Transcatheter Mitral Valve Replacement in the Transcatheter Aortic Valve Replacement Era

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After the success and worldwide adoption of transcatheter aortic valve replacement (TAVR), the percutaneous replacement of a diseased mitral valve (MV) rapidly became a target for investigators and industry. The rejuvenated enthusiasm of industry in this field is also corroborated by the fact that, in 2015, ≈2.5 billion dollars were invested in MV technology development and engineering, making this topic extremely timely. However, although transcatheter aortic Valve replacement has already become the standard of care for the treatment of aortic stenosis (AS) in patients considered at increased risk for conventional surgery,[1–3] transcatheter MV replacement (TMVR) has not yet achieved the same results.

MV disease is more common than AS,[4,5] and the surgical approach still remains the gold standard treatment for degenerative mitral regurgitation (MR).[3] For patients at high surgical risk who are denied surgery and for whom medical therapy is not sufficient,[6] TMVR may mature as a promising therapeutic option.[7]

As a matter of fact, MR is the most common valve disease, considering that in developed countries the prevalence of rheumatic heart disease and consequent mitral stenosis encountered a dramatic reduction in the past decades.[4] Moreover, the increased life expectancy and the growing incidence of ischemic heart disease, combined with advanced medical and interventional therapies, have led ischemic functional secondary MR and degenerative primary MR to further increase.[8] Consequently, this growing interest in the development of percutaneous treatment options for MV disease goes parallel with the much higher prevalence of this valvulopathy in the general population, combined with the increased group of high-risk elderly patients who could not benefit from the standard surgical treatment.[9]

Insights into the Technical Challenges Between TMVR Versus transcatheter aortic Valve replacement

Anatomical and pathophysiological reasons[1] traditionally led to a preference for an MV repair rather than a replacement,[10,11] thus contributing to the delay in the evolution of TMVR technology; only a relatively small number of cases of TMVR have been performed worldwide. Various trials studying different devices are still ongoing or in their early stage. TMVR can provide some advantages over percutaneous repair, in virtue of an extended use in difficult or complex MV anatomical features and with a theoretical more predictable result in terms of MR reduction. Nevertheless, different challenges have been influencing the development and growth of TMVR, especially if compared with transcatheter aortic Valve replacement.[12–14]

All the features and technical challenges of TMVR versus transcatheter aortic Valve replacement are presented as follows, and as listed in Table 1.

Demographic Variables

Demographic differences for the age can be encountered between patients with degenerative aortic and MV disease in surgical case series. The age of patients becomes even more important considering that the life expectancy of the treated patients can exceed the long-term durability of the valve itself. It has been estimated that a surgical bioprosthesis is prone to degenerate within 20 years.[15] This observation is really more demanding for patients who undergo surgical MV replacement who are on average 10 years younger than patients who undergo aortic valve replacement.[16] Indeed, it is well established that bioprosthetic valves have a higher tendency of structural degeneration in younger patients because of greater hemodynamic stress on the valve, differences in calcium metabolism, prosthesis-patient mismatch, or immune response.[17] As such, a structural bioprosthesis deterioration is more frequent in mitral than aortic valves, as the MV is

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Table 1. Challenges Between TMVR vs TAVR

Variable	TMVR	TAVR
Demographic differences	Younger patients	Older patients
Pathophysiological aspects	• Nonrheumatic DMR or ischemic FMR • Often associated with TR and/or AF	• Degenerative calcified AS • Often isolated
Gold standard treatment	• Surgical mitral valve repair preferred to replacement • Percutaneous repair in high-risk patients	• SAVR for aortic regurgitation and for bicuspid anatomy • TAVR in high- or intermediate-risk patients
Durability of bioprosthetic valve	Poor in mitral position	Satisfactory in aortic position
Access site	Mostly transapical or transfemoral with transseptal puncture	Mostly transfemoral
Inherent technical risks	• LVOT obstruction • Foreshortening in left atrium • Anchoring • PVLs	• Coronary obstruction during/after ViV procedure • PVLs
Clinical studies	• Early stage of safety and feasibility trials • Anecdotal case series	• Safety and feasibility trials • 5-y results available • Assessed in high, intermediate, and low surgical risk patients

AF indicates atrial fibrillation; AS, aortic stenosis; DMR, degenerative mitral regurgitation; FMR, functional mitral regurgitation; LVOT, left ventricle outflow tract; PVL, paravalvular leak; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; TMVR, transcatheter mitral valve replacement; TR, tricuspid regurgitation; ViV, valve in valve.

exposed to higher mechanical stress caused by the systolic pressure gradient, with a consequent impact on durability of mitral bioprosthesis, if compared with aortic ones. Transposing these epidemiological surgical observations to percutaneous treatment allows a better understanding as to how life expectancy is still a critical issue in TMVR development and diffusion rather than in transcatheter aortic Valve replacement.

