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Valvular Heart Disease (J Dal-Bianco, Section Editor)

Transcatheter Mitral Valve Replacement: An Update on the Current Literature

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Abstract

Purpose of review The purpose of this review was to evaluate the complexities and challenges associated with transcatheter mitral valve replacement and review the existing data.

Recent findings Many patients with mitral valve disease are not candidates for cardiac surgery and are in need of less invasive transcatheter therapies. The first transcatheter mitral valve replacement (TMVR) in a native valve was performed in 2012. However, the complexities and variability of the mitral valve anatomy and its relationship to neighboring structures have resulted in slower progress with this new therapy compared to the rapid uptake that has occurred with transcatheter aortic valve replacement. TMVR can be applied to degenerated prosthetic valves and annuloplasty rings or to a wide variety of native mitral valve disease. In cases of degenerated bioprosthetic valves, annuloplasty ring, and native valve mitral annular calcification, transcatheter heart valves (THVs) designed for the aortic position can be implanted with high procedural safety and success rates. In the case of native valve mitral regurgitation, the complexities have led to the development of several TMVR systems for native valve disease with different anchoring mechanisms and geometry; all are currently investigational and none are FDA approved at this time. It is clear from the initial experience with TMVR that careful patient selection and pre-procedural planning are necessary to maximize benefit and avoid complications.

Summary TMVR is an exciting complex therapy offering promise for patients who cannot be treated with existing techniques. The key to success will be a combination of appropriate patient selection, careful comprehensive pre-procedural planning, rising new technologies, as well as further research to appropriately define and mitigate the risks associated with the procedure.

Introduction

The mortality rate of untreated severe symptomatic mitral regurgitation (MR) is up to 50% at 5 years. [1, 2] A significant portion of these patients have secondary MR and are not referred for surgery due to a lack of strong evidence supporting surgical intervention in patients who are often high risk with multiple comorbidities including left ventricular (LV) dysfunction and pulmonary hypertension. [3] Recently, a large randomized trial has shown that transcatheter mitral valve edge-to-edge repair reduced heart failure hospitalizations and mortality in symptomatic heart failure patients with severe secondary MR who were on maximally tolerated doses of goal directed medical therapy. [4•] Transcatheter mitral valve replacement (TMVR) is an emerging frontier with unique challenges. TMVR serves as a less invasive approach for a broad spectrum of mitral valve diseases including native valve mitral regurgitation, valve in valve in degenerated bioprosthetic valves (ViV), valve in annuloplasty ring (ViR), and finally valve in mitral annular calcification (ViMAC). The TMVR clinical experience remains at an early stage and has not accelerated with the same tempo as transcatheter aortic valve replacement (TAVR). The stenotic aortic valve is a circular and tubular calcified structure which serves as an ideal anchor for a transcatheter valve. In contrast, the mitral valve anatomy is more complex with a saddle, D-shaped asymmetric annulus, with a complex subvalvular apparatus, and larger, more variable dimension of the mitral valve annulus requiring bulkier devices. Adding to the challenge is the absence of anchor or calcified structures in the case of native valve mitral regurgitation. Percutaneously placed mitral valves may impose on the left ventricular outflow tract (LVOT), other prostheses in the aortic position or displace the anterior mitral leaflet causing systolic anterior motion (SAM). This risk of LVOT obstruction complicates planning and success of the procedure. Furthermore, no long-term data exist regarding durability and optimal long-term anticoagulation strategies for TMVR prostheses. However, the surgical experience has shown that bioprosthetic valves in the mitral position are more likely to suffer from early structural degeneration compared to the aortic position and this risk is higher with younger patient age. [5] Currently, many of the patients treated with TMVR have high STS scores and reduced life expectancy; however, moving forward, durability of TMVR designs will have a growing importance. Many exciting technologies are under development and in various stages of investigation, and careful patient selection with multimodality imaging and clinical assessment will be crucial moving forward.

This review will describe new developments in TMVR in two broad categories. The first will be TMVR in mitral valve with use of aortic-designed transcatheter valves such as in deteriorated bioprosthetic valves, annuloplasty rings, and MAC. The studies evaluating these treatment categories are summarized in Table 1. The second will be TMVR in the native mitral valve regurgitation. Table 2 summarizes the current TMVR systems that are currently under evaluation (Fig. 1).

