz E, Sarralde A, García I, Berrazueta JR, Revuelta JM. Repeat mitral valve replacement: 30-years' experience.**Rev Esp Cardiol**. 2009; 62:929-932. doi: 10.1016/s1885-5857(09)72658-1

[4] Guerrero M, Vemulapalli S, Xiang Q, Wang DD, Eleid M, Cabalka AK, Sandhu G, Salinger M, Russell H, Greenbaum A, Kodali S, George I, Dvir D, Whisenant B, Russo MJ, Pershad A, Fang K, Coylewright M, Shah P, Babaliaros V, Khan JM, Tommaso C, Saucedo J, Kar S, Makkar R, Mack M, Holmes D, Leon M, Bapat V, Thourani VH, Rihal C, O'Neill W, Feldman T. Thirty-Day Outcomes of Transcatheter Mitral Valve Replacement for Degenerated Mitral Bioprostheses (Valve-in-Valve), Failed Surgical Rings (Valve-in-Ring), and Native Valve With Severe Mitral Annular Calcification (Valve-in-Mitral Annular Calcification) in the United States: Data From the Society of Thoracic Surgeons/American College of Cardiology/Transcatheter Valve Therapy Registry. Circ Cardiovasc Interv. 2020 Mar;13(3):e008425. doi: 10.1161/CIRCINTERVENTIONS.119.008425. Epub 2020 Mar 6. PMID: 32138529. https://www.ahajournals.org/doi/full/10.1161/CIRCINTERVENTIONS.119.008425

[5] Guerrero M, Urena M, Himbert D, Wang DD, Eleid M, Kodali S, George I, Chakravarty T, Mathur M, Holzhey D, Pershad A, Fang HK, O'Hair D, Jones N, Mahadevan VS, Dumonteil N, Rodés-Cabau J, Piazza N, Ferrari E, Ciaburri D, Nejjari M, DeLago A, Sorajja P, Zahr F, Rajagopal V, Whisenant B, Shah PB, Sinning JM, Witkowski A, Eltchaninoff H, Dvir D, Martin B, Attizzani GF, Gaia D, Nunes NSV, Fassa AA, Kerendi F, Pavlides G, Iyer V, Kaddissi G, Witzke C, Wudel J, Mishkel G, Raybuck B, Wang C, Waksman R, Palacios I, Cribier A, Webb J, Bapat V, Reisman M, Makkar R, Leon M, Rihal C, Vahanian A, O'Neill W, Feldman T. 1-Year Outcomes of Transcatheter Mitral Valve Replacement in Patients With Severe Mitral Annular Calcification. J Am Coll Cardiol. 2018 May 1;71(17):1841-1853. doi: 10.1016/j.jacc.2018.02.054. PMID: 29699609. https://www.sciencedirect.com/science/article/abs/pii/S0735109718334934?via%3Dihub

[6] Hasan R, Mahadevan VS, Schneider H, Clarke B. First in human transapical implantation of an inverted transcatheter aortic valve prosthesis totreat native mitral valve stenosis. Circulation 2013;128:e74-6.

[7] Sinning JM, Mellert F, Schiller W, Welz A, Nickenig G, Hammerstingl C. Transcatheter mitral valve replacement using a balloon-expandable prosthesis in a patient with calcified native mitral valve stenosis. Eur Heart J 2013;34:2609.

[8] Wilbring M, Alexiou K, Tugtekin SM, et al. Pushing the limits—further evolutions of trans-catheter valve procedures in the mitral position, including valve-in-valve, valve-in-ring, and valve-in-native-ring. J Thorac Cardiovasc Surg 2014;147:210-9.

[9] Ferrari E, Niclauss L, Locca D, Marcucci C. On-pump fibrillating heart mitral valve replacement with the SAPIEN XT transcatheter heart valve. Eur J Cardiothorac Surg 2014;45:749-51.

[10] Testa L, Popolo Rubbio A, Casenghi M, Pero G, Latib A, Bedogni F. Transcatheter Mitral Valve Replacement in the Transcatheter Aortic Valve Replacement Era. J Am Heart Assoc. 2019 Nov 19;8(22):e013352. doi: 10.1161/JAHA.119.013352. Epub 2019 Nov 7. PMID: 31694451; PMCID: PMC6915270. https://www.ahajournals.org/doi/full/10.1161/JAHA.119.013352