Percutaneous Access Site

transcatheter aortic Valve replacement is generally easily performed within a transfemoral access, after an accurate computed tomographic scan or angiographic evaluation. In the event that iliofemoral access is not available, also transsubclavian, transcarotid, transaxillary, transaortic, or transapical access can be used. Newer transcatheter aortic Valve replacement devices include smaller delivery sheaths if compared with the first generation and allow the possibility to reposition or recapture the device when in a suboptimal position. For TMVR, in light of the larger dimensions of the valves and delivery system currently used, transfemoral access with transseptal puncture is often demanding, in favor of a more invasive transapical or transatrial one. Indeed, transseptal access inevitably limits the maneuvers in the left atrium and valve positioning, increasing the difficulty of a high-profile prosthesis to reach an angled mitral annular plane. Consequently, this situation often requires highly curved or steerable guide catheters, with limited possibility to transmit torque to the system. On the contrary, if the transapical access provides an easier way to deploy a mitral device, this technique is impaired by a higher degree of myocardial damage, especially in elderly/frail patients, as the transcatheter aortic Valve replacement experience clearly showed.[18,19]

Anatomical and Pathophysiological Reasons

AS often occurs as an isolated cardiac condition in patients with preserved left ventricle (LV) ejection fraction or in patients with impaired LV contractility, which may recover once the outflow obstruction is removed. transcatheter aortic Valve replacement allows the deployment of an aortic device in a tubular, rigid, calcified annular structure, providing a stability similar to the surgical intervention.[20]

On the other hand, the MV is a functional apparatus rather than a "valve,"[21] and 2 completely different causes (primary or secondary) can be identified with various degrees of coexistence, particularly in elderly people. Alterations of both the valve and the subvalvular structures should be assessed to define the underlying mechanism of the pathological condition (annular dilation, leaflet alterations, chordal rupture, tissue calcifications, and so on) and consequently to decide the most appropriate approach for repair or replacement. Given the variability of anchoring and delivery of available prostheses, a detailed assessment of the MV anatomical features will be required for TMVR.

The characteristics of the annulus, in terms of shape, sizing, and calcification, and the dimensions of the LV, which

are critical to avoid any impairment of the outflow, should be carefully taken into account.[22]

The mitral annulus is larger than the aortic one and requires larger prostheses and, thus, larger delivery systems. At the same time, it provides less support than the aortic annulus, as a result of not being a complete fibrous ring and the lack of calcification.[23] It is well-known that annular and aortic root calcification load is important in the setting of transcatheter aortic Valve replacement, as it offers an increased grip and better seating of the prosthesis, although it may increase the risk of paravalvular leaks (PVLs) after the implant. Mitral annular calcifications are less common, and their presence may obviously condition the implant of a transcatheter mitral prosthesis too. 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 studied 116 patients who underwent TMVR with balloon-expandable aortic prosthesis, in presence of severe mitral annular calcification. This study showed the TMVR in this condition is feasible, but associated with high early and midterm mortality at 1 year, although patients who survived at 1-year follow-up present sustained improvement of symptoms.[24]

The mitral annulus can be defined as a junction of left atrium, LV, and mitral leaflets and represents a dynamic structure that can afford some degree of distortion itself as well as that of the surrounding structures; however, when a transcatheter valve is implanted, there is always a risk of migration of the prosthesis because of the phasic systolic contraction.

The D-shape configuration of the mitral annulus represents another major issue, as this asymmetrical conformation does not consent to achieve uniformly radial force, increasing the risk of PVLs or prosthesis migration. On the other hand, the rigid, often symmetrical, elliptical shape of the aortic valve permits a more correct device sizing and consequent sealing in transcatheter aortic Valve replacement. Likewise, the acquired experience and the success of transcatheter aortic Valve replacement have led, over time, to an expanded use of this procedure also in challenging anatomical features, such as bicuspid aortic valves, or different mechanisms of disease, such as aortic regurgitation.[25]

Differently from AS, MR is often coexistent with other valvular disease, such as tricuspid regurgitation, severe pulmonary hypertension, and atrial fibrillation, with significant and independent morbidity and mortality rates.[26,27] Indeed, in patients undergoing MV surgery, a concomitant tricuspid repair is often performed to prevent the recurrence of heart failure symptoms.[28] Moreover, atrial fibrillation in these patients tends to be chronic or recurrent because of atrial enlargement, with a low likelihood that sinus rhythm will be reestablished after surgery. In this case, adjunctive antiarrhythmia surgery as well as left atrial appendage excision can be performed.

The presence of tricuspid regurgitation and/or atrial fibrillation represents another important issue in the setting of TMVR; indeed, any tricuspid regurgitation is an exclusion criterion for clinical trials studying TMVR, and the results in this setting are therefore not well-known.

Device-Related and Technical Features

Both the surgical and percutaneous replacement of MV affects the overall performance of the LV, as a consequence of the impairment of the subvalvular structures.[29] In the earliest experience, percutaneous heart valves originally designed for the aortic valve, such as the Edwards SAPIEN XT, were generally adapted for TMVR.[30] As we learned from transcatheter aortic Valve replacement, calcifications are important to ensure adequate valve anchoring and deployment of an aortic prosthesis,[31] especially in the mitral position. As such, this technique is limited as severely calcified leaflets are uncommon in the MV.