Treatment options for valve-in-valve, valve-in-ring, and valve-in-MAC

In valve-in-valve, valve-in-ring, and valve-in-MAC, there is a pre-existing anchor and radiopaque landing zone in the mitral position for implantation. With this technique, a balloon-expandable transcatheter valve is expanded and anchored onto the sewing ring, annuloplasty ring or calcified mitral annulus using radial force. The presence of a prior failed surgical valve implant also allows for predictable sizing given known dimensions as well as a fabric covered ring to facilitate sealing and minimize paravalvular leak (PVL). Delivery approaches for this technique have included transapical [26] and transvenous transseptal implantation. [9, 27•] Procedural planning for valve-in-ring and valve-in-MAC can be more complex than valve in valve, due to the greater variability of annulus size; shape, rigidity, and circumferential coverage of annuloplasty ring or calcification; and the presence of the native anterior mitral leaflet that can be displaced into the LVOT resulting in obstruction.

Ye et al. [7] evaluated outcomes of valve-in-valve procedures in both aortic and mitral positions. Success rate was high at 98.6% and 31 out of the 73 patients underwent mitral ViV. Estimated survival rates in the 73 patients were 88.9% at 1 year. These patients were followed for several years with survival rates of 69.8, 61.9, and 40.5% at 2, 3, 4, and 5 years, respectively. At 2-year follow up, 100% of patients with mitral ViV were in New York Heart Association (NYHA) class I or II. One year outcomes of transseptal balloon-expandable valves were evaluated in 87 patients with TMVR for failed mitral bioprosthesis, ring annuloplasty, or MAC who were high risk for surgery (mean STS score 13). [9] Sixty patients had ViV, 15 ViR, and 12 ViMAC. Procedural success was

Table 1. Trials evaluating the use of transcatheter aortic valves in the mitral position in patients with ViV, ViR, and ViMAC

	Number of patients	Mean STS %	Access	Device	Technical success
Bouleti et al. 2015 [6]	6 ViV 11 ViR	18±22%	100% Transseptal	100% Edwards Sapien	82%
Ye et al. 2015 [7]	42 ViV aortic 31 ViV mitral	9.6% 9.7%	– –	100% Edwards Sapien	98.6%
Yoon et al. 2017 [8]	*n* = 248 176 ViV 72 ViR	8.9±6.8%	33.1%Transseptal 66.5% Transapical 0.4%Transatrial	89.9% balloon-expandable valve	 96%* 83.3%*
Eleid et al. 2017 [9]	 60 ViV 15 ViR 12 ViMAC	13±8%,	100% Transseptal	100% Edwards Sapien	 97%* 74%*
Guerrero et al. 2017 [10]	6 ViMAC with post-TMVR ASA	–	50% Transseptal 50% Transapical	–	100
Babaliaros et al. 2017 [11•]	3 ViR 1 ViMAC 1 valve in annuloplasty	8.2±3.6	100%Transseptal	100% LAMPOON/Edwards Sapien	N/A
Guerrero et al. 2018 [12•]	116 ViMAC	15.3±11.6	40.5%Transseptal 39.7% Transapical 19.8%Transatrial	98.1% Edwards Sapien	76.7%*
Yoon et al. 2019 [13•]	*n* = 521 322 ViV 141 ViR 58 ViMAC	9.0±7.0%	39.5%Transseptal 59.5% Transapical	90% Edwards Sapien	 94.4%* 80.9%* 62.1%*
Yoon et al. 2019 [14•]	*n* = 194	7.4	47.9% Transseptal 51.5% Transapical 0.5% Transatrial	89.7% balloon-expandable valves	81.4%
	107 ViV	7.3	43.9% Transseptal 55.1% Transapical 0.9% Transatrial	7.7% Lotus 2.6% Direct Flow	94.4%
	50 ViR	6.2	46% Transseptal 54% Transapical 0% Transatrial		74%
	37 ViMAC	8.8	62.2% Transseptal 37.8% Transapical 0% Transatrial		54.1%

Table 1. (Continued)

