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Transcatheter Mitral Valve Implantation

Current Status and Future Perspectives

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ABSTRACT: Mitral transcatheter therapies represent the treatment of choice for all patients deemed unsuitable for cardiac surgery. So far, the largest clinical experience has been limited to percutaneous repair techniques. However, given the complexity and heterogeneity of mitral valve anatomy and pathology, transcatheter mitral valve implantation will widen the mitral valve therapies horizon, toward a patient-tailored approach. Current data about transcatheter mitral valve implantation is still limited and, although some data are promising, there are still some issues to be addressed. This review provides a comprehensive insight into the available devices and describes potential advantages and limitations of transcatheter mitral valve implantation.

Key Words: bioprosthesis ■ heart valve disease ■ mitral valve ■ mitral valve insufficiency

Mitral regurgitation (MR) affects almost 10% of individuals >75 years.[1] Although open-heart surgery is the gold-standard treatment for severe MR, large clinical registries demonstrated that up to 50% of symptomatic patients with severe regurgitation are deemed not suitable for surgery due to high operative risk.[2] In this perspective, transcatheter mitral valve (MV) interventions, either repair or replacement, represent a valuable alternative therapeutic option. Leaflet repair with MitraClip (Abbott Vascular) has demonstrated its safety and efficacy and, with over 100 000 implantations performed, it is the most used transcatheter device for MV repair (transcatheter mitral valve repair [TMVR]).[3–5] TMVR has a steep learning curve and is associated with a 10% to 20% rate of persistent or recurrent MR >2+ after one year in different series, especially in the early experiences, largely depending on patient selection and on operators' experience.[6,7] Indeed, patient eligibility, variability of the MV disease, mechanism, and dependency upon operators' experience can be a limitation for TMVR, suggesting the need for a complementary and more reproducible percutaneous therapy.

Transcatheter MV replacement has been performed in different settings (valve-in-valve [ViV], valve-in-ring [ViR], valve-in-mitral annular calcification [ViMAC]), broadening the MV therapeutic horizons.

Tendyne (Abbott Vascular) is the first approved device for implantation in native MV. However, experience in the field of transcatheter MV implantation (TMVI) is still limited as compared to MitraClip (Figure 1), and some potential advantages are counterbalanced by several clinical and technological challenges. The purpose of this paper is to review the current available TMVI technologies and their application in different settings and to provide future perspectives for TMVI.

TMVI FOR VIV, VIR, VIMAC

A significant proportion of patients undergoing MV surgery requires reoperation during follow-up, reaching up to 35% during the 10 years after MV replacement or repair.[8] Although redo surgery is the treatment of choice after bioprosthesis or ring annuloplasty failure, it may be associated with significant early mortality (5%–12%), especially in patients with concurrent comorbidities.[9,10] Thus, TMVI with

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Nonstandard Abbreviations and Acronyms

LA	left atrial
LV	left ventricular
LVOTO	left ventricular outflow tract obstruction
MAC	mitral annular calcification
MR	mitral regurgitation
MV	mitral valve
MVARC	Mitral Valve Academic Research Consortium
PVL	paravalvular leakage
TMVI	transcatheter MV implantation
TMVR	transcatheter mitral valve repair
ViMAC	valve-in-MAC
ViR	valve-in-ring
ViV	valve-in-valve

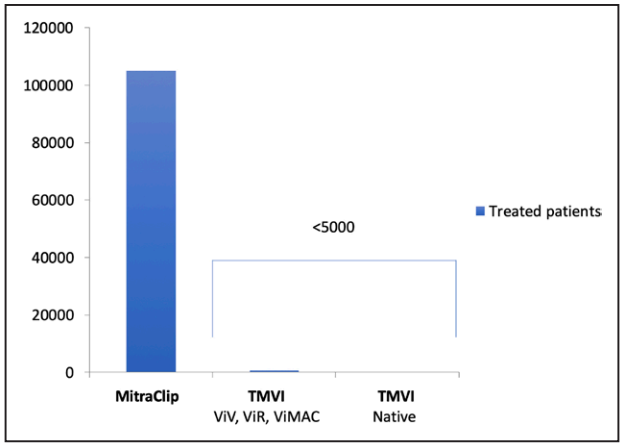

Figure 1. Comparison between MitraClip and transcatheter mitral valve implantantion (TMVI).
Number of treated patients with MitraClip (**left**) and with TMVI (**right**). ViMAC indicates valve-in-MAC; ViR, valve-in-ring; and ViV, valve-in-valve.

balloon-expandable valves has been attempted for treatment of failed mitral bioprosthesis or rings, mainly using the SAPIEN/XT prostheses (Edwards Lifesciences) through the transapical and, recently, transfemoral approach.

Latest short-term data from the Valve-in-Valve International Data registry about TMVI in failed surgical bioprosthesis and rings have been recently published[11] and showed the results of 857 patients undergoing TMVI for ViV and 222 for ViR with a median follow-up of 492 days. All patients included were at high risk for redo surgery. The most common access site was the transapical (62%) followed by transvenous/transseptal (37%) although this trend has inverted over the last years. The most used prostheses for replacement were the SAPIEN 3 (42%). Overall technical success was 91%. However, residual mean gradient >5 mm Hg occurred in 61% of patients. Mispositioning occurred in 3.3% of the cases, and in some of them, a second valve implantation was required. Left ventricular (LV) outflow tract obstruction (LVOTO) was reported in 2.6% of cases, being more common in the ViR group (5.9%). After ≥1-year follow-up MR greater than or equal to moderate was observed in less than 6% of the patients of ViV and in less than 20% in ViR group. Four-year survival rate was 62.5% in ViV versus 49.5% for ViR.