[11] Guerrero M, Dvir D, Himbert D, Urena M, Eleid M, Wang DD, Greenbaum A, Mahadevan VS, Holzhey D, O'Hair D, Dumonteil N, Rodés-Cabau J, Piazza N, Palma JH, DeLago A, Ferrari E, Witkowski A, Wendler O, Kornowski R, Martinez-Clark P, Ciaburri D, Shemin R, Alnasser S, McAllister D, Bena M, Kerendi F, Pavlides G, Sobrinho JJ, Attizzani GF, George I, Nickenig G, Fassa AA, Cribier A, Bapat V, Feldman T, Rihal C, Vahanian A, Webb J, O'Neill W. Transcatheter Mitral Valve Replacement in Native Mitral Valve Disease With Severe Mitral Annular Calcification: Results From the First Multicenter Global Registry. JACC Cardiovasc Interv. 2016 Jul 11;9(13):1361-71. doi: 10.1016/j.jcin.2016.04.022. PMID: 27388824. https://www.sciencedirect.com/science/article/pii/S1936879816304575

[12] Urena M, Brochet E, Lecomte M, Kerneis C, Carrasco JL, Ghodbane W, Abtan J, Alkhoder S, Raffoul R, Iung B, et al.. Clinical and haemodynamic outcomes of balloon-expandable transcatheter mitral valve implantation: a 7-year experience.**Eur Heart J**. 2018; 39:2679-2689. doi: 10.1093/eurheartj/ehy271. https://pubmed.ncbi.nlm.nih.gov/29788044/

[13] Yoon SH, Whisenant BK, Bleiziffer S, Delgado V, Schofer N, Eschenbach L, Fujita B, Sharma R, Ancona M, Yzeiraj Eet al.. Transcatheter mitral valve replacement for degenerated bioprosthetic valves and failed annuloplasty rings.**J Am Coll Cardiol**. 2017; 70:1121-1131. doi: 10.1016/j.jacc.2017.07. https://pubmed.ncbi.nlm.nih.gov/28838360/

[14] Eleid MF, Whisenant BK, Cabalka AK, Williams MR, Nejjari M, Attias D, Fam N, Amoroso N, Foley TA, Pollak PMet 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**. 2017; 10:1932-1942. doi: 10.1016/j.jcin.2017.08.014. https://pubmed.ncbi.nlm.nih.gov/28982556/

[15] Werner N, Kilkowski C, Sutor D, Weisse U, Schneider S, Zahn R. Transcatheter Mitral Valve Implantation (TMVI) Using Edwards SAPIEN 3 Prostheses in Patients at Very High or Prohibitive Surgical Risk: A Single-Center Experience. J Interv Cardiol. 2020 Jan 6;2020:9485247. doi: 10.1155/2020/9485247. PMID: 31992963; PMCID: PMC6973192. https://www.hindawi.com/journals/jitc/2020/9485247/

[16] Guerrero M, Pursnani A, Narang A, Salinger M, Wang DD, Eleid M, Kodali SK, George I, Satler L, Waksman R, Meduri CU, Rajagopal V, Inglessis I, Palacios I, Reisman M, Eng MH, Russell HM, Pershad A, Fang K, Kar S, Makkar R, Saucedo J, Pearson P, Bokhary U, Kaptzan T, Lewis B, Tommaso C, Krause P,

Thaden J, Oh J, Lang RM, Hahn RT, Leon MB, O'Neill WW, Feldman T, Rihal C. Prospective Evaluation of Transseptal TMVR for Failed Surgical Bioprostheses: MITRAL Trial Valve-in-Valve Arm 1-Year Outcomes. JACC Cardiovasc Interv. 2021 Apr 26;14(8):859-872. doi: 10.1016/j.jcin.2021.02.027. PMID: 33888231.

[17] Guerrero M, Wang DD, Pursnani A, Salinger M, Russell HM, Eleid M, Chakravarty T, Ng MH, Kodali SK, Meduri CU, Pershad A, Satler L, Waksman R, Palacios I, Smalling R, Reisman M, Gegenhuber M, Kaptzan T, Lewis B, Tommaso C, Krause P, Thaden J, Oh J, Douglas PS, Hahn RT, Kar S, Makkar R, Leon MB, Feldman T, Rihal C, O'Neill WW. Prospective Evaluation of TMVR for Failed Surgical Annuloplasty Rings: MITRAL Trial Valve-in-Ring Arm 1-Year Outcomes. JACC Cardiovasc Interv. 2021 Apr 26;14(8):846-858. doi: 10.1016/j.jcin.2021.01.051. PMID: 33888230.