	Need for second valve	% LVOT obstruction	Residual MR	Mean gradient mmHg	Outcomes
Bouleti et al. 2015 [6]	5.9%	–	≤ Mild 94%	8±3	18-month survival was 68±14% NYHA I-II at 22 months in 75%
Ye et al. 2015 [7]	1.4%	–	–	–	Estimated survival rates were 88.9, 79.5, 69.8, 61.9, and 40.5% at 1, 2, 3, 4, and 5 years, respectively. At 2-year follow-up 100% of mitral had NYHA class I or II.
Yoon et al. 2017 [8]		3.2%	≥ Moderate		The 1-year all-cause mortality rate
	2.8%	2.3%	6.8%	6.4±2.3	12.6%
	11.1%	2.3%	19.4%	5.8±2.7	28.7% More life-threatening bleeding, AKI. Failed annuloplasty ring was independently associated with all-cause mortality
Eleid et al. 2017 [9]		5%	≤ Mild 100%	7±3	At 1 year, 90% had NYHA I or II Survival free of death and cardiovascular surgery 30 day 1 year
	2%				95%, 86%
	13% 17%				78%, 68%
Guerrero et al. 2017 [10]	16.7%	100%	–	12.2	5 with immediate reduction in LVOT gradient and hemodynamics. One had persistent gradients but instability improved. One died on POD4 secondary to heart block and 1 had recurrence of obstruction POD thought to be secondary to septal edema
Babaliaros et al. 2017 [11•]	–	0	≤ Mild 100%	4.6±4.0	80% survival at 30 days with 0% LVOT obstruction in patients who were high risk for LVOT obstruction
Guerrero et al. 2018 [12•]	14.7%	11.2%	≥ 3+ Paravalvular MR: 4.9% 75% had 0 to trace MR	5.8±2.2	All-cause mortality 30 days 1 year 25%, 53.7%, At 1 year 71.8% were in NYHA I or II.
Yoon et al. 2019 [13•]			≥ Moderate	6.1±2.9	All-cause mortality (P<0.001) at 30 days 1 year

Table 1. (Continued)

		Need for second valve	% LVOT obstruction	Residual MR	Mean gradient mmHg	Outcomes
		2.5%	2.2%	5.6%		6.2%, 14%
		12.1%	5.0%	18.4%		9.9%, 30.6%
		5.2%	39.7%	13.8%	ViMAC 5.4±3.1	34.5%, 62.8%
Yoon et al. 2019 [14•]	–		13.4%	N/A	N/A	Procedural mortality: with LVOT obstruction 34.6% without LVOT obstruction: 2.4%
			1.9%			
			8.0%			
			54.1%			

*Technical success defined using the Mitral Valve Academic Research Consortium criteria

97% in the ViV group and 74% in the ViR/ViMAC group. Survival free of death and cardiovascular surgery was 95 and 86% in the ViV subgroup at 30 days and 1 year, respectively. Survival free of death and cardiovascular surgery was 78 and 68% in the ViR/valve an MAC subgroup at 30 days and 1 year, respectively, concluding that after a successful procedure, 1-year outcomes in carefully selected patients are favorable. As a result of this initial clinical experience with off-label use of balloon-expandable valves for mitral valve-in-valve, the use of the Sapien 3 valve received FDA approval for mitral valve-in-valve in June of 2017.

More recently, data from the TMVR multicenter registry was published by Yoon et al. [13•] evaluating procedural success and outcomes in this patient population. Five hundred twenty-one high-risk patients (STS 9%) were evaluated, with 322 ViV patients, 141 ViR patients, and 58 ViMAC patients. The majority of access was transapical; however, 39.5% were transseptal. Ninety percent used the balloon-expandable Sapien valve. Technical success was 89.1%, and a second valve implant was most frequently needed in ViR followed by ViMAC and ViV (12.1%, 5.2%, 2.5%, respectively). At 30 days, there was a higher rate of greater than or equal to moderate mitral regurgitation in ViR compared to ViV and ViMAC (18.4%, 5.6%, 13.8%, respectively). Patients with residual MR are known to have higher mortality as evaluated by prior mitral intervention studies. All-cause mortality was highest in ViMAC followed by ViR then ViR at both 30 days and 1 year. Patients with ViMAC had a mortality of 34.5% at 30 days and 62.8% at 1 year. No significant difference in mortality, stroke, valve embolization, or need for conversion to surgery was observed in transseptal compared to transapical access. However, TMVR via transseptal was associated with a higher rate of atrial septal defect closure, as well as lower rate of life-threatening or fatal bleeding. This group also evaluated the influence of operator experience on outcomes and noted a lower risk of complications and mortality in the late experience group most pronounced in the ViV outcomes. Exactly 78.9% of the patients evaluated in this study had data regarding anticoagulation, and the authors noted that the incidence of thrombosis was significantly higher in patients without anticoagulation who only received antiplatelet therapy compared to patients on therapeutic anticoagulation (6.6 vs. 1.6%).