Differences between surgical aortic and MV replacement are also maintained in the setting of valve-in-valve (ViV) procedures. ViV procedures comprise a second valve implanted within the first degenerated valve.[32,33] In case of aortic ViV, one of the main issues is the possible risk of coronary occlusion, whereas for mitral ViV, one of the main issues is the encumbrance caused by the second valve that may interfere with the LV outflow tract (LVOT).[34] The foreshortening of the valve in the left atrium may be unpredictable as well. However, the risk of LVOT obstruction remains the most important challenge in TMVR, independently from ViV and especially when nondedicated devices are used. The current reported incidence of LVOT obstruction in TMVR is on average ≈9.3%.[1] Potential predictors of LVOT obstruction are the angle of the MV in relation to the LVOT long axis, especially if they are perpendicular or in the presence of small LV cavity, bulging or severe hypertrophy of the basal interventricular septum, long anterior MV leaflets, and dynamic alterations as the pushing of the native anterior leaflet toward the LVOT. Also, prosthesis protrusion and device flaring could be potential risk factors for LVOT occlusion. This device protrusion leads to the creation of a "neo-LVOT," included among the device, the native anterior mitral leaflet, and the interventricular septum. Understanding individual valve geometry is detrimental to predict a potential feared and fatal condition, such as LVOT obstruction. To avoid this, a computed tomographic scan can predict the new LVOT geometry after a virtual implant, by embedding a cylindrical contour into the computed tomographic data set or the actual valve. Other techniques, such as TMVR septal ablation or laceration of the anterior mitral leaflet, can be used to avoid LVOT obstruction.[35–38]

PVL represents another important issue to focus on. In the transcatheter aortic Valve replacement experience, the

occurrence of PVL has been reduced with the new-generation prostheses that have skirts in the inflow portion of the frame and are usually recapturable and/or repositionable.[39] On the contrary, TMVR can be associated with a higher incidence of PVL because of reduced anatomical support, the asymmetrical shape of the annulus, or asymmetric leaflets. Balloon postdilation of mitral prostheses could be more difficult, considering the proximity to the circumflex artery, the aortic valve, and the conduction system. Future improvement of the design of TMVR should surely address this fundamental point.

Finally, MV repair is generally the treatment of choice. Over 60% of patients who are candidates for MV surgery undergo valve repair rather than replacement.[11] MV repair is associated with lower mortality and morbidity than replacement, although replacement could offer some advantages by giving a more complete and reproducible reduction in MR. Current guidelines widely emphasize that surgical repair, especially annuloplasty, is the preferred approach over replacement in primary MR.[3] This result is mostly driven by the possibility of conserving the subvalvular apparatus, particularly chordal structures, with the purpose of preserving LV function. On the other hand, while considering secondary MR, the most appropriate approach of treatment still remains controversial as the underlying LV dysfunction and the progressive annular dilation can impact outcome, durability, and long-term results. As such, high-risk patients with functional secondary MR may become the most likely recipients in which TMVR, if damage to subvalvular structures is avoided, could prove beneficial and successful.

TAVR Clinical Study

The treatment of AS in high- or intermediate-risk patients with transcatheter aortic Valve replacement is nowadays a consolidated therapy. Although initial experience of transcatheter aortic Valve replacement was conditioned by a limited number of early-generation prostheses, the widespread diffusion of this procedure has led over time to a growing interest to improve existing devices or develop newer ones, resulting in a wide selection being currently available (Figure 1). Comparisons among different transcatheter aortic Valve replacement devices are still limited, and the choice of a specific prosthesis depends on various reasons, such as annulus dimension, distribution of calcium, coronary ostium height, peripheral vasculature, and single operator preferences or center expertise.

The current lines of evidence for transcatheter aortic Valve replacement are supported by various clinical trials that evaluated the safety, the efficacy, and the satisfactory hemodynamic results of this procedure.[2,40–43]

The results of these studies, which confirmed the noninferiority of transcatheter aortic Valve replacement against conventional surgical therapy, are valid for both balloon-expandable and self-expanding valves. Over time, these randomized clinical trials have also been accompanied by experiences coming from different multicenter or single-center registries that have enriched the wealth of information that we have today on this procedure. The adequate hemodynamic profile of transcatheter aortic Valve replacement at 5-year follow-up has been recently reported by the PARTNER-1 (Placement of Aortic Transcatheter Valves) trial, which confirmed that the occurrence of structural valve deterioration in transcatheter aortic Valve replacement was low.[44] In a subanalysis, the PARTNER-1A trial showed similar valve performance between transcatheter aortic Valve replacement and surgical replacement, although the incidence of PVLs was superior in the transcatheter aortic Valve replacement group.[45] Attention to durability of transcatheter aortic Valve replacement is also confirmed by the FRANCE-2study that reported a low incidence of severe deterioration (2.5%) in transcatheter aortic Valve replacement at 5-year follow-up.[46] The growing success of transcatheter aortic Valve replacement has led to an expansion of the indication for the procedure to patients at low surgical risk. Two recent clinical trials, such as the PARTNER 3 (NCT02675114) and EVOLUT (NCT02701283) trials, confirmed that transcatheter aortic Valve replacement with the latest-generation balloon-expandable SAPIEN 3 and the self-expanding Corevalve, Evolut R, or Evolut PRO are superior or at least as good, respectively, as surgical replacement in low-risk patients.[47,48] Given these data, it looks reasonable to expect an extended use of transcatheter aortic Valve replacement in low-risk patients, with an equal indication for transcatheter aortic Valve replacement and surgery in guidelines. Considering that surgical bioprosthetic valves present a tendency to deterioration arising from 10 to 20 years, only the longest follow-up on transcatheter aortic Valve replacement series could confirm the real durability of the latest generation of valves used for transcatheter aortic Valve replacement and permit the formulation of real comparisons about durability between transcatheter aortic Valve replacement and surgery, particularly in patients with a long life expectancy.