Largest data about long-term follow-up were published by Yoon et al[12] providing a real-world snapshot about TMVI in these 3 different settings (ViV=322; ViR=141; ViMAC=58).[13] Transapical was the preferred access (59.5%) and SAPIEN valves devices were the most implanted (90%). Significant different results and outcome were observed among the three groups: 30-day and 1-year all-cause mortality in the ViV group was 6.2 and 14.0%, respectively. Such data are noteworthy if considered that in-hospital mortality for redo mitral replacement is between 9% and 12.6% and that the prevalence of functional etiology of the initial MR is high.[14–16] Reported adverse events were relatively low in ViV group with a 2.2% of LVOTO and 3.3% of paravalvular leakage (PVL) at 30-day echocardiogram.

In the ViR group, the 30-day and 1-year mortalities were higher than ViV (9.9 and 30.6%, respectively) as well as the rate of adverse events (LVOTO=5% and PVL=12.6%). Of note, failing surgical rings types were not specified; therefore, only marginal conclusions can be made on these data. In our experience, ViR outcomes are highly influenced by ring type.

The worst outcomes among the 3 groups are those of the ViMAC: 30-day mortality was 34.5% and 1-year all-cause death reached 62.8%. Of note, valve embolization was 6.9%, and residual significant MR was 13.2%. However, the highest concern was related to the high rate of LVOTO (39.7%) suggesting the importance of a careful preprocedural computed tomography analysis and how this group remains the most challenging.

Better results came from the TMVR in MAC Global Registry where LVOTO with hemodynamic compromise occurred in 11.2% of cases. The reduction of the LVOTO rate was due to increased awareness, but it remained the most important and independent predictor of 30-day and 1-year mortality.[17]

On the same line are the data by Eleid on 87 high-risk patients undergoing TMVI[18] and those coming from the ongoing MITRAL trial (Mitral Implantation of Transcatheter Valves; https://www.clinicaltrials.gov; Unique identifier: NCT02370511).[19] Interestingly, the only 3 cases of LVOTO with hemodynamic compromise were in the ViMAC group, and in 10 patients deemed at high risk for LVOTO, alcohol septal ablation was performed before valve replacement preventing LVOTO.

Finally, the very recent data from the Transcatheter Valve Therapy registry confirmed the low mortality and low complication rate at 30 days follow-up for the VIV as compared to VIR and ViMAC patients.[20] Table 1 summarizes main data on TMVI in the setting of ViV, ViR, and ViMAC.

Table 1. TMVI in ViV, ViR, Valve-in-MAC

	VIVID[11]		Yoon[12]			Eleid[18]			MITRAL			Guerrero[19]		
	ViV	ViR	ViV	ViR	Valve-in-MAC	ViV	ViR	Valve-in-MAC	ViV	ViR	Valve-in-MAC	ViV	ViR	Valve-in-MAC
	N=857	N=222	N=322	N=141	N=58	N=60	N=15	N=12	N=30	N=30	N=31	N=680	N=123	N=100
Access site	TS		TS			TS			TS	TS	TS	TAp		
	TAp		TAp								TAp	TS		
	Tat		TAt								TAt	Other		
Device type	Sapien, XT, 3		Sapien, XT,3			Sapien XT,3			Sapien XT,3			Sapien, XT, 3		
	Melody		Lotus									Other		
	Other		Direct Flow											
			Melody											
Procedural success, %	/	/	73.6	57.4	41.4	97	73	75	93.3	73.3	53.3	90.9	82.9	74
MR≥3 at 30-day, %	/	/	3.3	12.6	13.2	1.6	0	0	0	0	4.0	1.9	9.3	5.7
LVOTO, %	1.8	5.9	2.2	5.0	39.7	5	20	17	0	0	9.7	0.7	4.9	10
Valve embolization/ malpositioning, %	2.4	7.0	0.9	1.4	6.9	0	0	8.3	0	0	0	0.1	2.4	3
Second valve implantation, %	2.8	10.1	2.5	12.1	5.2	2	13	17	0	20	3.2	1.5	7.3	14
30-day mortality, %	6.5	8.6	6.2	9.9	34.5	5	0	17	3.3	6.7	16.7	8.1	11.5	21.8
1-year mortality, %	13.8	23.2	14.0	30.6	62.8	14	18	43	3.3	26.7	33.3	/	/	/

LVOTO indicates left ventricle outflow tract obstruction; MAC, mitral annular calcification; MITRAL, Mitral Implantation of Transcatheter Valves; MR, mitral regurgitation; TAp, transapical; TAt, transatrial; TMVI, transcatheter mitral valve implantation; TS, transseptal; ViR, valve-in-ring; ViV, valve-in-valve; and VIVID, Valve-in-Valve International Data.

TMVI FOR NATIVE MV

Over the last years, several devices with different designs have been tested (Figure 2). Pooling together available data from all the devices, the experience gained is still fairly limited with <1000 TMVI procedures and a high selection failure rate (>80%).[21] Mean anatomic eligibility criteria and most common causes for selection failures are summarized in Tables 2 and 3.[22,23] In the following paragraph, early experience of the most used technologies are presented.