Guerrero et al. have compiled the TMVR in MAC multicenter global registry to examine outcomes of the use of transcatheter valves in severe MAC, which is

Table 2. TMVR with In-Human experience currently under evaluation

Device	First in human implant	Anchoring design	Design	Valve positioning	Access
CardiAQ-Edwards	2012	Mitral annular clamping with atrial and ventricular flanges acting as opposing anchors.	Circular design ➔ no rotational alignment needed.	Supra-annular with polyester fabric sealing skirt intra-annular	Transapical transseptal
Neovasc Tiara	2014	Native leaflet engagement Ventricular anchors to grasp the free margins of the native leaflets	D-shaped design	Intra-annular	Transapical
Intrepid TMVR	2014	Radial forces and sub-annular cleats	Circular	Intra-annular	Transapical
Tendyne	2014	Apical tether	D-shaped (outer stent) Circular (inner frame)	Intra-annular	Transapical
Caisson	2016	External anchor. Mitral annulus capture with engagement at sub-annular fibrous groove	D shape	Supra-annular Has SAM management feature	Transseptal
MV valve system	2015	External anchor. Mitral annulus capture	Circular	Docking system compatible with commercially available valves	Transapical
NCSI NaviGate Mitral	2015	Annular winglets	Circular	–	Transapical Transseptal Transatrial
HighLife TMVR	2017	External anchor Mitral annulus capture	Circular	Sub-annular ring implant	Transapical Femoral artery for guidewire
Sapien M3	2018	Modified Sapien 3 with Dock	Circular	Intra-annular docking system	Transseptal
AltaValve System	2019	Nitinol frame of spherical shape	Circular	Supra-annular with fabric skirt to prevent perivalvular leak	Transapical

Table 2. (Continued)

Device	Delivery system	Recapture	Trials
CardiAQ-Edwards	33 F	NO	First in Human [15] 13 patients with 92.3% procedural success. All cause mortality 53.8% at 30 days
			Relief Trial: early feasibility was voluntarily paused by the company in early 2017 to re-evaluate one of the features
Neovasc Tiara	32F	NO	First in human [16]
			Tiara in patients with prior AVR and no LVOT obstruction [17]
			TIARA-I early feasibility in the USA
			TIARA II early feasibility in Europe
Intrepid TMVR	35 F	NO	First in Human [18]
			Feasibility trial [19]
			Apollo Trial
Tendyne	36F	Fully recapturable after complete deployment	First in Human [20]
			Feasibility Trial [21•]
			CE Mark Trial
Caisson	31F	Fully recapturable and retrievable	5 patients in early feasibility presented at PCR 2016
			PRELUDE: Prospective registry: 20 pts. finished enrolment.
			Interlude: now enrolling—completion by 2020.
MV valve system	32F	Fully recapturable and retrievable after full deployment	First In Human
			DOCK 1 with lotus: Early feasibility, Prospective registry, Thirty patients
NCSI NaviGate Mitral	30F	NA	First In Human
			Early feasibility and safety underway. Thirty patient is in 2 centers
HighLife TMVR	32F	Fully retrievable	First In Human [22]
			Results from first 6 patients presented at TCT 2016 [23]
Sapien M3	20F	Retrievable	Early feasibility presented TCT2018 with 30-day outcomes [24]
AltaValve System	32 F	Repositionable and partially retrievable	First In Human [25] Feasibility study planned

among the exclusion criteria in most early feasibility TMVR mitral trials. Data was first published in 2016 [28] with procedural and 30-day outcomes in 64 patients who underwent TMVR with compassionate use of balloon-expandable transcatheter valves. Then, in 2018 [12•], 1-year outcomes were published in 116 patients as the registry expanded. Delivery approach included transseptal, transapical, and direct transatrial with 76.7% technical success defined using the Mitral Valve Academic Research Consortium criteria. A second valve was needed in 17 patients. Thirty-day and 1-year all-cause mortality was 25 and 53.7%, respectively. Operator experience was also evaluated in this study with no statistically significant difference as far as mortality; however, there was a trend toward lower 30-day mortality and lower need for second valve.

