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THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Current Status and Future Prospects of Transcatheter Mitral Valve Replacement

JACC State-of-the-Art Review

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ABSTRACT

Mitral regurgitation (MR) is the most prevalent valvular heart disease and, when left untreated, it confers a poorer prognosis. Catheter-based repair therapies face some limitations like their applicability on challenging anatomies and the potential recurrence of significant MR over time. Transcatheter mitral valve replacement (TMVR) has emerged as a less invasive approach potentially overcoming some of the current limitations associated with transcatheter mitral valve repair. Several devices are under clinical investigation, and a growing number of systems allow for a fully percutaneous transfemoral approach. In this review, the authors aimed to delineate the main challenges faced by the TMVR field, to highlight the key aspects for procedural planning, and to describe the clinical results of the TMVR systems under clinical investigation. Finally, they also discuss what the future perspectives are for this emerging field.
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Mitral regurgitation (MR) is the most prevalent valvular heart disease in the United States (1). Owing to the associations between primary MR and age, and between secondary MR and heart failure, there will likely be an increase in the prevalence of MR in the coming years (2). Surgical mitral valve repair/replacement has been associated with excellent clinical outcomes in patients with severe MR. However, a high percentage of patients suffering this condition are still rejected from surgery because of their comorbidities and prohibitive surgical risk (3). Several catheter-based therapies have emerged over the past decades targeting this patient population, and particularly the transcatheter edge-to-edge mitral valve repair (TEER) technique is currently supported by a growing body of evidence (4–6). Nevertheless, TEER still faces significant drawbacks, such as its limited applicability to all anatomic substrates (e.g., leaflet thickening and calcification, short posterior mitral leaflet with limited motion), as well as its inability to both fully correct the severity of the regurgitation and prevent MR progression overtime (7,8). Transcatheter mitral valve replacement (TMVR) has emerged as a less invasive approach than standard surgery, which could overcome some of the current limitations associated with TEER. In the present review we aimed to outline the current challenges of the TMVR field, highlight the main considerations for TMVR planning, and provide an updated overview of the current TMVR systems under clinical evaluation along with their technical characteristics and clinical outcomes. TMVR using

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HIGHLIGHTS

- TMVR is less invasive than mitral valve surgery and may overcome some limitations associated with TEER.
- Early clinical experience with transfemoral-transeptal TMVR has been promising.
- Six TMVR systems under clinical investigation permit entirely percutaneous procedures.
- Larger trials with longer follow-up are needed to further evaluate the risks and benefits of TMVR in comparison with other catheter-based and surgical strategies for patients with advanced mitral valve disease.

transcatheter valves intended for the aortic position in patients with severely calcified mitral annuli, previous mitral annuloplasty, and valve-in-valve procedures for the treatment of mitral surgical bioprosthetic dysfunction are beyond the focus of this review.

MITRAL VALVE ANATOMY: CHALLENGES FOR TMVR

The complex and variable mitral valve anatomy has been one of the main challenges preventing a broader TMVR adoption. The mitral valve is D-shaped, has a variable 3-dimensional saddle annular morphology (with the anterior and posterior edges more apically placed) (9,10), and its dimensions are highly dependent on intravascular volume and hemodynamic status. Besides, the mitral valve system includes complex subvalvular components including multiple chordae tendinae and 2 papillary muscles, increasing the risk of entrapment and hindering device maneuverability. Compared with transcatheter aortic valve replacement (TAVR), where the aortic valve is frequently calcified allowing for a firm fixation of the implanted prosthesis, the calcium burden observed in patients with MR ultimately undergoing TMVR is usually lower. The lack of calcium may impede optimal device sealing and fixation, potentially increasing the risk of residual paravalvular leakage (PVL) and prosthesis embolization. Several mechanisms have been developed to ensure proper valve fixation and sealing: a) D-shaped frames to better fit the morphology of the mitral annulus; b) the addition of an apical tether to secure the prosthesis; c) radial expansion forces of the valve frame by means of valve oversizing; d) the use of ventricular tabs or tines to fix to the edges of the mitral annulus; e) ventricular anchors capturing the mitral leaflets and subvalvular chordae; and f) the use of 2-step synching mechanism to secure the valve.

Mitral annular calcification (MAC) is highly prevalent among high risk MR patients, and its distribution is highly asymmetric for most patients, involving predominantly the posterior mitral annulus and sparing the mid and lateral segments of the anterior annulus (11). In addition, due to the close anatomic relationship between the left ventricle outflow tract (LVOT) and the mitral valve, TMVR poses an important risk for LVOT obstruction. Finally, the spectrum of valve disease mechanisms and underlying conditions observed in patients with MR (e.g., scallop prolapse or flail, annular calcification, asymmetric leaflet thickening, left ventricular dysfunction, and wall motion abnormalities with apical displacement of the mitral leaflets) (12) is much broader than that associated with aortic stenosis, which is essentially related to valve calcification (13).

ABBREVIATIONS AND ACRONYMS

AML = anterior mitral leaflet
CCT = cardiac computed tomography
LVOT = left ventricle outflow tract
MAC = mitral annular calcification
MR = mitral regurgitation
PVL = paravalvular leakage
TEE = transesophageal echocardiography
TEER = transcatheter edge-to-edge mitral valve repair
TMVR = transcatheter mitral valve replacement
TTE = transthoracic echocardiography

PRE-PROCEDURAL WORKUP FOR TMVR: CARDIAC IMAGING

The severity, etiology, and mechanisms of MR should be carefully evaluated, as well as the association of any degree of mitral stenosis or any other valvular abnormality (e.g., annular calcification and its extension). Also, the pre-TMVR cardiac imaging examination should help to determine patient eligibility according to the anatomic measurements and anatomic variables used for every specific device, to inform on the risk of potential procedural complications and their likelihood, and to localize the most suitable points for access and puncture.

ECHOCARDIOGRAPHY. Pre-procedural transthoracic echocardiography (TTE) is mandatory and should be the first cardiac imaging examination for patients with a suspicion of mitral valve disease, as it is noninvasive and provides a first characterization of the magnitude and etiology of the mitral valve disease. Transesophageal echocardiography (TEE) enables better determination of the presence of any degree of mitral valve stenosis, to evaluate some anatomic landmarks before TMVR (e.g., height/distance between the optimal puncture site at the interatrial septum and the mitral coaptation plane), and to verify the image quality that would be available during TEE guidance for transcatheter valve implantation. During the procedure, the echocardiographer will provide continuous image guidance

TABLE 1 Basic Measurements Concerning TEE and TMVR

Pre-Procedural TEE	Intraprocedural TEE
Degree of MR	Pre-intervention images: confirming findings, rule out thrombus, baseline study to serve as comparator
Presence of MS	Interatrial septum puncture guidance: bicaval and short axis of the aorta for supero-inferior and antero-posterior views, respectively
Morphologic characterization of mitral leaflets	LV apex localization for transapical approach
Hemodynamic assessment	High-support guidewire localization and positioning
Mitral annular dimensions and calcium burden	Delivery system orientation while crossing the interatrial septum
Interatrial septum features: shunt, defect, aneurysm, thickness	Valve orientation with regard to mitral annulus and LVOT; tilting and rotation if necessary
Subvalvular apparatus morphological characterization: calcification, number, and position of chordae tendineae	Implantation depth within the LV and LA
Rule out left atrial appendage thrombus	Capture of the mitral leaflets (depending on valve anchoring system)
Geometry of the LV and interventricular septum	Perivalvular leakage assessment after deployment
LVOT characterization: diameter, relation with adjacent structures	Final hemodynamic assessment: residual MR, mitral gradients
Coexisting valve disease	Rule out LVOT obstruction and LVOT gradients measurement

LA = left atrium; LV = left ventricle; LVOT = left ventricle outflow tract; MR = mitral regurgitation; MS = mitral stenosis; TEE = transesophageal echocardiography; TMVR = transcatheter mitral valve replacement.

with TEE in close collaboration with the interventional team. Bicaval and aortic short-axis views may help to select the appropriate septal puncture site (ideal position usually slightly superior and posterior from the midpoint of interatrial septum). TEE is also used to guide the advancement and positioning of the TMVR prosthesis within the native MV annulus, and final adjustments (e.g., rotation, retrieving, valve tilting) are performed based on TEE image (14). The most relevant echocardiographic features to be considered before and during TMVR are listed in Table 1.