TMVI DEVICES

Tendyne

Tendyne valve (Abbott) has 3 porcine pericardial tissue leaflets sewn onto a circular nitinol inner stent. This is sutured to an outer D-shaped stent, designed to facilitate sealing. The prosthesis is connected to a braided fiber tether passing through the LV apex and secured to an external pad. Of note, it is fully retrievable until the end of the procedure (Movie I in the Data Supplement).

Data from the Global Feasibility Study and from CE-mark approval study have recently been published.[24] It included a total of 100 patients (mean Society of Thoracic Surgeons score 7.8±5.7), mostly affected by secondary MR Implant success was obtained in 97% of cases while 3 implants were abandoned or retrieved. One-year mortality was 26% and a total of nine device-related adverse events were reported (3 hemolysis and 6 thrombosis). A clinical improvement and durable echocardiographic results were also reported both at short- and long-term follow-up.[25]

Currently, it is the only Conformitè Europeenne (CE)-mark approved and is indicated for patients unsuitable for MV repair or at high operative risk. In addition, it has been successfully used to treat ViMAC. Its D-shape and the retrievability might represent 2 important advantages while the peculiar design and anchoring system might limit its use only to transapical approach.

Tiara

Tiara (Neovasc Inc) consists of a trileaflet bovine pericardial and D-shaped valve mounted within a self-expanding nitinol alloy frame. The fixation is based on the combination of radial force, and 3 anchors capturing the native leaflets from the ventricular side whereas the atrial skirt provides a seal against possible PVL.

So far, a total of 79 patients, including the TIARA-I (Tiara Transcatheter Mitral Valve Replacement Study), TIARA-II, and compassionate use, have been enrolled.[26] No procedural deaths were reported, whereas 7 deaths occurred after 30-day follow-up not considering the compassionate procedures. Prostheses performances were excellent after 1-year follow-up with all patients showing mild or less residual MR

Like Tendyne prostheses, its D-shaped design might represent an important feature to limit the risk for PVL alongside the anterior mitral leaflet capture which reduces the risk of LVOTO. A transfemoral system is

	Tendyne (Abbott) N=100	Tiara (Neovasc) N=79	Intrepid (Medtronic) N=50	Evoque (Edwards) N=15	Sapien M3 (Edwards) N=15	Highlife (Highlife SAS) N=15	Cardiovalve (Valtech) N=5
Frame	Nitinol double frame SE	Nitinol SE	Nitinol double frame SE	Nitinol SE	Cobalt-chromium BE	Nitinol SE	Nitinol SE
Leaflets	3 porcine	3 bovine	3 bovine	3 bovine	3 bovine	3 bovine	3 bovine
Anchoring mechanism	Apical tether	Leaflet engagement	Small cleats + Radial force	Annulus clamping	Nitinol dock system	External anchor	Leaflet grasping
Approach	Transapical	Transapical	Transapical	Transfemoral	Transfemoral	Transapical	Transfemoral
Delivery system, Fr	36	32-36	35	30	20	39	28
FMR aetiology, %	89	62	72	27	/	73	100
Technical success, %	97	93	98	93	87	73	100
30-day mortality, %	6	13	14	7	3	20	60
1-year mortality, %	26	/	/	/	/	20	60

Figure 2. Transcatheter mitral valve implantation in native mitral valve.
BE indicates balloon-expandable; FMR, functional mitral regurgitation; Fr, French; and SE, self-expandable.

under development possibly contributing to a wider use of the device.

Intrepid

The Intrepid (Medtronic) has a dual stent design: a conformable outer stent engages the annulus, providing fixation and sealing while the circular inner stent houses a tricuspid bovine pericardial valve. Fixation is achieved by a cork effect produced through variable stiffness along the height of the outer stent and by frictional elements.

Early experience is based on 50 patients, mostly affected by functional MR.[27] Device success rate was 98% with 30-day mortality of 14%. MR at 6 months was less than mild in all patients, and both symptoms and quality of life were improved.

Possible strong points are represented by the recapturability and the rotational orientation needless, whereas its circular shape might increase the risk for PVL.

Evoque

Evoque (Edwards Lifesciences), consists of a trileaflet bovine pericardial valve mounted within a circular, self-expanding nitinol frame, covered with polyester to minimize PVL. Fixation is provided by two opposing sets of anchors that capture the native leaflets. Both transfemoral and transapical delivery systems have been developed.[28]

A total of 15 patients undergoing transfemoral/transseptal approach have been enrolled so far, including compassionate use (n=8) and early feasibility study (n=7) cases.[29] Technical success was achieved in all cases but one requiring conversion to surgery. At 30-day follow-up, one death occurred (7%) while PVL closure and LVOTO needing intervention were performed in two and one patient, respectively. The transfemoral delivery availability might be promising for the device.

Highlife

The HighLife (HighLife Medical) is a 2-component system: a subannular implant creates a closed loop with a fixed perimeter around the patient's native valve leaflets and chordae. Then, the prosthesis is implanted anchoring

Table 2. Mean Anatomic Eligibility Criteria for TMVI

	Value
CT scan parameters	
Mitral annulus area (systolic), cm^2	<8.6
Dmean, mm	≤38.3
Aortomitral angulation, °	>130
Annulus-to-apex distance (diastolic), mm	>100
Anteroposterior diameter, mm	>41.6
Transesophageal echocardiography parameters	
C-C diameter, mm	<39
LVESD, mm	>32

C-C indicates commissure-to-commissure; CT, computed tomography; Dmean, mean mitral annulus diameter; LVESD, left ventricle end-systolic diameter; and TMVI, transcatheter mitral valve implantation.