Left ventricular outflow tract obstruction with hemodynamic compromise occurred in 11.2% of the patients, and was noted to be an independent predictor of mortality at 30 days and 1 year. Risk factors include a less obtuse aorto-mitral annular angle, septal hypertrophy, small left ventricular size, and device protrusion and flaring into LVOT. Strategies to evaluate and treat these risk factors to avoid complications are being evaluated, including pre-procedural three-dimensional multidetector row computed tomography (MDCT) planning and patient selection. NeoLVOT is defined as the new LVOT area that exists following TMVR that can be estimated by virtually implanting a valve into the mitral annulus on MDCT utilizing 3D modeling software. The estimated NeoLVOT area shows an inverse correlation with peak LVOT gradient and a strong linear correlation with actual NeoLVOT area as assessed with post-procedural MDCT measurements. No cut point threshold for NeoLVOT area has been clearly defined, although one study found that a NeoLVOT area of less than 189 mm^2 was associated with clinically significant LVOT gradients. [29] In addition, mitral annulus to interventricular septum distance has been shown to be of excellent predictive value for LVOT obstruction. This measurement is simple and easily performed by echocardiography without simulating the TMVR procedure, providing potential adjunctive role to MDCT. These methods are not however well validated in patients with reduced ejection fraction and dilated LVs. [14•] Preemptive alcohol septal ablation as well as percutaneous anterior mitral valve laceration are techniques to reduce the risk of LVOT obstruction based on the pre-procedural imaging. Some experience now exists with the use of alcohol septal ablation, initially as a bail-out strategy after the development of obstruction, and more recently as a preemptive technique to avoid LVOT obstruction altogether post-TMVR [10, 30, 31•]. The LAMPOON procedure (Laceration of the Anterior Mitral leaflet to Prevent left ventricular Outflow tract ObstructioN) is a novel technique to split the anterior mitral valve leaflet and prevent iatrogenic LVOT obstruction immediately prior to TMVR. [11•] Two retrograde guides are advanced via a retroaortic approach and positioned across the aortic valve. The first in-human experience of this technique was published in 2017 [11•], including three patients with prior mitral valve rings, one mitral annuloplasty, and one valve in MAC. These patients had risk factors for LVOT obstruction that were prohibitive for TMVR including long leaflet length (>30 mm) combined with an acute aorto-mitral angle. In patients at high risk for hemodynamic collapse secondary to LVOT obstruction following TMVR, the LAMPOON procedure allowed for TMVR without LVOT compromise and was not associated with short term hemodynamic deterioration. Four of five patients were alive at 1 month. One death occurred on day 23 secondary to right heart failure that did not improve post-TMVR.

A recent study by Yoon et al. [14•] attempted to define a NeoLVOT cut point predictive of obstruction. NeoLVOT was pre-procedurally estimated with MDCT in patients undergoing TMVR for failed bioprosthetic valves (n=107), annuloplasty ring (n=50), and severe MAC (n=37). LVOT obstruction (defined as an increase in LVOT gradient ≥10 mmHg from baseline) was observed in 13.4%, with the majority of these cases occurring in ViMAC and associated with a higher procedural mortality compared to patients without LVOT obstruction (34.6 vs. 2.4%). Receiver operating characteristics showed that an estimated NeoLVOT area ≤1.7 cm^2 predicted LVOT obstruction with sensitivity of 96.2% and specificity of 92.3%. The difference noted between the trials as far as incidence of LVOT obstruction (54.1% in Yoon et al. [14•] compared to 11.2% in Guerrero et al. [12•]) in patients with ViMAC is likely attributable to careful patient selection and pre-procedural planning with estimation of NeoLVOT using MDCT.

Observational data for ViV TMVR has demonstrated excellent outcomes for degenerated bioprosthetic valves with adequate patient selection, pre-procedural planning, and operator experience. However, TMVR for ViR and ViMAC is associated with higher risk of procedural complications and increased of mortality following TMVR. Patient selection and multimodality imaging including MDCT is critical to optimize procedural

outcomes in this population. Evidence thus far favors long-term anticoagulation for all of these patients given increased risk of valve thrombosis in patients only on antiplatelet therapy; however, further information is needed.

The MITRAL (Mitral implantation of Transcatheter Valves) trial is a US FDA-approved, investigator-sponsored, prospective, multicenter, pilot investigational device exemption trial that is currently underway (recruitment completed) to evaluate the safety and feasibility of Edwards Sapien valves in native valves with severe MAC, failed surgical rings, and failed surgical bioprosthesis. The results of this trial will provide further information to guide the management of these highly complex patients.

Treatment options for native mitral valve regurgitation

TMVR for non-calcific MR is challenging given the lack of a rigid scaffold, and the variability of the annulus size and surrounding structures. The absence of significant annular calcification limits the use of radial force to achieve a fixed prosthesis position, and thus alternative methods for anchoring are necessary. Furthermore, the anterior mitral leaflet and its displacement by the transcatheter valve may contribute to LVOT obstruction and hemodynamic compromise.