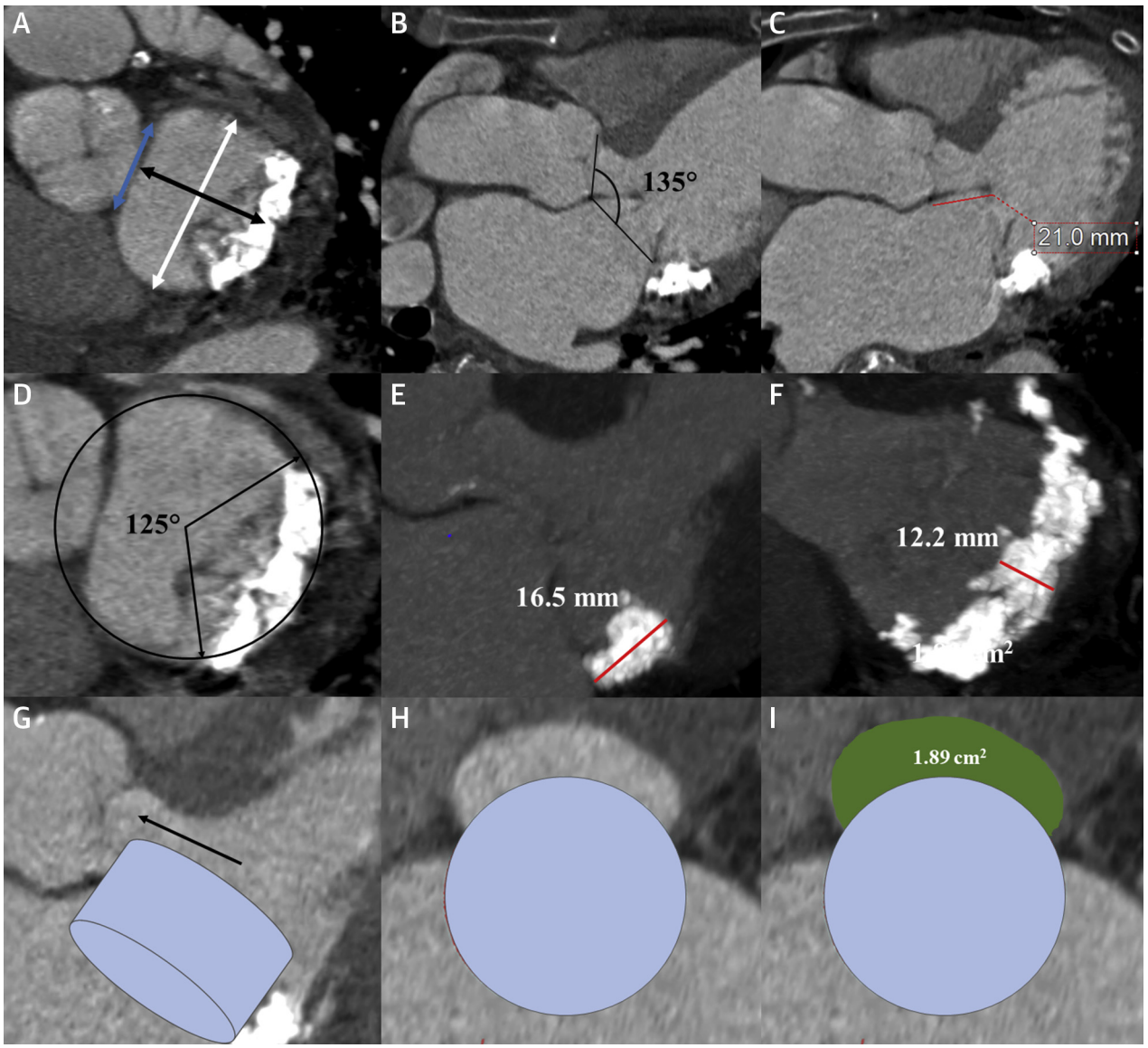
CARDIAC COMPUTED TOMOGRAPHY. Despite the important amount of information obtained from TEE, cardiac computed tomography (CCT) is considered to be essential for TMVR planning. Contrast-enhanced thin-sliced CCT allows for sub-millimeter spatial resolution, facilitating accurate mitral geometry assessment and annular sizing. In the setting of TMVR planning, the use of electrocardiography-gated CCT is mandatory, and the use of retrospective gating allowing for time-resolved (4-dimensional) data is very advisable, as it facilitates 3-dimensional reconstruction along any plane throughout the cardiac cycle. In case of prospective electrocardiography-triggered acquisition, the whole systolic phase should be covered for LVOT estimation purposes, and the minimal R-R interval recommended for dataset reconstruction is 10%. All TMVR systems under clinical evaluation use CCT to evaluate patient suitability. CCT assessment for TMVR is subject to ongoing refinement, and it has become more complex and exhaustive during the past years. There are some common anatomic points routinely evaluated for all TMVR valve systems (Figures 1A to 1C) (15–18), although other CCT-based measures are device specific, leading to different CCT workup and evaluation algorithm for each valve system. Table 2 lists the most relevant CCT aspects evaluated for TMVR, regardless of the valve system finally implanted.

CCT is the most important examination for the assessment and quantification of MAC if present, as it provides detailed and clear definition of the extent and severity of annular calcium. Of note, some measures easily obtained with contrast-enhanced CCT are commonly used during the initial experience of TMVR in MAC, such as the maximal height and thickness of the observed calcification, as well as its circumferential extent (ranging between 0° for no calcium, and 360° for calcific involvement of the entire mitral annulus) (Figures 1D to 1F). Interestingly, a novel score that considers calcium thickness, distribution, and trigone and leaflet involvement has been proposed for TMVR in MAC cases (19).

Other methodologies have also been described, such as the calculation of the calcium score with the Agatston method as for TAVR (20,21). A nonenhanced thorax CT is necessary when calculating the mitral calcium score with the Agatston method and, although a nonenhanced thorax CT scan is advisable in transapical procedures as it helps to determine the best intercostal space for transapical access, its implementation is not mandatory for transeptal cases.