TMVR Devices Under Clinical Study

Different transcatheter devices have been designed for the treatment of MR (and, in some cases, for off-label treatment of mitral stenosis).[19] Differently from transcatheter aortic Valve replacement, most of the TMVR technologies are still under clinical investigation or in their early experience in safety and feasibility trials (Table 2). Therefore, information about their durability, structural deterioration, or comparison with surgery is still far. The principal devices on study are presented below (Figure 2).

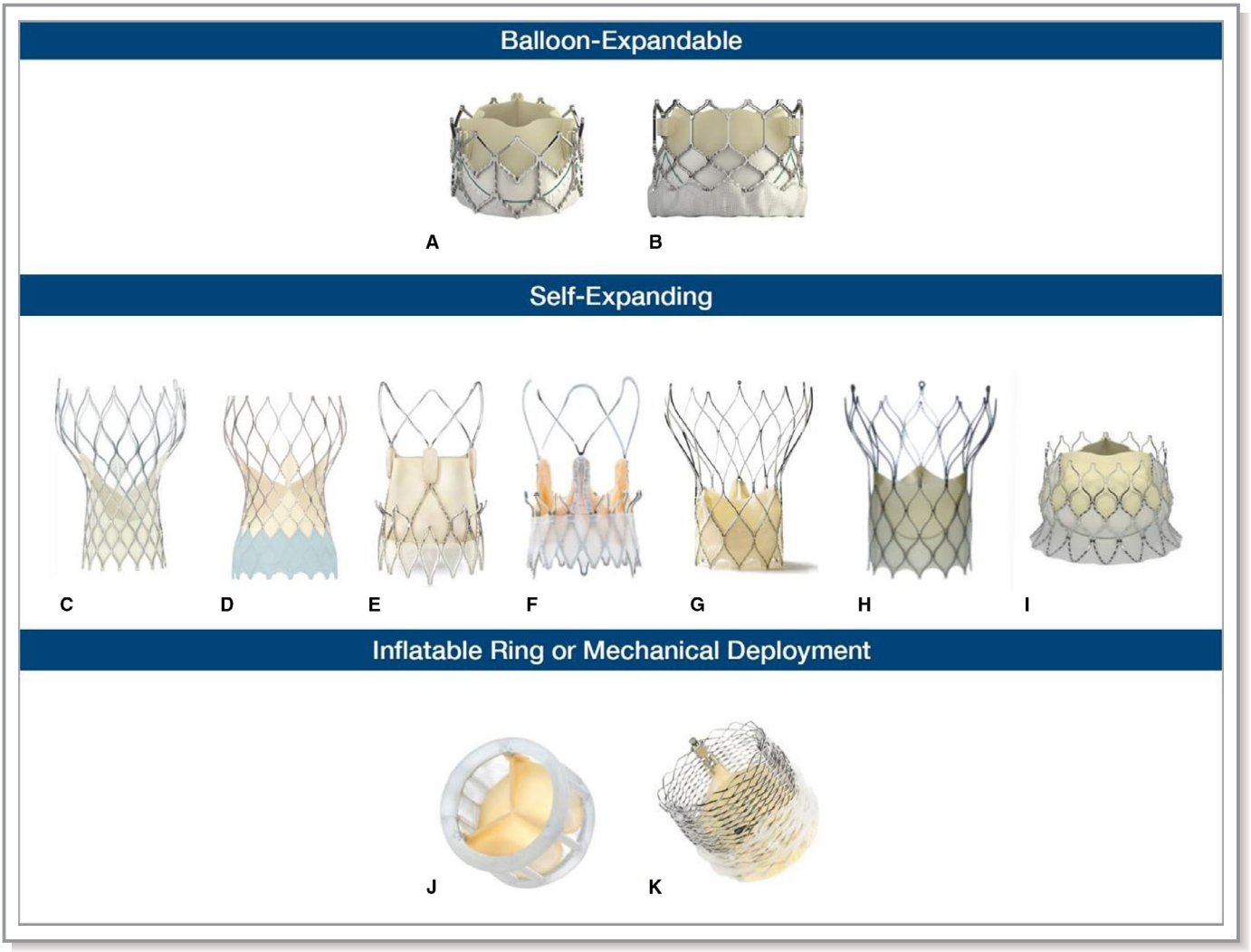

Figure 1. Current transcatheter aortic valve replacement devices. **A**, Edwards SAPIEN XT (Edwards Lifesciences Inc). **B**, Edwards SAPIEN 3 (Edwards Lifesciences Inc). **C**, CoreValve Evolut R (Medtronic Inc). **D**, CoreValve Evolut PRO (Medtronic Inc). **E**, Acurate NEO (Boston, Marlborough). **F**, Acurate TA (Boston, Marlborough). **G**, Portico (Abbott). **H**, Biovalve (Biotronik). **I**, Centera (Edwards Lifesciences Inc). **J**, Direct Flow (Direct Flow Medical Inc), not commercially available. **K**, Lotus (Boston), not commercially available. There was recent US Food and Drug Administration approval for the new Lotus Edge.

The CardiAQ (Edwards Lifesciences Inc) valve is a nitinol self-expanding trileaflet valve, composed of bovine pericardial tissue, which was the first dedicated device for TMVR in 2012 in high-risk patients with severe MR. The second generation of the device was used for the first time in 2014. It is the only device that offers both a transapical and transfemoral-transseptal approach. The previous generation of CardiAQ valve was then completely abandoned, and the new redesigned version was renamed the EVOQUE valve. The EVOQUE valve offered an innovated system with 2 valve sizes and lower profile, to guarantee a transfemoral approach with enhanced maneuverability and depth control, and lower ventricular projection, to avoid LVOT obstruction. The first 2 trials in 2015 were rapidly withdrawn for commercial reasons. Currently, the Edwards EVOQUE TMVR Early Feasibility Study (NCT02718001) is recruiting: it will assess feasibility at 30 days. Recently, the RELIEF (Reduction or Elimination of Mitral Regurgitation in Degenerative or Functional Mitral Regurgitation With the CardiAQ-Edwards™ Transcatheter Mitral Valve)=CardiAQ-Edwards TMVR Study (NCT02722551) was stopped by the Edwards Company for further design validation. This stop could delay the Conformité Européene (CE) marker in Europe approval that was initially expected for 2018. From the first results presented, 13 patients have been treated under compassionate use, with a technical success (defined as successful valve delivery, valve deployment, and delivery system retrieval) of 92% and a high rate (45%) of mortality at 30 days.[49,50]

The Tiara (Neovasc Inc, Canada) valve is a self-expanding trileaflet bioprosthesis of bovine pericardial tissue leaflets, mounted inside a nitinol alloy frame. This valve fits the

Table 2. TMVR Device Characteristics, Primary Outcomes, and Studies

Device Name	Description	Primary Outcomes	Status