The goal of TMVR treatment of native MR is to anchor the prosthesis in a D-shaped, non-calcified structure avoiding migration into the left ventricle, development of paravalvular leak, and displacement of the anterior mitral valve leaflet into the LVOT. Unlike the aortic valve, the mitral valve has a highly dynamic morphology and is subjected to a high closing pressure generated by the left ventricle during systole, increasing the risk of prosthesis migration as well as paravalvular leak. Transseptal delivery is the least invasive access strategy, requiring flexible delivery catheters that can accommodate extreme angles and a large valve prosthesis. Several different TMVR systems have been designed to address these fundamental concerns: unique anchoring mechanisms and sealing strategies in a D-shaped annulus (circular vs. D-shaped design). LVOT obstruction is accounted for in some valve designs with supra-annular positioning to minimize both the ventricular profile and risk of LVOT obstruction often combined with a sealing skirt to prevent PVL (Table 2). Some of the more recent transseptal mitral valve designs employ docking systems that are implanted first, followed by a more simplified valve prosthesis that is expanded within the dock. The anchoring mechanisms themselves as well as techniques for device delivery are described in the individual published papers describing first in human experience (Fig. 2).

No TMVR devices have been cleared by the FDA and nearly all trials are in the early feasibility trial stage with small enrollment. [15, 16, 18, 20, 22, 25, 32–35, 36•, 37] The first TMVR for native MR in a human was performed in 2012 in Denmark using the CardiAQ valve system (Edwards Lifesciences, Irvine, CA). [38] Since then, many in-human experiences and some early feasibility trials have been published using different TMVR systems. This review will only discuss the devices that have in-human experience as detailed in Table 2. Several other devices are in development but have not been implanted in humans yet. Many feasibility trials are underway and have experienced challenges recruiting patients in part due to anatomic restrictions and strict inclusion/exclusion criteria.

Early experience with TMVR in native severe MR was summarized by Reguiero et al. Small human early feasibility studies were performed in several unique TMVR systems including Tendyne (Abbott Vascular, Abbott Park, IL) (30 patients), Intrepid (Medtronic, Minneapolis, MN) (27 patients), Neovasc Tiara (Neovasc, Richmond, British Columbia, Canada) (19 patients), CardiAQ-Edwards (Edwards Lifesciences, Irvine, CA) (13 patients), Fortis (Edwards Lifesciences, Irvine, CA) (13 patients), HighLife (HighLife Medical, Irvine, CA) (6 patients), Caisson (Maple Grove, MN) (5 patients), MValve (Herzliya, Tel Aviv, Israel) (1 patient), and NCS NaviGate (NaviGate Cardiac Structures, LakeForest, CA) (7 patients). The FORTIS TMVR system is no longer available secondary to valve thrombosis. [39, 40•] Most of the published TMVR experience for native MR involves two TMVR systems: Tendyne and Intrepid. Mean STS score of patients included in these trials was 7.5 with an ejection fraction (EF) of <50% in 75.6% of patients. Technical success was 88.4% with a procedural mortality of 8.8%. Very few of these TMVR systems were transfemoral as most initial device iterations were designed for transapical access. Thirty-day mortality was noted to be 23.2%. Only 1% had LVOT obstruction and 1.3% had equal to or greater than moderate residual regurgitation, an important finding given the association of residual mitral regurgitation with less favorable outcomes.

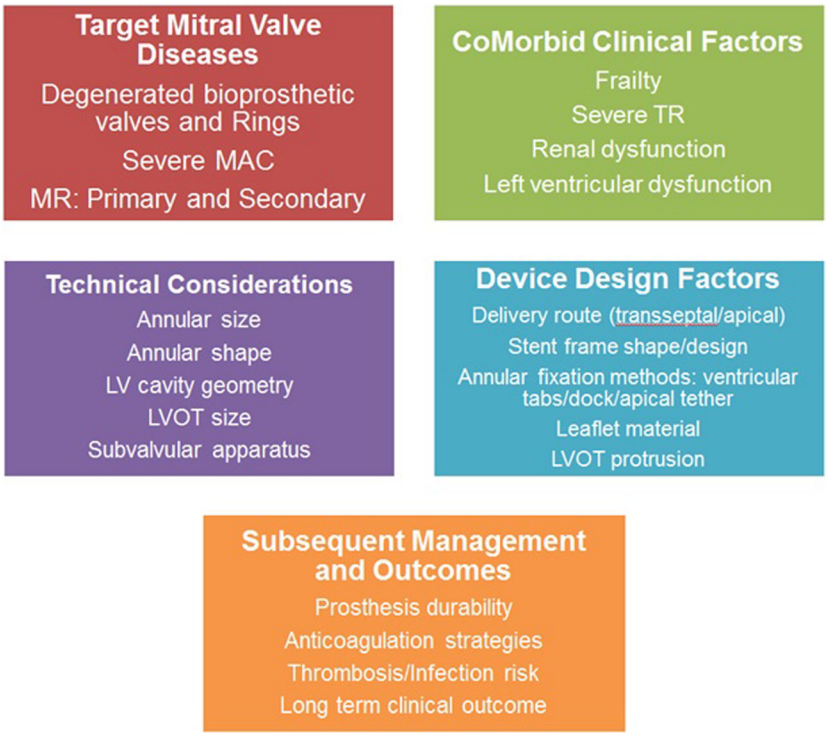

Fig. 1. Considerations for TMVR in this era.