[18] Guerrero M, Wang DD, Eleid MF, Pursnani A, Salinger M, Russell HM, Kodali SK, George I, Bapat VN, Dangas GD, Tang GHL, Inglesis I, Meduri CU, Palacios I, Reisman M, Whisenant BK, Jermihov A, Kaptzan T, Lewis BR, Tommaso C, Krause P, Thaden J, Oh JK, Douglas PS, Hahn RT, Leon MB, Rihal CS, Feldman T, O'Neill WW. Prospective Study of TMVR Using Balloon-Expandable Aortic Transcatheter Valves in MAC: MITRAL Trial 1-Year Outcomes. JACC Cardiovasc Interv. 2021 Apr 26;14(8):830-845. doi: 10.1016/j.jcin.2021.01.052. PMID: 33888229.

[19] Wang DD, Eng M, Greenbaum A, Myers E, Forbes M, Pantelic M, Song T, Nelson C, Divine G, Taylor Aet al.. Predicting LVOT obstruction after TMVR.**JACC Cardiovasc Imaging**. 2016; 9:1349-1352. doi: 10.1016/j.jcmg.2016.01.017

[20] Wang DD, Eng MH, Greenbaum AB, Myers E, Forbes M, Karabon P, Pantelic M, Song T, Nadig J, Guerrero Met al.. Validating a prediction modeling tool for left ventricular outflow tract (LVOT) obstruction after transcatheter mitral valve replacement (TMVR).**Catheter Cardiovasc Interv**. 2018; 92:379-387. doi: 10.1002/ccd.27447

[21] Yoon SH, Bleiziffer S, Latib A, Eschenbach L, Ancona M, Vincent F, Kim WK, Unbehaum A, Asami M, Dhoble A, Silaschi M, Frangieh AH, Veulemans V, Tang GHL, Kuwata S, Rampat R, Schmidt T, Patel AJ, Nicz PFG, Nombela-Franco L, Kini A, Kitamura M, Sharma R, Chakravarty T, Hildick-Smith D, Arnold M, de Brito FS Jr, Jensen C, Jung C, Jilaihawi H, Smalling RW, Maisano F, Kasel AM, Treede H, Kempfert J, Pilgrim T, Kar S, Bapat V, Whisenant BK, Van Belle E, Delgado V, Modine T, Bax JJ, Makkar RR. Predictors of Left Ventricular Outflow Tract Obstruction After Transcatheter Mitral Valve Replacement. JACC Cardiovasc Interv. 2019 Jan 28;12(2):182-193. doi: 10.1016/j.jcin.2018.12.001. PMID: 30678797.

[22] Ailawadi G, Lim DS, Mack MJ, Trento A, Kar S, Grayburn PA, Glower DD, Wang A, Foster E, Qasim A, Weissman NJ, Ellis J, Crosson L, Fan F, Kron IL, Pearson PJ, Feldman T; EVEREST II Investigators. One-Year Outcomes After MitraClip for Functional Mitral Regurgitation. Circulation. 2019 Jan 2;139(1):37-47. doi: 10.1161/CIRCULATIONAHA.117.031733. PMID: 30586701. https://www.ahajournals.org/doi/full/10.1161/CIRCULATIONAHA.117.031733

[23] McNeely C, Zajarias A, Robbs R, Markwell S, Vassileva CM. Transcatheter Aortic Valve Replacement Outcomes in Nonagenarians Stratified by Transfemoral and Transapical Approach. Ann Thorac Surg. 2017 Jun;103(6):1808-1814. doi: 10.1016/j.athoracsur.2017.02.056. Epub 2017 Apr 24. PMID: 28450135.

[24] Khan JM, Rogers T, Schenke WH, Mazal JR, Faranesh AZ, Greenbaum AB, Babaliaros VC, Chen MY, Lederman RJ. Intentional laceration of the anterior mitral valve leaflet to prevent left ventricular outflow tract obstruction during transcatheter mitral valve replacement: Pre-clinical findings.**JACC Cardiovasc Interv**. 2016; 9:1835-1843. doi: 10.1016/j.jcin.2016.06.020

[25] Babaliaros VC, Greenbaum AB, Khan JM, Rogers T, Wang DD, Eng MH, O'Neill WW, Paone G, Thourani VH, Lerakis Set al.. Intentional percutaneous laceration of the anterior mitral leaflet to prevent outflow obstruction during transcatheter mitral valve replacement: first-in-human experience.**JACC Cardiovasc Interv**. 2017; 10:798-809. doi: 10.1016/j.jcin.2017.01.035

[26] Søndergaard L, De Backer O, Franzen OW, Holme SJ, Ihlemann N, Vejlstrup NG, Hansen PB, Quadri A. First-in-human case of transfemoral CardiAQ mitral valve implantation. **Circ Cardiovasc Interv**. 2015; 8:e002135.