Table 3. Most Common Selection Failure Causes for TMVI in Native MV

Anatomic	
Risk of LVOT obstruction	+++
Large native MV	+++
Small native MV	+
Severe MAC	+
Baseline SAM	+
Clinical	
LV dysfunction	+
Low surgical risk	+
Elevated sPAP	+
Severe TR	+

LV indicates left ventricular; LVOT, left ventricle outflow tract; MAC, mitral annular calcification; MV, mitral valve; SAM, systolic anterior motion; sPAP, systolic pulmonary arterial pressure; TMVI, transcatheter mitral valve implantation; and TR, tricuspid regurgitation.

the entire system to the subannular implant. According to early experience (15 patients), 30-day and 1-year mortality were 20% and 27%, respectively.[30] No PVL was observed while only one case of LVOTO and one case of mean transvalvular gradient >5 mm Hg was reported.

The delivery and anchoring system, reminding a valve-in-ring, might reduce PVL incidence. However, data are still limited to draw conclusions.

Sapien M3

Sapien M3 (Edwards Lifesciences) is a balloon-expandable valve with a cobalt-chromium frame and 3 bovine leaflets. It is implanted through the transfemoral route. Early experience reported technical success in 87% of cases and no deaths after 30-day follow-up although one stroke and three rehospitalizations were recorded.[31] At 30 days, all patients showed no/mild residual MR but one with 3+ PVL.

Putting together all the Sapien devices, a wide experience has been gained. The transfemoral approach, its use in multiple settings, and the acquaintance with the delivery system might represent possible advantages for this system.

Cardiovalve System

The Cardiovalve system (Valtech Cardio, Ltd) features a self-expanding pericardial bovine valve mounted on a nitinol frame, specifically designed to be delivered through a transfemoral/ transseptal approach (Movie II in the Data Supplement).

Currently, a prospective, multicenter and single-arm pilot study is underway (AHEAD Trial [European Feasibility Study of the Cardiovalve Transfemoral Mitral Valve System]). In the early experience (5 patients) none/mild residual MR was observed.[32] However, more data are needed and the study plans to enroll a total of 30 patients while the early feasibility study (AHEAD US) has also started to enroll patients in the United States.

The low device profile limits the risk of LVOTO while allowing tridimensional maneuvering within the left atrial (LA) and LV chamber, to achieve optimal alignment for leaflet grasping. However, available data are still limited to define potential advantages and limitations.

Cephea

The Cephea system (Cephea Valve Technologies) has a dual-frame design allowing conformability to variable anatomies. It is fully repositionable and recapturable and it is specifically designed for transatrial and transseptal delivery. First-in-human experience has been recently described with good echocardiographic and clinical early results.[33]

Altavalve

Altavalve (4C Medical Technologies) is a self-expanding, spherical-shaped, nitinol and 3 bovine leaflets device. Currently, only first-in-human case has been described.[34] It was implanted transapically although transseptal approach will be soon available. Procedure was technically successful and after 30 days of follow-up no adverse events were reported. An early feasibility study (https://www.clinicaltrials.gov; Unique identifier: NCT03997305) is underway.

Its peculiar atrial-suprannular design abolishes the risk for LVOTO and for embolization, making the whole procedure less echocardiography dependent. On the other side, given the atrial nitinol frame, thrombosis might be an issue.

HOW TO CHOOSE TMVI DEVICES

Currently, the experience with TMVI devices is too limited to establish criteria to select the best device for a given patient. Considering common causes for selection failure, the following issues should be evaluated in the device selection:

- Prostheses available sizes: as one of the main anatomic reason for refusal is too large mitral annulus or too small anatomy, the selection of a device with a wide range of sizes and with a low impact on LVOT (low profile) represents a key feature for the device selection.
- Access sites: the current experience with TMVI is mainly based on transapical approach. However, apical access might be complicated by apical tear, life-threatening apical bleeding, myocardial damage, coronary damage, and infections. For this reason, the availability of delivery systems for different access sites might represent an advantage.
- Repositionability and retrievability: these features are important to achieve the desired position.

- Valve shape: D-shape devices are expected to achieve a better sealing and, in turn, to limit the risk of PVL.
- Although data are still limited, Tendyne has been preferred in case of calcified anatomy.

INITIAL, CURRENT, AND FUTURE CHALLENGES

Over the years, TMVI technologies faced several challenges. The Fortis (Edwards Lifesciences) clinical program was interrupted in 2015 for valve thrombosis, although 2-years follow-up data suggest that the thrombotic risk is higher in the periprocedural phase.[35,36] Similarly, the Prelude (https://www.clinicaltrials.gov; Unique identifier: NCT02768402) and Interlude (https://www.clinicaltrials.gov; Unique identifier: NCT03661398) trials for the Caisson valve are still active but not currently recruiting following the fixation/anchoring issues resulting in 79% technical success with 4 cases requiring surgical conversion and 1 valve retrieved.[37]

Alongside these, there are further open issues for TMVI with LVOTO being the threatening complication.

LVOT Obstruction

LVOTO is due to the prosthesis pushing the anterior mitral leaflet towards the septum and represents the most important concern for TMVI. It may occur in up to 40% in ViMAC[12] predicting high 1-year mortality rate,[17] and, at the same time, it is the most frequent cause of selection exclusion in the screening phase.

Currently, no univocal definition has been established. According to MVARC (Mitral Valve Academic Research Consortium), iatrogenic LVOTO is defined by an increase in peak LVOT gradient >10 mm Hg from baseline, as assessed by echocardiography. Alternatively, a peak gradient of >30 mm Hg has been used in some studies.[38] Such different definitions might explain different incidence of LVOTO among studies.