The first in-human use of the Intrepid valve (Medtronic, Minneapolis, Minnesota) occurred in 2014. [18] This is a circular bovine pericardial self-expanding prosthesis delivered via transapical approach with anchoring achieved via "champagne cork-like" conformation producing a radial force. An Intrepid clinical trial [19] was completed in 50 patients with mean STS of 6.4% with severe symptomatic MR who met specific CT-based anatomic inclusion criteria, excluding patients with LV EF less than 20%. Valve deployment was successful in 48/50 of the patients with an average deployment time of 14 min. No disabling stroke or repeat interventions at 30 days occurred; however, mortality was 14%. All patients had mild or less residual mitral regurgitation with no MR in the majority of patients. After median follow up of 173 days, there was significant improvement in NYHA and Minnesota Heart Failure Questionnaire scores. [19] The APOLLO trial is an ongoing, randomized trial that will include 1:1 randomization to TMVR vs. MV surgery in patients who have acceptable surgical risk (goal recruitment of 650 patients) and TMVR in patients who are ineligible for the surgical procedure (goal of 550 patients). The first patient was enrolled in October 2018 and the results are not expected until 2021.

Tendyne, a D-shaped porcine pericardial self-expanding prosthesis delivered via a transapical approach and secured via a unique apical tethering device, was first implanted in a human patient in October 2014. [20] A feasibility trial was performed in 30 patients with severe symptomatic MR who were poor surgical candidates (STS 7.3%) with successful valve implantation achieved in 28 patients. [35] One patient had mild MR, with the remainder having none. At 30 days, there was no cardiac death, stroke, or MI. LV end diastolic volume index improved from 90.1 to 72 at follow up while the LV end systolic volume index decreased from 48.4 to 43.1. At 1 year follow up, there were no strokes, 5 deaths (non-procedure related), and 3 heart failure hospitalizations. Exactly 21/22 of the patients had no MR at 1 year. Furthermore, the results for the first 100 patients treated with Tendyne were presented at the EuroPCR meeting in 2018. Thirty-day mortality was 6% in a population with a mean STS predicted risk of mortality of 7.9%, suggesting that growing experience with TMVR with improved patient selection and pre-procedural planning can lead to favorable clinical