[27] Søndergaard L. CardiAQ-Edwards TMVR. Paper presented at: PCR London Valves; September 2016; London, United Kingdom.

[28] Cheung A, Stub D, Moss R, Boone RH, Leipsic J, Verheye S, Banai S, Webb J. Transcatheter mitral valve implantation with Tiara bioprosthesis. **EuroIntervention**. 2014; 10:U115–U119

[29] Cheung A. The TIARA Program: Attributes, Challenges, and Early Clinical Data. TVT 2019; June 2019; Chicago, IL

[30] Regueiro A, Ye J, Fam N, Bapat VN, Dagenais F, Peterson MD, Windecker S, Webb JG, Rodés-Cabau J. 2-Year outcomes after transcatheter mitral valve replacement. **JACC Cardiovasc Interv**. 2017; 10:1671-16

[31] Sorajja P, Moat N, Badhwar V, Walters D, Paone G, Bethea B, Bae R, Dahle G, Mumtaz M, Grayburn P, Kapadia S, Babaliaros V, Guerrero M, Satler L, Thourani V, Bedogni F, Rizik D, Denti P, Dumonteil N, Modine T, Sinhal A, Chuang ML, Popma JJ, Blanke P, Leipsic J, Muller D. Initial feasibility study of a new transcatheter mitral prosthesis: the first 100 patients. **J Am Coll Cardiol**. 2019; 73:1250-1260.

[32] Bapat V, Rajagopal V, Meduri C, Farivar RS, Walton A, Duffy SJ, Gooley R, Almeida A, Reardon MJ, Kleiman NS, Spargias K, Pattakos S, Ng MK, Wilson M, Adams DH, Leon M, Mack MJ, Chenoweth S, Sorajja P. Intrepid global pilot study investigators early experience with new transcatheter mitral valve replacement. **J Am Coll Cardiol**. 2018; 71:12-2

[33] Barbanti M, Piazza N, Mangiafico S, Buithieu J, Bleiziffer S, Ronsivalle G, Scandura S, Giuffrida A, Popolo Rubbio A, Mazzamuto M, Sgroi C, Lange R, Tamburino C. Transcatheter mitral valve implantation using the HighLife system. **JACC Cardiovasc Interv**. 2017; 10:1662-1670

[34] Makkar RR. Transcatheter Mitral Valve Replacement with the SAPIEN M3 System: 30-Day Outcomes - U.S. Early Feasibility Study. TCT 2018; September 2018; San Diego, CA

[35] Maisano F. Cardiovalve: device attributes, implant, procedure and early results. TCT 2018; September 2018; San Diego, CA

[36] Granada JF. Cephea TMVR System: device description, clinical appraisal and development plans. TCT 2018; September 2018; San Diego, CA

[37] Modine T, Vahl TP, Khalique OK, Coisne A, Vincent F, Montaigne D, Godart F, Van Belle E, Granada JF. First-in-Human Implant of the Cephea Transseptal Mitral Valve Replacement

System. Circ Cardiovasc Interv. 2019 Sep;12(9):e008003. doi: 10.1161/CIRCINTERVENTIONS.119.008003. Epub 2019 Sep 12. PMID: 31510775.

[38] Alperi A, Dagenais F, Del Val D, Bernier M, Vahl TP, Khalique OK, Modine T, Granada JF, Rodés-Cabau J. Early Experience With a Novel Transfemoral Mitral Valve Implantation System in Complex Degenerative Mitral Regurgitation. JACC Cardiovasc Interv. 2020 Oct 26;13(20):2427-2437. doi: 10.1016/j.jcin.2020.08.006. PMID: 33069643.

[39] Généreux *P. ALTA* Valve: device attributes, implant procedure, and first-in-human. TCT 2018; September 2018; San Diego, CA

[40] Navia JL, Baeza C, Maluenda G, Kapadia S, Elgharably H, Sadowski J, Bartuś K, Beghi C, Thyagarajan K, Bertwell R, Quijano RC. Transcatheter mitral valve replacement with the NaviGate stent in a preclinical model. **EuroIntervention**. 2017; 13:e1401–e1409.

[41] Navia JL, Kapadia S, Elgharably H, Maluenda G, Bartuś K, Baeza C, Nair RK, Rodés-Cabau J, Beghi C, Quijano RC. Transcatheter tricuspid valve implantation of navigate bioprosthesis in a preclinical model. **JACC Basic Transl Sci**. 2018; 3:67-79.