Predictors of LVOTO comprise multiple factors (3 P):

1. Prosthesis-related factors: they include the device profile and its fixation/anchoring mechanism.
2. Patient-related factors: multiple anatomic features may influence the risk for LVOTO (Figure 3). In particular, neo-LVOT should be carefully quantified in the preprocedural computed tomography scan analysis.[39] Cutoffs vary from <190 mm^2 to <170 mm^2 (as measured in the mid/end-systole phase) and an inverse relationship between neo-LVOT area and gradient has been demonstrated in computational models.[40] Such values have not been validated and might vary for each device. In addition, neo-LVOT depends on some anatomic features as shown in Figure 3.[33]
3. Procedure-related factors: device implantation depth may affect neo-LVOT and should be carefully balanced with the thrombotic risk in case of too atrial implantation (Figure 3). Moreover, the degree of device flaring may reduce neo-LVOT area.

To prevent LVOTO, alcohol septal ablation has been proposed although it requires suitable vessels and time for LV to remodel (2–4 weeks). Alternatively, starting from a small surgical experience, a fully percutaneous technique has been described to achieve an intentional anterior mitral leaflet laceration.[41,42] Its efficacy has been demonstrated in 30 patients at high risk for LVOTO: LAMPOON (Intentional Laceration of the Anterior Mitral

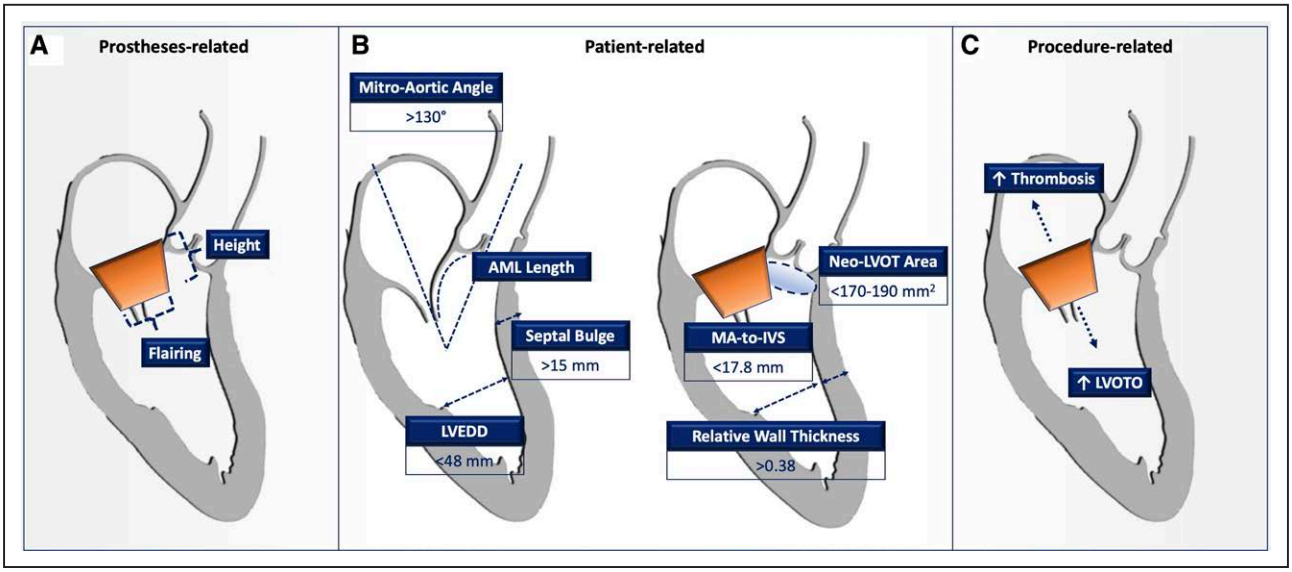

Figure 3. Left ventricle outflow tract obstruction (LVOTO) risk factors according to prostheses (A), patient (B), and procedure features (C).
Relative wall thickness: ratio between the posterior wall thickness and the left ventricle end-diastolic diameter (LVEDD). AML indicates anterior mitral leaflet; IVS, interventricular septum; LVOT, left ventricle outflow tract; and MA, mitral annulus.

Leaflet to Prevent Left Ventricular Outflow Tract Obstruction During Transcatheter Mitral Valve Implantation) was successful in 100% of patients, and 30 days survival was 93%.[43] However, the procedure is challenging, requires highly expert operators, it might be unfeasible (calcific leaflets), and might not abolish the risk for LVOTO.

Anatomy and Fixation

The MV is an integrating part of the LV and includes the leaflets, annulus, chordae, papillary muscles, LA, and the aortic valve continuity (mitral complex). MV anatomic features make TMVI more complex than TAVI: asymmetrical shape of the mitral annulus and leaflets, large annular dimensions, the absence of calcifications in most cases, and the complex subvalvular anatomy. Of note, anatomic changes might differ according to the different MR etiologies and to MR degree and those might influence also LA and LV anatomic changes. For all these reasons, the "one device fits all" myth is still far from becoming true, in spite of being appealing. Following this issues, Tendyne sizing chart provided plenty of different measures to better adapt to MV different anatomies.