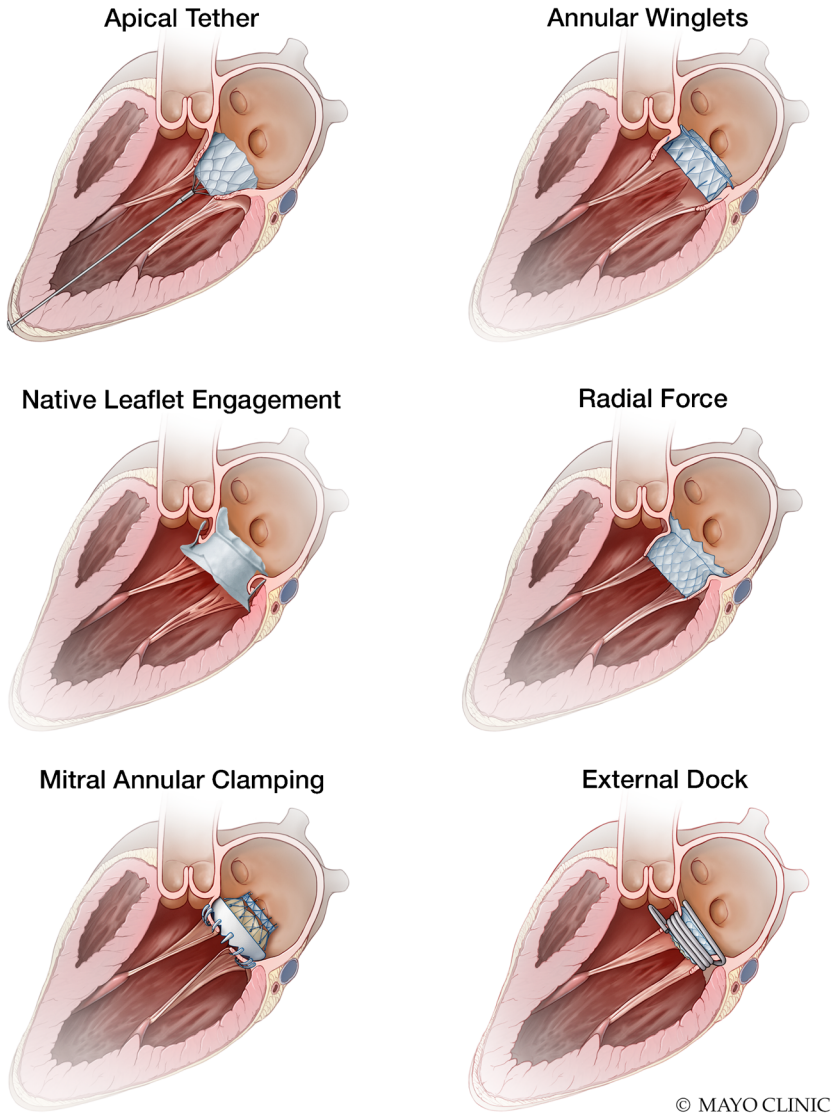

Fig. 2. Anchoring mechanisms of transcatheter mitral valves.

outcomes. Technical success was 97% with no stroke or emergency surgery needed. Exactly 98.7% had no/trace mitral regurgitation at 30 days, and significant reduction in LV volumes and improvements in functional class occurred [41].

Patients with prior AVR are often excluded from TMVR trials because of the potential risk for LVOT obstruction or interaction with the aortic prosthesis. The Tiara valve was evaluated in 12 patients with prior AVR and severe symptomatic MR (compassionate use) [17]. These patients had mean STS score of 10.5% with EF of 35% and were at prohibitive surgical risk, with 50% having secondary MR. Careful pre-procedural planning was done including confirming a NeoLVOT of ≥2.0 cm2 at end systole as part of the eligibility criteria to avoid hemodynamic compromise secondary to LVOT obstruction. Procedural success rate was 100% with no major adverse cardiovascular events at 30 days including no deaths. The TMVR did not interfere with prior aortic valve prosthesis which acted as an angiographic marker during the procedure. These results were encouraging, however it is very important to note that pre-procedural patient selection and planning likely played a large role in the outcomes noted, specifically evaluation of virtual NeoLVOT.

Several other feasibility trials are ongoing with unique TMVR systems. However, enrollment has been slow, which was a subject of investigation by Niikura et al. [42] In this study, 203 patients with symptomatic severe MR with high surgical risk were screened for research participation (Intrepid and Tendyne) in early feasibility TMVR studies, and 89% of these patients were found to be ineligible. The most common reasons cited included frailty (15.3%) followed by severe TR (15.3%), prior AV valve therapy (14.2%), severe MAC (7.4%), and LVOT obstruction risk (4.4%). Exactly 62.6% of patients ineligible for TMVR underwent surgery (27 replacement, 15 repair) or transcatheter edge-to-edge repair, with the remainder treated medically (37.4%) (85). Incidence of cardiac death at 1 year was 2.4% for treated patients and 11.8% for medically managed patients ($p<0.0001$). Differences in outcomes remained significant after exclusion of patients with excessive frailty or medical futility in multivariate adjustment. Only 103 patients in this study underwent CTA to evaluate anatomic and ineligibility prior to consideration for trial, and clinical variables were used for exclusion prior to anatomic criteria, which may explain the low numbers of exclusion secondary to anatomy. The exclusions for TMVR were mostly protocol driven, further highlighting the importance of patient selection.

Summary

The approach to severe MR patients at high risk for conventional surgery continues to be complex, relying on the heart team approach to consider all potential interventions including surgery, transcatheter edge-to-edge repair, or TMVR with commercial or investigational devices. In patients undergoing TMVR for native valve mitral regurgitation, careful patient selection and pre-procedural assessment are key. The complexity of the mitral valve anatomy requires multimodality imaging including transthoracic and transesophageal echocardiography with 3D imaging and ECG gated cardiac CT. These techniques facilitate delineation of the type and severity of MR, as well as mitral annulus dimensions, annular calcification, subvalvular apparatus morphology, and LVOT anatomy to confirm eligibility depending on valve design. Imaging also allows for assessment of risk of complications, especially with MDCT, as well as optimizing fluoroscopic angles for use during the procedure. Improved participation in feasibility trials will serve to grow and more fully understand the role of this exciting field. Although the TMVR field has already made many important advances in the setting of complex mitral valve disease, important data are lacking data regarding the optimal patient, optimal valve design, durability, anticoagulation strategy as well as the ongoing role of multimodality imaging for pre-procedural assessment.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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