CardiAQ-EVOQUE (Edwards Lifesciences Inc)	• Nitinol self-expanding trileaflet valve, composed of bovine pericardial tissue • Transapical/transseptal • EVOQUE valve: new redesigned version of the valve	Compassionate use (n=13) Technical success, 92% Mortality at 30 d, 45%	• Early Feasibility Study of the CardiAQ TMVI System (Transfemoral and Transapical DS) (NCT02515539M); withdrawn • A Clinical Study of the CardiAQ TMVI System (Transapical DS) (NCT02478008); early termination • RELIEF (CardiAQ-Edwards TMVR Study) (NCT02722551); withdrawn • Edwards EVOQUE TMVR Early Feasibility Study (NCT02718001); still recruiting
Tiara (Neovasc Inc, Canada)	• Nitinol self-expanding trileaflet valve of bovine pericardial tissue • Transapical	Initial results (n=30) Technical success, 90% Mortality at 30 d, 10%	• TIARA-I (Early Feasibility Study of the Neovasc Tiara: Mitral Valve System) (NCT02276547); still recruiting • TIARA-II (Tiara Transcatheter Mitral Valve Replacement Study) (NCT03039855); still recruiting
FORTIS (Edwards Lifesciences Inc)	• Nitinol self-expanding trileaflet valve of bovine pericardial tissue • Transapical	Compassionate use (n=13) Technical success, 76.9% Mortality at 30 d, 38.5%	• High rate of valve thrombosis; the company put the studies on hold
Tendyne (Abbott Inc)	• Self-expanding trileaflet valve of porcine pericardial tissue, mounted on nitinol double-frame stent • Transapical	Initial results (n=100) Technical success, 96% Mortality at 30 d, 6%	• Expanded Clinical Study of the Tendyne Mitral Valve System—Global Feasibility Study (NCT02321514); still recruiting • SUMMIT (Clinical Trial to Evaluate the Safety and Effectiveness of Using the Tendyne Mitral Valve System for the Treatment of Symptomatic Mitral Regurgitation) (NCT03433274); still recruiting • Feasibility Study of the Tendyne Mitral Valve System for Use in Subjects With Mitral Annular Calcification (NCT03539458); still recruiting
Intrepid (Medtronic Inc)	• Nitinol self-expanding trileaflet valve of bovine pericardial tissue • Transapical (transseptal approach under development)	Initial results (n=50) Technical success, 96% Mortality at 30 d, 14%	• APOLLO (Transcatheter Mitral Valve Replacement With the Medtronic Intrepid TMVR System in Patients With Severe Symptomatic Mitral Regurgitation) (NCT03242642); still recruiting
Caisson (LivaNova, UK)	• Nitinol self-expanding trileaflet valve of porcine pericardial tissue, with a D-shaped anchor • Transseptal	Still not known	• PRELUDE (Caisson TMVR System Early Feasibility Study) (NCT02768402); active, not recruiting • INTERLUDE (Caisson TMVR) (NCT03661398); active, not recruiting
HighLife (HighLife SAS, France)	• Two separate components: nitinol alloy-based self-expanding frame with a trileaflet valve of bovine pericardium tissue and a subannular implant • Transapical/transatrial (transseptal approach under development)	Anecdotal cases	• Anecdotal cases • HighLife Transcatheter Mitral Valve Replacement System Study (NCT02974881); still recruiting
SAPIEN M3 (Edwards Lifesciences Inc)	• Nitinol docking system and a modified SAPIEN 3 valve • Transseptal	Initial results (n=15) Technical success, 86.7% Mortality at 30 d, 0%	• Early feasibility study (NCT03230747); recruitment not known