Due to the complex anatomy, sealing and reliable fixation represent another concern of TMVI. Radial forces as the only mechanism providing fixation might be not enough and might increase the risk of compression and damage to adjacent structures such as the LVOT, the conduction system, the coronary sinus, the left circumflex artery, and the aortic root. Consequently, different fixation methods have been designed.[44] The dynamic, D-shaped, and noncalcified nature of native MV may affect both fixation and sealing contributing to prostheses embolization and to paravalvular leakage.

With regards to the ViR subset, different rings may have different suitability due to different stiffness properties. In general, complete radiopaque semi-rigid rings are ideal for ViR procedures.

Device Delivery

Following TAVI experience, transfemoral-transseptal TMVI is more appealing than transapical approach. However, it requires high experience with the management of transseptal puncture and most of the current available devices have large delivery system profiles to accommodate large prostheses.[45] The experience with transapical approach in the aortic field has demonstrated poorer outcomes mainly due to myocardial injury and thoracotomy in frail patients.[46–48] Temporal trend described in the TVT aortic registry (Transcatheter Valve Therapy), has shown a decrease in the use of transapical approach in favor of transaxillary.[49] Therefore, future engineering efforts will aim at reducing delivery systems caliber modifying valve design accordingly and at providing enough flexibility to the system to allow transfemoral route as the first-choice access.

Durability and Thrombogenicity

Currently, no data exist about the long-term durability of transcatheter prostheses in mitral position. According to surgical experience with bioprosthesis, the degeneration process begins 5 years after MV intervention and the freedom from structural valve deterioration varies from 70% to 90% at 10 years, with mitral position bioprosthesis performing worse than aortic ones.[50] This might be due to the different mechanical stress between mitral and aortic position valves.[51,52] Of note, the rate of surgical bioprosthesis degeneration is higher in younger patients than in elderly ones.[53]

Multiple factors influence the thrombogenicity and degeneration risk. Most of them are valve-related factors and include device profile, shape, and leaflet/stent material. As for the TAVI technologies, TMVI prostheses leaflets are either porcine or bovine. Although no in vivo nor ex vivo data exist and retrospective analysis in surgical valves excludes any difference in survival rates at 10 years, biophysical tissue properties of porcine and bovine valves are different with potential implications for crimping performance, hemodynamic, and subsequent leaflet thrombosis or deterioration.[54,55] Based on the lesson learnt from surgical prostheses and although no univocal approach in terms of drugs choice and duration of therapy has been established, it is highly advisable to use at least one antiplatelet/anticoagulant drug. Tables 4 and 5 summarize the antiplatelet/anticoagulant schemes used in the main TMVI studies. In general, lifelong anticoagulation may represent a limitation for TMVI, especially in young or low-risk categories.

Flow Dynamics

The MV plays a key role for the flow pattern within the LV and LA. In general, considering an apical 3-chamber view, in the early diastolic phase two 3-dimensional vortices are described in healthy subjects: a dominant anterolateral clockwise vortex (due to anterior mitral leaflet) and a weaker posterior anticlockwise one. The latter dissipates during the diastole, whereas the former fills most of the LV cavity and directs the blood towards the aorta in systole. Its fluid-dynamic function prevents energy loss and optimizes fluid-structure interaction.[56] Loss of the vortex-like circulation is associated with increased LV stress and kinetic energy dissipation and with less efficient work.[57] The 3-leaflet design of the currently available TMVI prostheses might impair LV flow dynamic with possible consequences for the LV performance. Moreover, flow dynamic patterns may change also in LA, impairing the LV filling phase and, in case of prostheses high implantation, promoting blood stagnation and thrombus formation.

Finally, due to the abrupt MR resolution, the risk of afterload mismatch should be carefully considered especially in those patients with severely failing LV.[58]

Table 4. Antithrombotic Therapies in Native TMVI

	Tendyne[21]	Tiara[26]	Intrepid[25]
	N=100	N=79	N=50
Therapy at discharge	1. ASA only (initial protocol)	...	VKA (INR 2.5–3.5)+SAPT for at least 3 mo
	2. VKA (INR 2.5–3.5) for at least 3 mo after protocol change		
Cerebrovascular events	Disabling stroke	3%	Nondisabling stroke
	3%		0–30-day: 4%
			>30-day: 2.4%
Bleeding	32%	...	0–30-day: 18%
Device thrombosis	6%	...	0
30-day mortality	6%	13%	14%

ASA indicates aspirin; INR, international normalized ratio; SAPT, single antiplatelet therapy; TMVI, transcatheter mitral valve implantation; and VKA, vitamin K antagonist.

Indications: To Repair or to Replace?

The field of application for the recent CE marked Tendyne is MR in patients at high risk for surgery or with unfavorable anatomic features for repair. The most appealing advantages of TMVI are the relative simplicity and reproducibility of the procedure. MR reduction is highly predictable with TMVI, whereas up to one-third of patients undergoing MV repair show more than moderate residual MR which, in turn, affects mortality and rehospitalisation.[59,60]

Regarding the etiology, TMVI has been studied mostly in patients with functional MR and this might represent the target for this therapy. Indeed, the advantages of repair over replacement are more evident in patients with degenerative MR with regards to life expectancy and quality of life.[61,62] However, the benefits of surgical repair in patients with functional MR are less clear as prognosis is mainly influenced by the underlying LV dysfunction rather than the type of intervention.[63,64] In a large randomized trial comparing valve repair to chordal-sparing valve replacement in ischemic functional MR patients, no differences in LV reverse remodeling nor survival at 1 year were observed.[65] However, the positive results from recent trial pushed the bar even upwards and direct comparison data between TMVI and repair with MitraClip are necessary. For this reason, current trials on TMVI (NCT03242642, NCT03433274) introduced the edge-to-edge arm in their study design. Issues to