CCT also helps to identify patients at risk for TMVR-related complications, especially LVOT obstruction. LVOT obstruction is one of the most common complications associated with TMVR, and its presence has been identified as an independent predictor of worse early outcomes in patients undergoing valve-in-valve, valve-in-ring, or valve-in-MAC procedures (22). The main mechanisms associated with LVOT obstruction after TMVR are not yet completely understood, and several factors (most of them measurable by CCT) are thought to play a role in its occurrence: an acute angulation between the mitral and aortic valve planes, the distance between the mitral annulus and the interventricular septum, the interventricular septum thickness, the size of the

FIGURE 1 CCT Data for TMVR Planning



(A) Mitral valve plane demonstrating trigone to trigone distance **(blue double arrow line)**, intercommissural distance **(white double arrow line)**, and septo-lateral distance **(black double arrow line)**. **(B)** Aorto-mitral angle. **(C)** Anterior mitral leaflet length. **(D)** Mitral annular calcification (MAC) extension (ranging from 0° to 360°). **(E)** Maximum-intensity projection image: maximum height of MAC in a long-axis view **(red line)**. **(F)** Maximum-intensity projection image: maximum thickness of MAC in a short-axis view **(red line)**. **(G)** Neo-LVOT assessment. Virtual implantation of the transcatheter mitral valve **(blue structure)** and LVOT central axis **(black arrow)**. **(H and I)** Minimal neo-LVOT area. Short axis demonstrating the virtually implanted device **(blue circle)** and the neo-LVOT assessment **(green area)**.
CCT = cardiac computed tomography; LVOT = left ventricular outflow tract; TMVR = transcatheter mitral valve replacement.

ventricular end of the implanted valve and its protrusion into the left ventricular cavity, a small mitral to apex distance, the length of the anterior mitral leaflet (AML), and the coaxiality of the prosthesis related to the mitral annular plane (23–26). The "neo-LVOT" is an important concept that has emerged over the past years (23). This novel structure has been defined as the space remaining between the anteriorly displaced AML, the transcatheter valve, and the antero-septal wall of the left ventricle after mitral valve replacement. The neo-LVOT can be calculated by means of CCT by segmenting a cylindrical volume

TABLE 2 Global Baseline CCT Assessment Before TMVR

Anatomic Structure	Measures
Mitral annulus	Latero-medial (intercommissural) diameter Antero-posterior (septal-lateral) diameter Inter-trigone distance Perimeter Area Annular calcification (description and quantification) Fluoroscopic views: en face, 2- and 3-chamber
Mitral leaflets	Length Thickness Calcification
Interatrial septum	Thickness Morphological anomalies Puncture site (height and angulation toward the mitral valve)
Left atrium	Size and morphology Exclusion of thrombus
Left ventricle	Size and morphology Distance between left ventricular apex and mitral valve plane
Papillary muscles	Distance between the heads Projected distance between mitral plane and papillary muscles plane
LVOT	Aorto-mitral angle Baseline area (diastolic and systolic) Neo-LVOT assessment after virtual valve implantation

CCT = cardiac computed tomography; other abbreviations as in Table 1.

in the expected position of the prosthesis in the mitral valve using dedicated 3-dimensional software (Figures 1G to 1I). The volume of the cylinder can be selected according to the diameter and height of the prothesis to be implanted, and models that virtually embed a device-dedicated contour are available. A center line is then traced along the neo-LVOT central axis, allowing for cross-sectional assessment of the neo-LVOT area throughout the cardiac cycle. Notably, the virtual implantation simulated on the CCT should account for the atrial-ventricular ratio of the valve, with a more atrial placement significantly increasing the risk for valve embolization and improper sealing of the prosthesis skirt against the native annulus. At the same time, a more ventricular position translates into a higher risk of LVOT obstruction. In addition, some degree of valve oversizing is always advisable, as it helps prevent embolization and PVL. This fact ultimately leads to a certain flaring of the ventricular end of the prosthesis, which should be considered when determining the neo-LVOT area (27). Various approaches have been proposed for neo-LVOT segmentation (e.g., for valve-in-valve mitral procedures either an alignment of the stent post tips delineating the space needed for the new prosthesis or a virtual implantation of the new valve could be used). Recent dedicated guidelines offer more insight on neo-LVOT assessment and segmentation (28). In terms of neo-LVOT cutoff values, an area of 1.7 cm^2 for the estimated neo-LVOT after TMVR has predicted LVOT obstruction accurately, with sensitivity and specificity values of 96.2% and 92.3%, respectively (22); however, these results were based on a cohort of patients receiving nondedicated transcatheter mitral devices. Interestingly, a recent CCT-based analysis of patients screened for a purposely dedicated TMVR device (Intrepid valve) showed that the correlation between estimated and observed neo-LVOT was poor when applying the usual methodology (i.e., considering the smaller neo-LVOT value during mid-late systole); hence, an average or an early-systolic CCT assessment of the neo-LVOT was proposed. This new approach improved the predictability of significant LVOT obstruction after TMVR, and may allow for a lower rejection rate of patients based on the risk of LVOT obstruction (29).

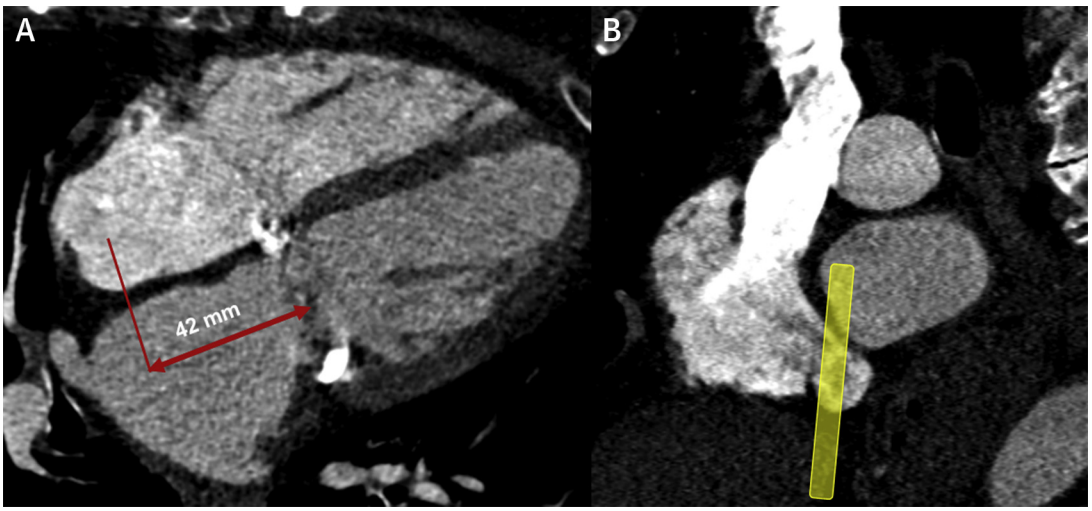
CCT may also help to select the most suitable location for transeptal puncture based on the characteristics of the interatrial septum (e.g., thickness and morphology) and on the estimated distance between the puncture plane and the targeted mitral valve (Figure 2). A more extensive computed tomography examination aiming to evaluate femoral vein diameters and tortuosity may also be useful. In addition, a thoracic scan may be used to assess the most appropriate intercostal space for a transapical approach (30).

CARDIAC MAGNETIC RESONANCE. Cardiac magnetic resonance (CMR) can provide an accurate quantification of mitral regurgitant volume/fraction and ventricular remodeling, as well as excellent tissue characterization and myocardial fibrosis assessment. CMR may be used when concerns exist about the severity of MR after TTE/TEE assessment. Compared with CCT, CMR also allows for 3-dimensional reconstruction and has the advantage of not relying on ionizing radiation for image acquisition. However, its poorer spatial resolution favors the use of CCT over CMR for procedural planning. In addition, CMR-3D whole heart sequence for multiplanar reconstruction is usually obtained during diastolic phase and is not suitable for measuring neo-LVOT (measured in systole). Although a number of cine-SSFP sequences can be obtained, model valve placement and predicting neo-LVOT is not currently possible with CMR.