Continued

Table 2. Continued

Device Name	Description	Primary Outcomes	Status
Cardiovalve (Cardiovalve, Israel)	• Dual nitinol frame with a trileaflet bovine pericardium valve • Transseptal	Initial results (n=5) Technical success, 100% Mortality at 30 d, 60%	• AHEAD (European Feasibility Study of the Cardiovalve Transfemoral Mitral Valve System) (NCT03339115); still recruiting • Feasibility Study of Patients With Severe MR Treated With the Cardiovalve TMVR System (NCT03714412); withdrawn (amended and merged with AHEAD-EU [European Union] study) • AHEAD (Cardiovalve Transfemoral Mitral Valve System) (NCT03813524); still recruiting • Cardiovalve Transfemoral System—FIM Study (NCT03958773); still recruiting
Cephea (Cephea Valve Technologies)	• Self-expanding double-disk and trileaflet bovine pericardium tissue • Transseptal/transatrial	Preclinical models First-in-human cases recently started	• Cephea Transseptal Mitral Valve System FIH (NCT03988946); still recruiting
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)	• No trials ongoing; feasibility study planned
NaviGate (NaviGate Cardiac Structures Inc)	• Nitinol self-expandable system with several annular winglets • Transapical	First-in-human case (n=1)	• No trials ongoing; use in tricuspid regurgitation rather than mitral disease
MValve (MValve Ltd, Israel)	• Docking system combined with Lotus heart valve • Transapical	First-in-human case (n=1)	• DOCK 1 (Mitral Valve Replacement With MValve Dock and Lotus) (NCT02719912); not yet recruiting, status unknown

DE indicates device; FIH: first in human; FIM: first in man; TMVI: transcatheter mitral valve implantation; TMVR, transcatheter mitral valve replacement.

asymmetric D-shaped mitral annulus and has a large atrial skirt aimed at preventing PVLs. The first implant was performed in Vancouver in 2014. The TIARA-I (Early Feasibility Study of the Neovasc Tiara Mitral Valve System) (NCT02276547) is still enrolling patients, as well as the latest TIARA-II (Tiara Transcatheter Mitral Valve Replacement Study). Preliminary results in 71 patients, mostly in functional MR (61%), showed 94% technical success, with a mortality rate of 11.3% at 30 days.[51,52]

The FORTIS (Edwards Lifesciences Inc) valve is a self-expanding bioprosthesis of bovine pericardial tissue. The first implant was performed in 2014, and results on 13 patients showed procedural success in 76.9%.[53] In the early experience, valve thrombosis was often documented. For this reason, the company put the studies on hold.

The Tendyne MV system (Abbott Inc) is a self-expanding trileaflet porcine pericardial valve, mounted on a nitinol double-frame stent, implanted within transapical access; and it can be completely retrieved or repositioned. An atrial cuff has been designed to guarantee optimal sealing of the prosthesis and reduction of PVLs. The outer stent presents a D-shaped configuration, to properly seat the valve in the annulus. The first implant was performed in 2014. The Tendyne experience concerns an international feasibility trial (n=30) and an expanded CE Mark study (still ongoing: Feasibility Study of the Tendyne Mitral Valve System for Use in Subjects With Mitral Annular Calcification; NCT03539458). Results of the first 100 treated patients were recently published.[54] The technical success was 97%, with no periprocedural mortality and a rate of death of 6% at 30-day outcome. Most patients (98.8%) presented trivial-trace or mild residual MR at 30 days. Nonetheless, the slow enrollment in this trial contributed to a delay in obtaining CE Mark, which is expected in 2019. Further information about the Tendyne experience will be also derived from 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), an ongoing randomized trial that proposes to randomize the Tendyne valve versus conventional MV surgery in 1010 participants at