Table 5. Antithrombotic Therapies in ViV, ViR, and Valve-in-MAC TMVI

	VIVID registry[11]	Yoon et al[12]	Guerrero et al[19]
Device implanted	Sapien, XT and 3	Sapien, XT, 3	Sapien, XT, 3
	Melody	Lotus	Other
	Others	Direct flow	
		Melody	
Clinical setting	ViV=857	ViV=322	ViV=680
	ViR=222	ViR=141	ViR=123
		Valve-in-MAC=58	Valve-in-MAC=100
Therapy at discharge	SAP+anticoagulant=38%	Available for 411 pts	Anticoagulants=71%
	VKA=27%	VKA=47%	ASA alone=53%
	SAP=13%	SAP+VKA=23%	DAPT=29%
	DAPT=11%	DAPT=22%	
	NOACs=4%	SAP=26%	
	DAPT+anticoagulant=3%	NOACs=2%	
Cerebrovascular events	1%	2%	2%
Bleeding	8%	Major=4%	Major=4%
		Life-threatening=4%	Life-threatening=6%
Device thrombosis	Not reported	Not reported	0.2
30-day mortality	7%	10%	10%

ASA indicates aspirin; DAPT, double antiplatelet therapy; MAC, mitral annular calcification; NOAC, new oral anticoagulants; SAP, single antiplatelet; TMVI, transcatheter mitral valve implantation; ViR, valve-in-ring; ViV, valve-in-valv; VIVID, Valve-in-Valve International Data; and VKA, vitamin K antagonist.

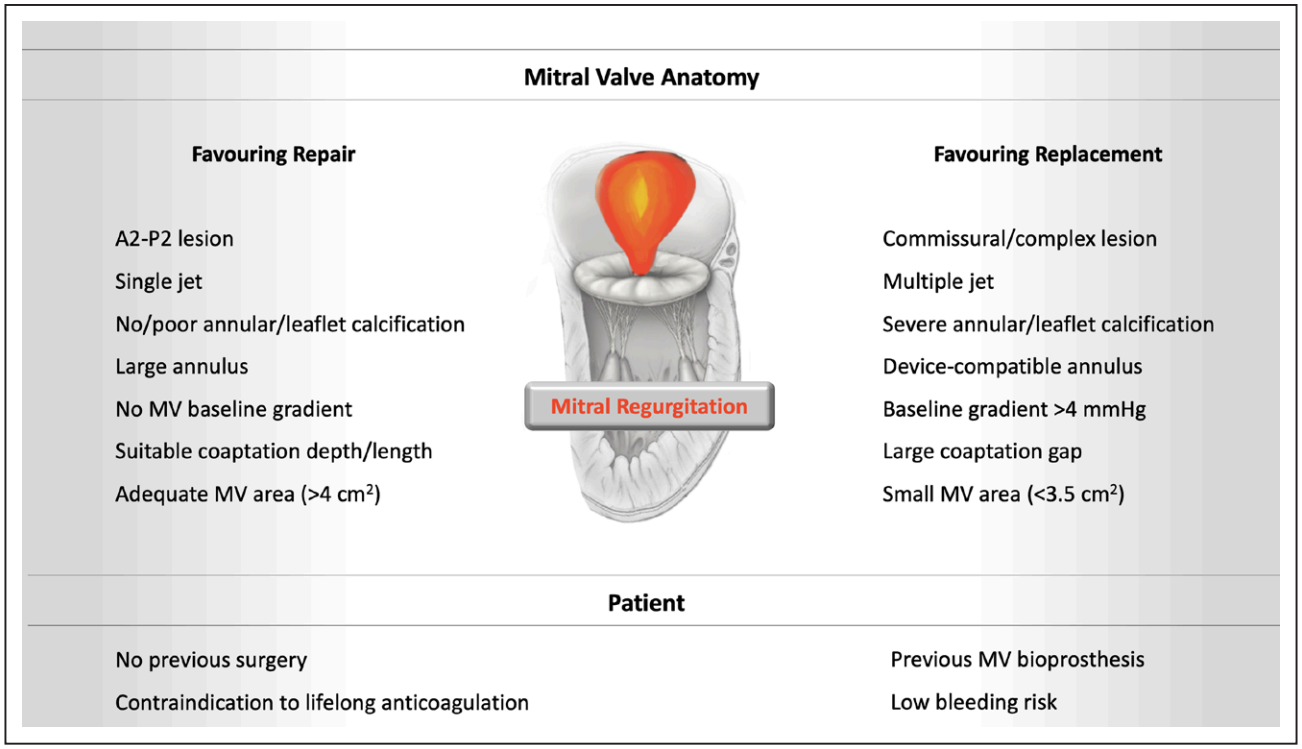

Figure 4. Issues to be considered in the selection between transcatheter mitral valve (MV) repair and transcatheter MV implantation. A2-P2 indicates MV scallops.

be considered in the decisional algorithm between TMVI and TMVR are reported in Figures 4 and 5. When successful and durable repair is achievable, it should be preferred over replacement. For this reason, accurate echocardiographic assessment investigating MV anatomy and lesion definition is of utmost importance.