TMVR DEVICES UNDER CLINICAL EVALUATION

Overall, 9 different TMVR systems are currently under clinical evaluation (Table 3).

FIGURE 2 Transeptal Puncture Planning on CCT



(A) Four-chamber CCT view displaying the best point for transeptal crossing **(red line)** allowing for an optimal distance height between the transeptal access and the mitral valve plane (42 mm, **red double-headed arrow**). **(B)** Bi-caval CCT view demonstrating the passage of the guiding catheter through the interatrial septum in an en face view of the interatrial septum. Abbreviations as in Figure 1.

TENDYNE. Device description. The Tendyne system (Abbott, Menlo Park, California) consists of 2 self-expanding nitinol frames and a trileaflet porcine pericardial valve (Table 3, Figure 3). The outer frame is designed to fit the mitral annulus and should be aligned with the straight edge oriented anteriorly against the aorto-mitral continuity. The prosthesis is secured in a stable position after deployment by means of a braided, high-molecular-weight polyethylene tether, which is ultimately attached to an apical epicardial pad (31).

Procedural aspects. The deployment of the valve begins at the atrial level, and the prosthesis is progressively deployed while unsheathing, with no need for rapid pacing. The system allows for repositioning and retrieval. The length and tension of the tether is adjusted to optimize the position of the prosthesis for MR reduction and to minimize the risk of device displacement.

Clinical results. Two studies reported data on procedural and clinical outcomes following Tendyne valve implantation in 109 patients (32,33), a 100-patient cohort from the early feasibility study, and a second study including 9 patients with severe MAC (Table 4). The technical success rate was high (97.2%), and the 30-day mortality and stroke rates were of 5.5% and 1.8%, respectively. The most common major complication was the composite of major or life-threatening bleeding, observed in 21 patients (19.3%) at 30 days. At 1-year follow-up, the mortality rate was 26%, mostly driven by cardiovascular mortality (22 of 26 cases) (Table 5). Freedom from MR at follow-up was very high, with 1-year echocardiography showing ≤mild residual MR in all patients. The 2-year follow-up data from the early feasibility trial showed a cumulative mortality rate of 39%, with refractory heart failure as the most frequent cause of death (14%). Valve performance as evaluated by echocardiography remained optimal, with ≤mild MR in all patients (34). Also, a recent analysis of CCT data demonstrated favorable left ventricular reverse remodeling 1-month after Tendyne implantation (35).

Future perspectives. The device received CE Mark approval on January 2020 (first TMVR system approved for clinical use in Europe). Currently, 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) trial is enrolling patients aiming to compare TMVR with the Tendyne system versus TEER with the MitraClip device (Abbott, Menlo Park, California) (Table 6). In addition, there are 2 single-arm studies for nonrepairable anatomies and patients with MAC. Data from the first 11 patients in the MAC arm were recently presented, showing a technical success rate of 100% (36).

TIARA. Device description. The Tiara system (Neovasc Inc., Richmond, Canada) consists of a

TABLE 3 Characteristics of Current Transcatheter Mitral Valve Replacement Devices

	Manufacturer	Structure	Leaflets	Delivery System	Access	Anchoring Mechanism	Available Sizes
AltaValve	4C Medical Technologies, Minneapolis, Minnesota	Self-expanding, nitinol	3 bovine leaflets	32 F	Transapical Transfemoral	Spherical frame shape, supra-annular position	27-mm internal valve Annular ring sizes: 40, 46, and 54 mm
CardioValve	Cardiovalve Ltd., Israel			28 F	Transfemoral		3 sizes
Cephea	Abbott, Menlo Park, California	Self-expanding nitinol double-disc structure	3 bovine leaflets	32 F	Transfemoral	Axial compression forces	36 mm
Evoque	Edwards Lifesciences, Irvine, California	Self-expanding, nitinol	3 bovine leaflets	28 F	Transfemoral	Multiple anchors enabling annulus, leaflets and chords anchoring	44 mm 48 mm
Highlife	HighLife SAS, Irvine, California	Self-expanding, nitinol. Subannular implant: polymer tube, covered with a polyester graft with a nitinol hook	3 bovine leaflets	39 F	Transapical Transfemoral	Valve in subannular mitral ring; external anchor	31 mm
Intrepid	Medtronic Inc., Minneapolis, Minnesota	Double stent, self-expanding, nitinol	3 bovine leaflets	35 F	Transapical Transfemoral	Radial force and small cleats on outer stent engage leaflets	27 mm Outer frame sizes: 43, 46, and 50 mm
M3	Edwards Lifesciences, Irvine, California	Balloon-expandable. Cobalt-chromium frame.	3 bovine leaflets	20 F	Transfemoral	Self-expandable nitinol dock system	29 mm
Tendyne	Abbott, Menlo Park, California	Double nitinol frame, self-expandable	3 porcine leaflets	34-36 F	Transapical	Apical tether and epicardial pad	External frame ranges 30–43 mm in the septo-lateral dimension and 34-50 in the intercommissural dimension.
Tiara	Neovasc Inc., Richmond, Canada	Self-expanding, nitinol 3	3 bovine leaflets	32 F 36 F	Transapical	Ventricular anchoring tabs	35 mm 40 mm

nitinol self-expanding outer frame with 3 inner bovine pericardial leaflets (**Figure 3, Table 3**). The frame is D-shaped in order to mimic the mitral annulus morphology and facilitate valve anchoring. A large atrial skirt seals the mitral inflow to prevent PVL. Device fixation is provided by 2 mechanisms: 1) radial expansion of the system; and 2) the presence of ventricular tabs (2 anterior tabs anchor the valve onto the fibrous aorto-mitral curtain and a single posterior tab lands behind the posterior mitral leaflet onto the muscular posterior shelf of the mitral annulus). To date, 2 sizes are available (35 and 40 mm), requiring introducers of 36-F and 40-F, respectively (37).

Procedural aspects. The Tiara valve is implanted transapically and the use of an atraumatic and self-dilating tip allows easy entry into the ventricular cavity. Valve delivery, deployment, and resheathing is achieved by a simple turn knob mechanism. The valve is fully retrievable up to anchor release.

Clinical results. The main results of the initial 79 patients treated with the Tiara valve were recently reported (merged data from the compassionate clinical use + TIARA-I and TIARA-II trials). There was no procedural mortality and technical success was obtained in 73 patients (92.4%) (38) (**Table 4**). Thirty-day outcomes from the early 71-patient experience (39) showed a mortality and stroke rates of 11.3% and 8.5%, respectively. No long-term data are available for this device.

Future perspectives. Currently, the TIARA-I (Early Feasibility Study of the Neovasc Tiara Mitral Valve System; NCT02276547) and TIARA-II (Tiara Transcatheter Mitral Valve Replacement Study; NCT03039855) single-arm studies are still ongoing (**Table 6**). The transfemoral-transeptal system, which has been tested in animal models, will allow for valve retrievability up to the last point of full device release and will be implanted through 30-F or smaller bore introducers (38).