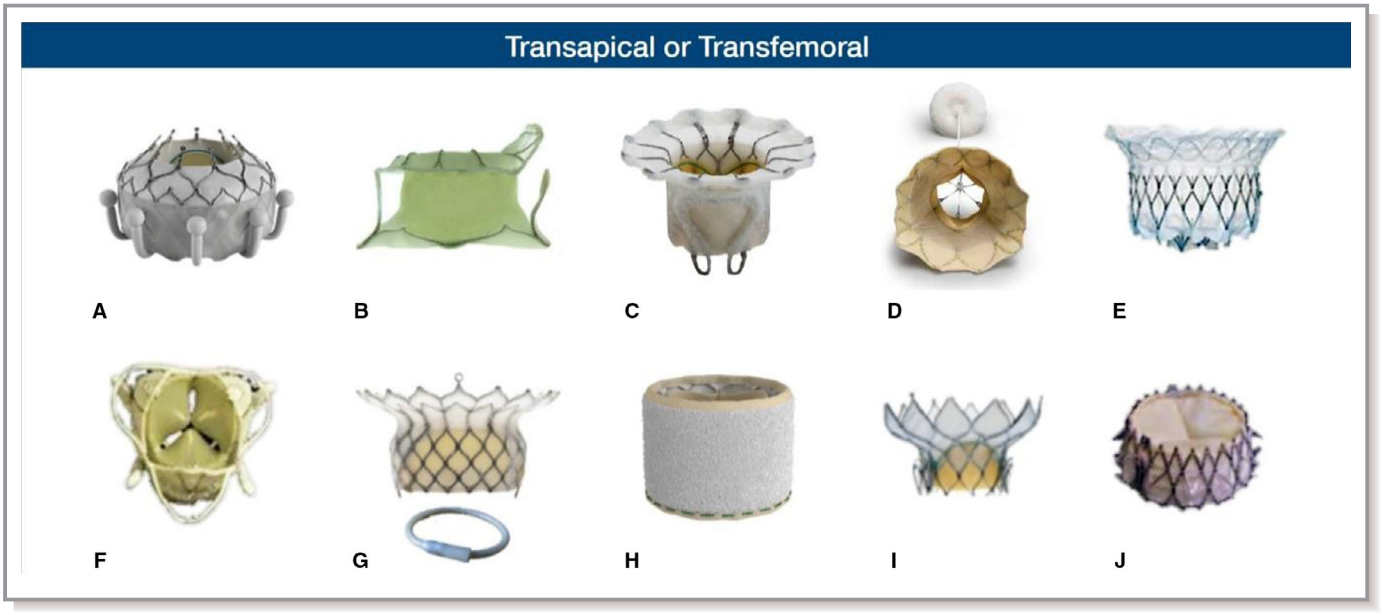

Figure 2. Current transcatheter mitral valve replacement devices. **A**, CardiAQ/EVOQUE (Edwards Lifesciences Inc). **B**, Tiara (Neovasc Inc, Canada). **C**, FORTIS (Edwards Lifesciences Inc). **D**, Tendyne (Abbott Inc). **E**, Intrepid (Medtronic Inc). **F**, Caisson (LivaNova, UK). **G**, HighLife Bioprosthesis and Subannular Implant (HighLife SAS, France). **H**, SAPIEN M3 (Edwards Lifesciences Inc). **I**, Cardiovalve (Cardiovalve, Israel). **J**, NaviGate (NaviGate Cardiac Structures, Inc, CA).

different centers and that is expected to be completed in 2026.

The Intrepid (Medtronic Inc) valve is a trileaflet bovine pericardial valve, sewn onto a self-expanding nitinol frame. The inflow atrial part is large and responsible for sealing, avoiding obstruction of LVOT. The valve does not rely on radial forces and presents a fixation ring to accommodate the native annulus. The device is implanted via transapical access, whereas a transseptal approach is being developed. The first implant was performed in 2014.[55] An initial pilot study enrolled 50 high-risk patients with MR and reported a successful device deployment in 96%; 30-day mortality rate was 14%. Trivial-trace or mild residual MR was achieved at 30 days in all of the recruited patients.[56] The multicenter, global, randomized APOLLO (Transcatheter Mitral Valve Replacement With the Medtronic Intrepid TMVR System in Patients With Severe Symptomatic Mitral Regurgitation; NCT03242642) trial is still recruiting. In this trial, patients are randomized in a 1:1 proportion to receive the Intrepid valve or conventional mitral surgery. The patients will be evaluated at 30 days, 6 months, and annually, up to 5 years follow-up, with estimated study completion date in 2025.

The Caisson (LivaNova, UK) system is a device made by a trileaflet porcine pericardial valve, mounted in a self-expanding nitinol frame, and a D-shaped anchor.[1] Currently, the experience with this valve is limited to a few case reports. The initial feasibility study, as the PRELUDE (Percutaneous Mitral Valve Replacement Evaluation Utilizing IDE Early Feasibility Study) (Caisson Transcatheter Mitral Valve Replacement System Early Feasibility Study; NCT02768402), was completed in August 2018, although LivaNova has not released data from it, but touted "positive patient outcomes." Further and complete information should be derived from the following feasibility study, as the INTERLUDE (Caisson Transcatheter Mitral Valve Replacement; NCT03661398), for which, however, results are still active but which is not recruiting.