In the field of redo surgery (failing bioprosthesis/rings), the convincing results for the ViV suggest that it

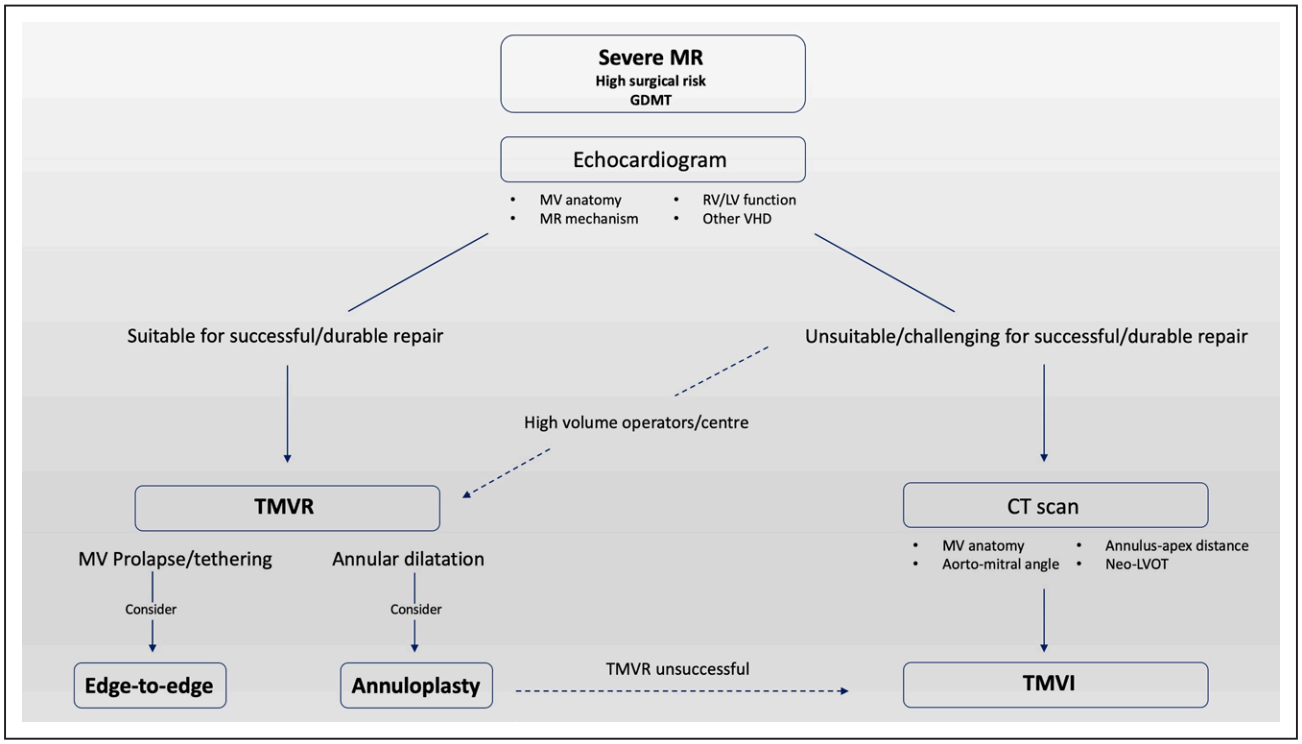

Figure 5. Proposed decisional algorithm for transcatheter therapies correcting mitral regurgitation (MR) in native mitral valve (MV). CT indicates computed tomography; GDMT, guideline-directed medical therapy; LV, left ventricle; LVOT, left ventricle outflow tract; RV, right ventricle; TMVI, transcatheter mitral valve implantation; TMVR, transcatheter mitral valve repair; and VHD, valvular heart disease.

should be considered as first-line option, especially in intermediate-high surgical risk patients, although no randomized data comparing redo surgery with ViV exist.

In this perspective, the role of the TMVI is expected to be complementary to repair rather than competitive and 2 drivers are going to guide the treatment selection.

First, safety should be taken into account in patients with severe MR and little or no symptoms. In such circumstances, TMVR might be preferred over TMVI due to the potential disadvantages of permanent prostheses and the high safety profile of the procedure.

Second, a major role will be played by the heart team: timing for intervention is crucial to obtain a significant prognostic benefit in both degenerative MR and functional MR. An early treatment furtherly favors TMVR over TMVI: for a procedural safety profile, for prostheses-related complication and because TMVR might not exclude later TMVI.[66] However, as the toolbox for transcatheter MV treatment becomes wider, the role of experienced operators and high-volume centers, being able to offer more than one treatment solution with good outcomes (surgery versus percutaneous, repair versus replacement) will be fundamental (centers of excellence).[67,68] As for surgery, the TVT registry confirmed how the experience and the operator volume influence the outcome in MitraClip procedure.[69] In this perspective, the role of interventional imagers with a dedicated education, is going to be central not only for procedural guidance but also for the preprocedural planning, postprocedural management being active protagonists during the decision-making processes.

CONCLUSIONS

Although the growth of TMVI has been slow over the last years, the recent approval for the first dedicated TMVI prostheses, alongside with some technical improvements (eg, LAMPOON and ELASTA-Clip [Electrosurgical Laceration and Stabilization of MitraClip]) are going to shake MV interventions field. Currently, TMVR has gained wide experience and is going to be preferred over TMVI due to durability, safety, and pathophysiological concerns. TMVI is going to have a complementary role and be considered for high-risk patients with poor valve repair features, whereas ViV might become the treatment of choice, especially for those cases at higher surgical risk. In this regard, careful patient selection will be extremely important with proper imaging work-up alongside centers and operators' experience.[70]

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Supplemental Materials

Online Movies I and II

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