INTREPID. Device description. The Intrepid system (Medtronic, Minneapolis, Minnesota) is composed of a nitinol-based structure with 2 concentric frames: the circular outer fixation frame (43, 46, or 50 mm diameter) engages within the mitral valve anatomy, whereas the circular inner stent frame (27 mm) accommodates the valve (3-leaflet bovine pericardium) (**Figure 3, Table 3**). A flexible atrial brim is attached to the outer frame to facilitate visualization. The outer frame has a more flexible portion (atrial end), and a more rigid and wider

TABLE 4 Baseline and Procedural Characteristics and 30-Day Outcomes of Patients Undergoing Transcatheter Mitral Valve Replacement With New-Generation Devices

										Global		
	AltaValve (n = 2)	CardioValve (n = 5)	Cephea (n = 4)	Evoque (n = 14)	Highlife (n = 15)	Intrepid (n = 50)	M3 (n = 45)	Tendyne* (n = 109)	Tiara (n = 79)	TF* (n = 68)	TA* (n = 247)	Overall* (n = 315)
Age, yrs	83 (77-89)	74 ± 5	80.2 (77-83)	84 [79-88.5]	69 (59-70)	72.6 ± 9.4	75 ± 9.8	75.5 (75.4-75.6)	74±9.3	77.1 (76.2-78)	74.1 (73.9-74.4)	74.8 (74.5-75.1)
Male	2 (100)	4 (80)	2 (50)	9 (64.3)	12 (80)	29 (58)	20 (44.4)	74 (67.9)	58 (73.4)	35/68 (51.5)	175/255 (68.8)	210/323 (65.0)
STS-PROM score, %	11.3 (n = 1)	6 ± 7	6.9 (n = 1)	4.6 (3.9-5.6)	NA	6.4 ± 5.5	6.4 ± 3.9	7.77 (7.75-7.79)	7.9 ± 6.7	6 (5.8-6.2)	7.6 (7.5-7.7)	7.3 (7.2-7.4)
MR etiology												
Organic	1 (50)	0	4 (100)	4 (28.6)	4 (27)	8 (16)	25 (55.6)	11/100 (11)	7 (8.9)	33/68 (48.5)	31/246 (12.6)	64/314 (20.4)
Functional	1 (50)	5 (100)	0	3 (21.4)	11 (73)	36 (72)	16 (35.6)	89/100 (89)	49 (62)	24/68 (35.3)	186/246 (75.6)	210/314 (66.9)
Mixed	0	0	0	7 (50)	0	6 (12)	4 (8.9)	0	23 (29.1)	11/68 (16.2)	29/246 (11.8)	40/314 (12.7)
LVEF, %	30 (n = 1)	33 ± 6	58.3 (40.5-76)	54 [43.5-60]	38 (27-54)	43.4 ± 11.8	43.5 (n = 10)	47.2 (46.7-47.7)	37 ± 9	43.8 (39.5-48.1)	42.9 (42.3-43.4)	42.9 (42.3-43.5)
Procedural outcomes												
Approach												
Transapical	2 (100)	0	0	0	15 (100)	50 (100)	0	109 (100)	79 (100)			247 (78.4)
Transfemoral	0	5 (100)	4 (100)	14 (100)	0	0	45 (100)	0	0			68 (21.6)
Technical success	2 (100)	5 (100)	4 (100)	13 (92.9)	8/11 (72.7)	48 (96)	40 (88.9)	106 (97.2)	73 (92.4)	62/68 (91.2)	237/251 (94.4)	299/319 (93.7)
Procedural mortality	0	1 (20)	0	0	2/11 (18.2)	0	0	NA	0	1/68 (1.5)	2/142 (1.4)	3/210 (1.4)
Malposition	0	0	0	0	NA	1 (2)	0/10	2 (1.8)	4/71 (5)	0/33 (0)	7/232 (3)	7/265 (2.6)
Conversion to open surgery	0	0	0	1 (7.1)	2/11 (18.2)	0	0	0	5/71 (7)	1/68 (1.5)	7/243 (2.9)	8/311 (2.6)
Device embolization	0	0	0	0	0	0	0	0	0/71	0/68	0/247	0
In-hospital/30-day outcomes												
Mortality	1 (50)	3 (60)	0	1 (7.1)	3 (20)	7 (14)	1 (2.2)	6 (5.5)	8/71 (11.3)	5/68 (7.3)	25/247 (10.1)	30/315 (9.5)
Stroke	0	0	0	1 (7.1)	0	2 (4)	3 (6.7)	2 (1.8)	6/71 (8.5)	4/68 (5.9)	10/247 (4)	14/315 (4.4)
Major or life-threatening bleeding	1 (50)	2 (40)	0	3 (21.4)	NA	9 (18)	1/10 (10)	21 (19.3)	NA	6/33 (18.2)	31/161 (19.3)	37/194 (19.1)
Acute kidney injury	0	NA	1	0	NA	5 (10)	NA	10 (9.2)	12/37 (32.4)	1/18 (5.6)	27/198 (13.6)	28/216 (13)
MR severity												
None/Trace/Mild	2 (100)	5 (100)	4 (100)	13 (93)	15 (100)	42 (100)	38/41 (92.7)	96/97 (99)	37/40 (92.5)	60/64 (93.8)	192/196 (98)	252/260 (96.9)
Moderate/Severe	0	0	0	1 (7)	0	0	3/41 (7.3)	1/97 (1)	3/40 (7.5)	4/64 (6.2)	4/196 (2)	8/260 (3.1)
Mitral valve mean gradient, mm Hg	1.5 (1-2)	3.4 ± 1.7	2.2 (2-2.5)	3 (2-4.3)	NA	4.1 ± 1.3	6 [5-6] (n = 9)	NA	NA	2.9 (2.8-3.1)	4 (3.9-4.1)	3.7 (3.5-3.8)
LVOT obstruction	0	0	0	1 (7.1)	1 (6.6)	0	0	NA	0/71	1/68 (1.5)	1/139 (0.7)	2/207 (1)
Device thrombosis	0	0	0	2 (14.3)	1/11 (6.6)	0	0	1 (1)	NA	2/68 (2.9)	2/172 (1.2)	4/240 (1.7)

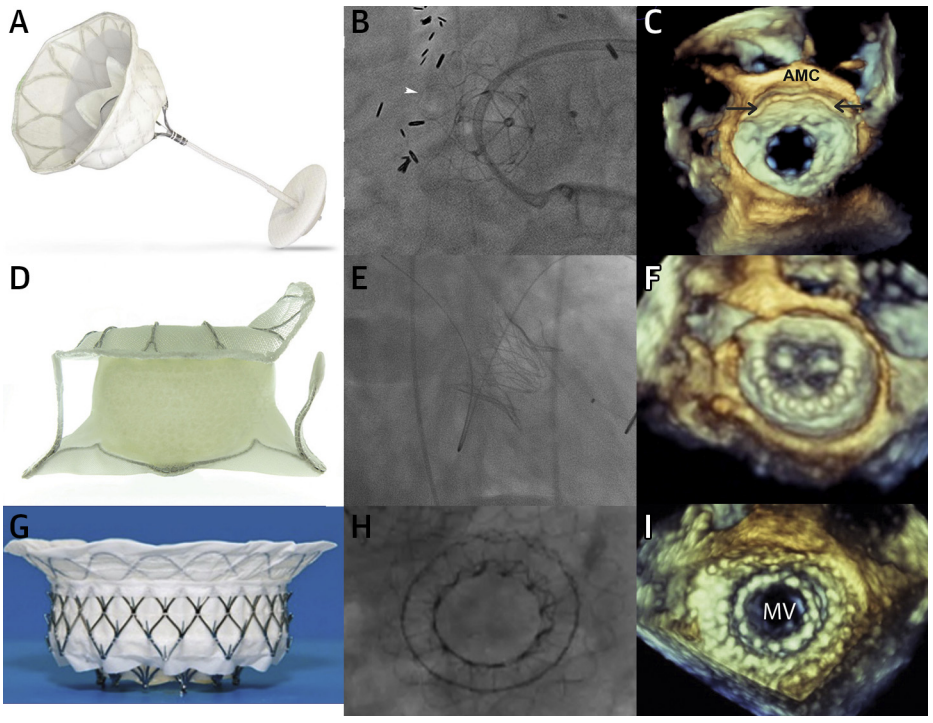
Values are mean (range), mean ± SD, median [interquartile range], n (%), or n, unless otherwise indicated, as reported by authors. *Values expressed as weighted mean (95% confidence interval) or as counts (n/N [%]) for quantitative and qualitative variables, respectively.