The HighLife (HighLife SAS, France) valve is a 2-component system. The valve is implanted in the mitral position and is anchored by a transarterial retrograde positioned subannular implant. Anecdotal initial cases are reported showing acceptable results of the valve.[57] A feasibility trial (NCT02974881) is still ongoing.

The SAPIEN M3 (Edwards Lifesciences Inc) valve is a newer transseptal system composed by a nitinol docking system and a modified SAPIEN 3 valve. The design features include a knitted polyethylene terephthalate (PET) skirt that facilitates sealing between the native MV and the dock. The dock facilitates the anchoring of the 29-mm SAPIEN M3 valve. This valve has been investigated in an early feasibility study for severe MR. From the initial results in 15 patients, technical success was achieved in 86.7%, with a reduction of MR of 93.3% and no mortality at 30 days.[58]

The Cardiovalve (Cardiovalve, Israel) system is a bovine pericardium valve, mounted in a dual nitinol frame with a

proven surgical design adapted for TMVR. This newer system offers a robust radial strength and contains 24 grasping legs designed for an atraumatic anchoring of the device in the mitral annulus. It is characterized by a low ventricular profile, reducing the risk of LV interference, without atrial protruding, and 3 different sizes to fit different anatomical features. Its low profile allows an antegrade transseptal delivery, and the system provides a multisteerable catheter for coaxial implantation. The AHEAD (European Feasibility Study of the Cardiovalve Transfemoral Mitral Valve System; NCT03339115) will evaluate the safety and the device performance in reducing MR of the Cardiovalve system. A total of 30 patients will be enrolled in this feasibility study, and the first 5 cases performed showed 100% of technical success with reduction of MR and absent or at least trivial residual PVLs.[59]

An emerging newer device prone to be studied in humans is the Cephea system.

The Cephea (Cephea Valve Technologies) system is a frame structure valve designed for TMVR with multilevel conformability, with low device profile to permit an antegrade transseptal delivery of the device. The device is both repositionable and recapturable. The frame structure allows reducing the risk of LVOT obstruction and anchoring independently from subvalvular apparatus. The valve was tested in preclinical models that supported the performance of the device at 90 days' follow-up, and first-in-human studies are awaited to confirm these positive preclinical results.[60]

Another attractive system, the AltaValve (4C Medical Technologies Inc), was recently presented. This system presents a different concept in contrast with the other TMVR devices. Indeed, it is composed by a self-expanding supra-annular device, with a bovine tissue valve mounted into a spherical nitinol frame, inserted into the left atrium (with a transseptal or transapical delivery system), thus completely preserving the LV. Preclinical studies in animals were completed, and a first-in-human case was performed in Canada in 2018, with satisfactory results.[61]

It is also possible to find in the literature other interesting systems that were then abandoned or readapted for other uses. Among them, we can cite the NaviGate system and the MValve System.

The NaviGate (NaviGate Cardiac Structures Inc) valve is a self-expandable system composed of a nitinol stent frame, with several annular winglets that anchor the valve in the mitral annulus. The valve can only be delivered via transapical access. The first-in-human implant was performed in 2015 in Chile in a 53-year-old man with severe MR. No further results in humans have been reported yet, and only preclinical model results have been shown.[62] After an initial interest of this valve in mitral position, the mitral implants were then abandoned in favor of the percutaneous treatment of tricuspid regurgitation with the transatrial or transjugular approach.[63]

The MValve (MValve Ltd, Israel) system is a docking system designed to anchor other percutaneous valves. The system can be delivered via transapical route. First-in-human implantation was performed in 2015.[1] A feasibility and safety study (DOCK 1; NCT02719912) of the MValve in conjunction with Lotus transcatheter heart valve (Boston Scientific, MA) was supposed to start in 2016, although the trial never started and the device has been abandoned.

In a small percentage of cases, TMVR was also used for the treatment of high-risk patients with mitral stenosis with severe annulus calcifications. Most of these patients have been treated with balloon expandable valves or newer aortic valves, such as the Direct Flow (Direct Flow Medical) and LOTUS valve (Boston Scientific).[64,65] The use of aortic Edwards SAPIEN XT and SAPIEN 3 (Edwards Lifesciences Inc) for TMVR in calcified mitral stenosis is currently under study by the MITRAL (Mitral Implantation of Transcatheter Valves) trial (NCT02370511), although the trial is still active but not recruiting.

Other technologies are in developing or preclinical studies. Among these, we can cite the AccuFit system (Sino Medical Science Technology, China), Saturn technology (HT Consultant, Switzerland), and MitrAssist Valve (MitrAssist Ltd, Israel).[1,19]

Conclusions

Several demographic, anatomical, and technical reasons contributed to the slow development of TMVR compared with transcatheter aortic Valve replacement. The latter has been already confirmed safe and effective, whereas TMVR is still far from being part of the daily routine. However, although MV repair is often the preferred treatment, especially for MR, a replacement therapy will be the future when repair is not feasible or can lead to unsatisfactory results.

Disclosures

None.

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Key Words: aortic valve stenosis • mitral regurgitation • transcatheter aortic valve implantation