CABG = coronary artery bypass graft; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; LVEF = left ventricle ejection fraction; NA = not available; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; TA = transapical; TF = transfemoral; other abbreviations as in Table 1.

portion (ventricular end). The outer frame serves as mechanical protection for the inner structure, preventing valve deformation by external compression forces throughout the cardiac cycle. Valve fixation is achieved by 2 mechanisms: device oversizing (which is recommended between 10% and 30% in relation to the annular CCT-derived measures) and the presence of cleats on the outer frame that act as frictional members to engage the native mitral leaflets. The device profile is 17 to 18 mm, and is currently designed for transapical delivery using a 35-F delivery catheter (40).

Procedural aspects. Once the delivery catheter is advanced into the left atrium, the atrial flange is

FIGURE 3 Transapical/Transapical-Transfemoral TMVR Systems (Part 1)



(A) Tendyne valve. **(B)** Fluoroscopic view of Tendyne. **(C)** Three-dimensional echocardiography (surgical view) of Tendyne valve. **(A to C)** Reprinted from Muller et al. (31) and Sorajja et al. (32) with permission from Elsevier. **(D)** Tiara valve. **(E)** Fluoroscopic view of Tiara. **(F)** Three-dimensional echocardiography (surgical view) of Tiara valve. **(D to F)** Reprinted from Cheung et al. (37) with permission from Elsevier. **(G)** Intrepid valve. **(H)** Fluoroscopic view of Intrepid. **(I)** Three-dimensional echocardiography of the Intrepid valve. **(G)** Reprinted from Meredith et al. (40) with permission from Europagroup. **(H)** Reprinted from Del Val et al. (42) with permission from the publisher. **(I)** Reprinted from Bapat et al. (41) with permission from Elsevier. Abbreviation as in **Figure 1**.

expanded using a hydraulic delivery mechanism. After coaxiality and landing zone verification, the valve is deployed by retracting the catheter while using rapid ventricular pacing. The current available system allows full valve retrievability before final release.

Clinical results. The early experience with this valve (n = 50) yielded promising results, with successful implantation of the valve in 48 cases (one failure was due to sizing miscalculation and the other was not attempted because of transapical access bleeding). Seven patients (14%) died during the first 30 days after procedure, and 2 strokes (4%) were reported (**Table 4**). At a median follow-up of 6 months, all patients exhibited residual MR grades ≤mild with no evidence of LVOT obstruction (**Table 5**) (41,42).

Future perspectives. The APOLLO (Transcatheter Mitral Valve Replacement With the Medtronic Intrepid TMVR System in Patients With Severe Symptomatic Mitral Regurgitation; NCT03242642) trial aims to evaluate TMVR with the Intrepid system (**Table 6**). An addition of a single-arm substudy for patients exhibiting significant MAC is also ongoing. Besides, a transfemoral system implanted through a 35-F femoral introducer was developed and the initial in-human experience with this system is currently ongoing. A 29-F bore catheter for transfemoral use is expected in the near future (43).

HIGHLIFE. Device description. The Highlife system (Highlife SAS, Irvine, California) is composed of 2 separate parts: the subannular implant and the valve (**Figure 4, Table 3**). The subannular implant is a polymer tube covered with polyester that holds a nitinol hook in order to create a whole ring around the mitral subannular apparatus. The subannular implant comprises 2 distal ends mounted on each side of a previously placed guidewire loop surrounding the native mitral valve. The first end is tapered with a

TABLE 5 Midterm Outcomes After Transcatheter Mitral Valve Replacement With New-Generation Devices

										Global		
	AltaValve (n = 2)	CardioValve (n = 5)	Cephea (n = 4)	Evoque	Highlife (n = 15)	Intrepid (n = 50)	M3	Tendyne* (n = 109)	Tiara	TF* (n = 9)	TA* (n = 176)	Overall* (n = 185)
Follow-up, months	16	24	6		12	7 ± 7		23* (22.4–23.6)		8.2 (5.1–11.3)	17.8 (16.6–18.9)	17.4 (16.3–18.6)
Any cause mortality	1 (50)	3 (60)	0	NA	4 (26.7)	11/50 (22)	NA	40 (36.7)	NA	3/9 (33.3)	56/176 (31.8)	59/185 (31.9)
Cardiovascular mortality	0	3 (60)	0	NA	NA	11/50 (22)	NA	34/100 (34)	NA	3/9 (33.3)	45/152 (29.6)	48/161 (29.8)
Stroke	0	NA	0	NA	0	3/50 (6)	NA	5 (4.6)	NA	0/4 (0)	8/176 (4.5)	8/180 (4.4)
Myocardial infarction	0	NA	0	NA	0	0	NA	4 (3.7)	NA	0/4 (0)	4/176 (2.3)	4/180 (2.2)
NYHA functional class				NA	NA		NA		NA			
I-II	1/1 (100)	1/1 (100)	4 (100)			34/43 (79.1)		40/49 (91.6)		5/5 (100)	122/138 (88.4)	127/143 (88.9)
III-IV	0	0	0			9/43 (20.9)		9/49 (18.4)		0	16/138 (11.6)	16/143 (11.1)
Heart failure hospitalization	0	0/1	0	NA	NA	8 (19.5)	NA	33 (30.3)	NA	0/5 (0)	41/161 (25.5)	41/166 (24.7)
Mitral reintervention	0	0/1	0	NA	NA	0	NA	5 (4.6)	NA	0/5 (0)	5/161 (3.1)	5/166 (3.0)
Device endocarditis	0	0/1	0	NA	NA	0	NA	5 (4.6)	NA	0/5 (0)	5/161 (3.1)	5/166 (3.0)
Device thrombosis	0	0/1	0	NA	NA	0	NA	6 (5.5)	NA	0/5 (0)	6/161 (3.7)	6/166 (3.6)
Device fracture	0	0/1	0	NA	NA	0	NA	0	NA	0/5 (0)	0/161 (0)	0/166 (0)
Device embolization	0	0/2	0	NA	NA	0	NA	0	NA	0/5 (0)	0/161 (0)	0/166 (0)
MR severity				NA			NA		NA			
None/trace/mild	1 (100)	2 (100)	4 (100)		5/5 (100)	42/42 (100)		62/62 (100)		6/6 (100)	110/110 (100)	116/116 (100)
Moderate/severe	0	0	0		0	0		0		0	0	0
Mitral valve mean gradient	2	NA	2.5 (1.9–3)	NA	NA	NA	NA	3±1.1	NA	2.5	3.0	2.9
LVOT obstruction	0	0	0	NA	NA	0	NA	0	NA	0/6 (0)	0/161 (0)	0/167 (0)

Values are n, mean ± SD, mean (range), or n (%), as reported by authors. *Values expressed as weighted mean (95% confidence interval) or as counts (n/N [%]) for quantitative and qualitative variables, respectively.

Abbreviations as in Tables 1 and 4.

nitinol clip, and the second end has a flared shape designed to host the nitinol clip. The second element, the valve itself, consists of a nitinol self-expanding frame, covered with a polyester graft, along with 3 porcine pericardial leaflets. The frame shape has a preformed groove in the annular region allowing for an optimal surface of contact with the previously placed subannular implant (44).

Procedural aspects. The subannular implant is placed using an 18-F catheter through the femoral artery, and it is advanced over a guidewire loop previously positioned. The valve itself is then introduced through a 39-F catheter delivery system, which is positioned in a way that allows the prosthetic valve's outflow to completely deploy in the ventricle, distal to the subannular implant. The valve outflow is then manually pushed toward the atrium until a close contact against the subannular groove is reached. Finally, the inflow end of the transcatheter mitral valve is deployed (44).

Clinical results. The initial 15-patient experience with the transapical system, as well as the first-in-human transfemoral implantation, were recently reported (45). Three of the 15 transapical patients (20%) died within 30 days after procedure, and the rates of LVOT obstruction and valve thrombosis were approximately 7% each (1 case for each complication) (Table 4).

Future perspectives. The Early Feasibility Study of the HighLife 28 mm Trans-Septal Transcatheter Mitral Valve Replacement System (NCT04029337) will offer more insight into the feasibility and early outcomes associated with this system (Table 6).

CARDIOVALVE. Device description. The Cardiovalve (Cardiovalve, Or Yehuda, Israel) is a self-expandable bovine trileaflet TMVR valve (Figure 4, Table 3). The valve is anchored into the mitral annulus over 24 focal "sandwiching" points, with a symmetrical design that does not require rotational positioning. Three valve sizes are available, covering an intracommissural annular size from 36 mm to 53 mm. The height of the crimped valve is 32 mm. Once the valve is deployed, the protrusion into the left ventricle is approximately 12 mm.

Procedural aspects. The system is advanced using a 32-F capsule with a 24-F shaft, and a multi-steerable catheter facilitates coaxial implantation. Initially both mitral leaflets are grasped, and then an atrial flange is delivered followed by the complete apposition of the entire valve.

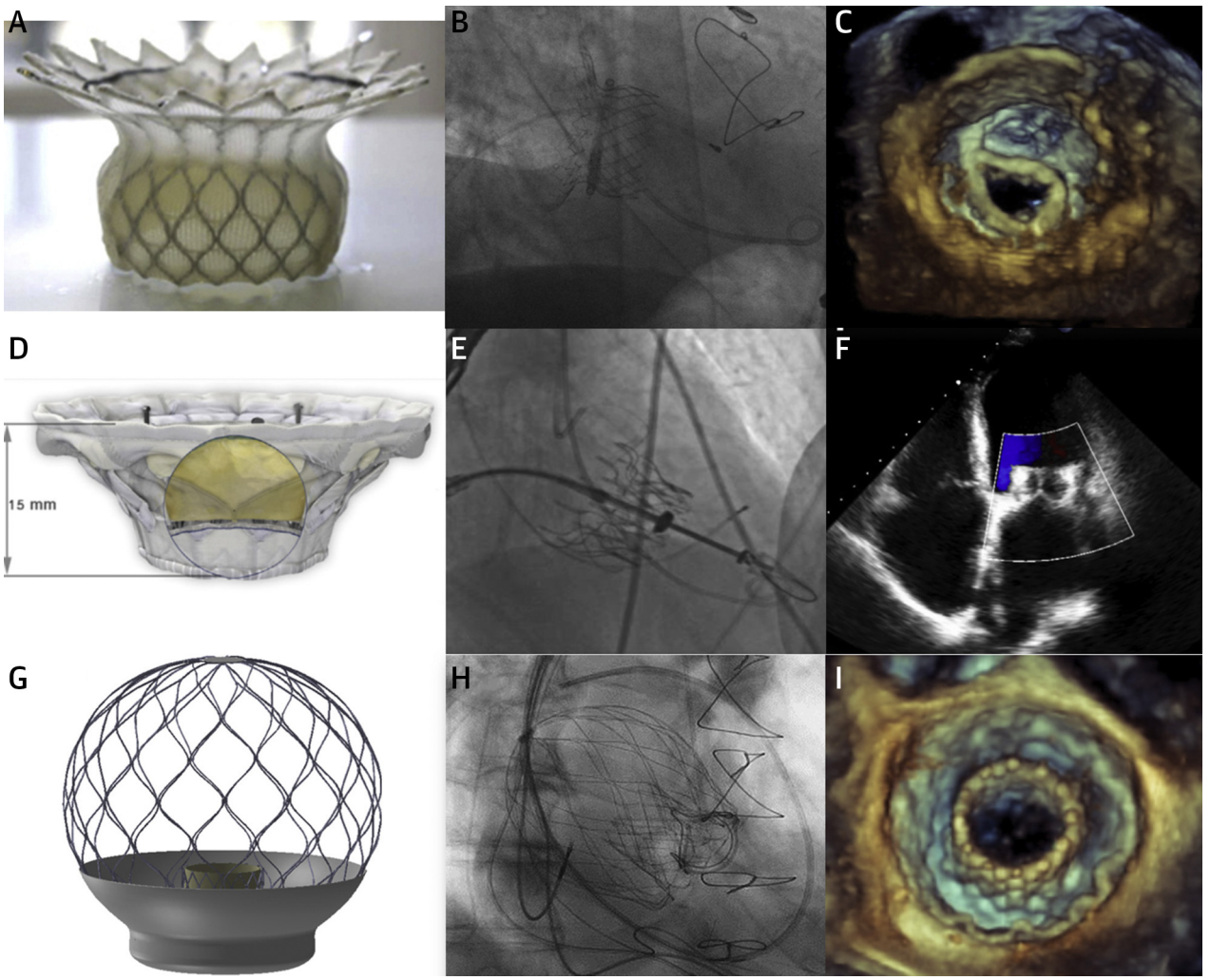
Clinical results. To date, the results of a case series including 5 patients treated with the transfemoral

TABLE 6 Ongoing and Future Studies in the Transcatheter Mitral Valve Replacement Field

	Name of the Study	Design of the Study	Country	Estimated Enrollment	Inclusion Criteria	Main Outcomes
AltaValve	AltaValve Early Feasibility Study	Prospective, open-label, single-arm, multicenter study	USA Japan	15	- NYHA II-III-IV - Severe MR - LVEF >25% - Prior surgical mitral valve repair, annuloplasty or MitraClip allowed	Major adverse cardiac events at 30 days
CardioValve	AHEAD EU	Prospective, multicenter, single-arm pilot clinical study	20 European sites: Germany, Italy, Switzerland	30	For both studies: - NYHA II-III-IV - MR grade 3-4+ - LVEF>30% - LV end-diastolic diameter <70 mm - Lack of severe annular or leaflets calcification - No prior valve intervention	For both studies: freedom from all-cause mortality, all-cause hospitalization, major adverse cardiac events, major device- or procedure-related serious adverse events
	AHEAD US EFS	Prospective, multicenter, single-arm pilot clinical study	USA	15		
Cephea	Early feasibility study (in development)					
Evoque	Edwards EVOQUE TMVR Early Feasibility Study	Multicenter, prospective, single-arm, open-label	USA and Canada	58	- NYHA II-III-IV - MR grade ≥3+ - LVEF >30% - High surgical risk but operable - No prior mitral valve intervention - Lack of severe calcification of any component of the mitral valve	Safety assessed by freedom from device or procedure-related adverse events at 30 days
Highlife	EFS of the Highlife Trans-septal system	Prospective, multicenter, single arm		15	- NYHA III or IV - MR grade ≥3+ for FMR - MR grade 4 for DMR	Device safety: freedom from adverse cardiovascular events
Intrepid	APOLLO single-arm	Single-arm, multicenter study	USA, Europe, and Japan	250	- Inoperable - No prior mitral valve intervention - MR grade ≥3+	For all Intrepid studies: All-cause mortality, disabling stroke, reintervention, and cardiovascular hospitalization at 1 yr
	APOLLO MAC Cohort	Single-arm, multicenter study	USA, Europe, and Japan	250	- Inoperable - MR grade ≥3+ or MR grade 3 and mitral stenosis - Presence of MAC	
	Transfemoral Intrepid EFS	Single-arm, multicenter study		15	NA	
M3	M3 Early feasibility study (ENCIRCLE trial)	Single-arm, multicenter study	USA and Canada	400	- NYHA II-III-IV - MR ≥3+ - Unsuitable for commercially available options	Composite of death or heart failure hospitalization
Tendyne	Global feasibility / CE study	Single-arm, multicenter study	USA	350	- LVEF >30% - LVEDD <70 mm - MR grade ≥3+	Device success and freedom from device and procedure-related serious adverse events per MVARC criteria
	SUMMIT trial					
	a) Randomization arm	Randomized trial 1:1 vs. MitraClip	USA, Canada	382	- LVEF >30% - LVEDD <70 mm - MR grade ≥3+	Survival free of heart failure hospitalization at 12 months post index procedure
	b) Nonrepairable arm	Single-arm	USA, Canada	313	- Unsuitable for transcatheter mitral valve repair	A composite of all-cause mortality, cardiovascular-related hospitalizations, stroke or mitral valve reintervention or reoperation
	c) Severe MAC arm	Single-arm	USA, Canada	103	- Severe MAC	Survival free of heart failure hospitalization at 12 months post index procedure
Tiara	TIARA I: early feasibility	Single-arm, multicenter study	USA and Canada	30	- NYHA III-IV - High surgical risk - Severe MR	Freedom from all-cause mortality and major adverse cardiovascular events
	TIARA II: extended early feasibility study	Single-arm, multicenter study	Europe	115	- NYHA III-IV - High surgical risk - Severe MR	Freedom from all-cause mortality, freedom from adverse events and reduction of MR to optimal or acceptable

DMR = degenerative mitral regurgitation; FMR = functional mitral regurgitation; LVEDD = left ventricular end-diastolic diameter; MAC = mitral annular calcification; SMVR = surgical mitral valve replacement; other abbreviations as in Tables 1 and 4.

FIGURE 4 Transapical/Transapical-Transfemoral TMVR Systems (Part 2)



(A) Highlife valve. **(B)** Fluoroscopic view. **(C)** Three-dimensional echocardiography, subannular implant. **(A to C)** Reprinted from Barbanti et al. (44) with permission from Elsevier. **(D)** Cardiovalve. **(E)** Fluoroscopic view of Cardiovalve. **(F)** Echocardiography (4-chamber view) of Cardiovalve. **(D to F)** Reprinted from Maisano et al. (47) with permission from Elsevier. **(G)** AltaValve. **(H)** Fluoroscopic view of AltaValve. **(I)** Three-dimensional echocardiography of AltaValve. **(G)** Reprinted from Nunes Ferreira-Neto et al. (49) with permission from Elsevier. Abbreviation as in **Figure 1**.

Cardiovalve system have been reported (46) (**Table 4**). All attempted valve implants were successful, with residual MR ≤mild in all patients. However, the mortality rate at 30 days was high (60%), mainly due to major bleeding events. Recently, the 2-year follow-up of the first-in-human transfemoral Cardiovalve implantation was reported (47), showing good clinical outcomes and optimal valve performance.

Future perspectives. The AHEAD (European Feasibility Study of High Surgical Risk Patients With Severe Mitral Regurgitation Treated With the Cardiovalve Transfemoral Mitral Valve System) trials (ongoing in Europe and the United States) are evaluating the feasibility and early outcomes of the transfemoral Cardiovalve system (NCT03339115).

ALTAVALVE. Device description. The AltaValve System (4C Medical Technologies, Minneapolis, Minnesota) uses a supra-annular, atrial-only fixation technology. The device is made of a spherical self-expanding nitinol frame, which is sized between 50 and 95 mm (**Figure 4, Table 3**). The implant ball dimensions are oversized between 10% and 30% in

relation to the left atrium measures, and the targeted annular ring oversizing is 5% to 20% with respect to the maximum diameter of the native mitral valve. The cells contained in the nitinol frame fit a 24-F catheter. A 27-mm trileaflet bovine pericardium valve is located at the interior of the frame, and the valve size is similar for all implant sizes. This trileaflet valve is hydrodynamically equivalent to a 29-mm surgical valve. A skirt fabric is placed at the lowest third of the frame aiming to prevent PVL. Currently, there are 3 annular ring sizes for the AltaValve: 40 mm, 46 mm, and 54 mm diameter.

Procedural aspects. After gaining access to the left atrium (either by a transeptal or transapical approach), the delivery catheter is advanced with the use of a dilator. Then, the valve is loaded and progressively deployed by pulling back the delivery catheter. During this maneuver, valve repositioning is feasible by performing gently angulations and/or pushing-pulling movements (48).

Clinical results. The published data with this system is limited to 2 case reports, both of them performed transapically (49,50) (**Table 4**). Technical success rate was 100% and postprocedural valve performance was optimal in both patients. One patient died early after the procedure due to severe bleeding, while the other patient experienced significant clinical improvement up to more than 12 months of follow-up. The first case performed through transfemoral access has been reported recently (51).

Future perspectives. More data will be available in the near future and the ongoing early feasibility study will further inform about the clinical outcomes obtained with the AltaValve transfemoral system (**Table 6**).

SAPIEN M3. Device description. The Sapien M3 system (Edwards Lifesciences, Irvine, California) is composed of 2 different parts: the dock and the valve (**Figure 5, Table 3**). The dock is made of nitinol and covered with polytetrafluoroethylene, and it is designed to encircle the chordae tendineae below the level of the mitral annulus by means of a leading turn with a large diameter (37 mm). The subsequent turns of smaller diameter (25.5 mm) serve as an anchor for the valve, and their polyethylene terephthalate covering helps to avoid migration/embolization. The Sapien M3 valve is identical to the 29-mm diameter Sapien 3 aortic valve (52), with the addition of an external knitted polyethylene terephthalate seal that covers the entire outer surface of the valve frame. The whole system can be implanted through a 20-F femoral introducer.

Procedural aspects. While connected to the delivery catheter, the dock is fully retrievable. The valve is balloon-expandable and is implanted into the aforementioned dock under rapid pacing, in a very similar fashion as the Sapien 3 valve for the treatment of mitral prosthesis degeneration.

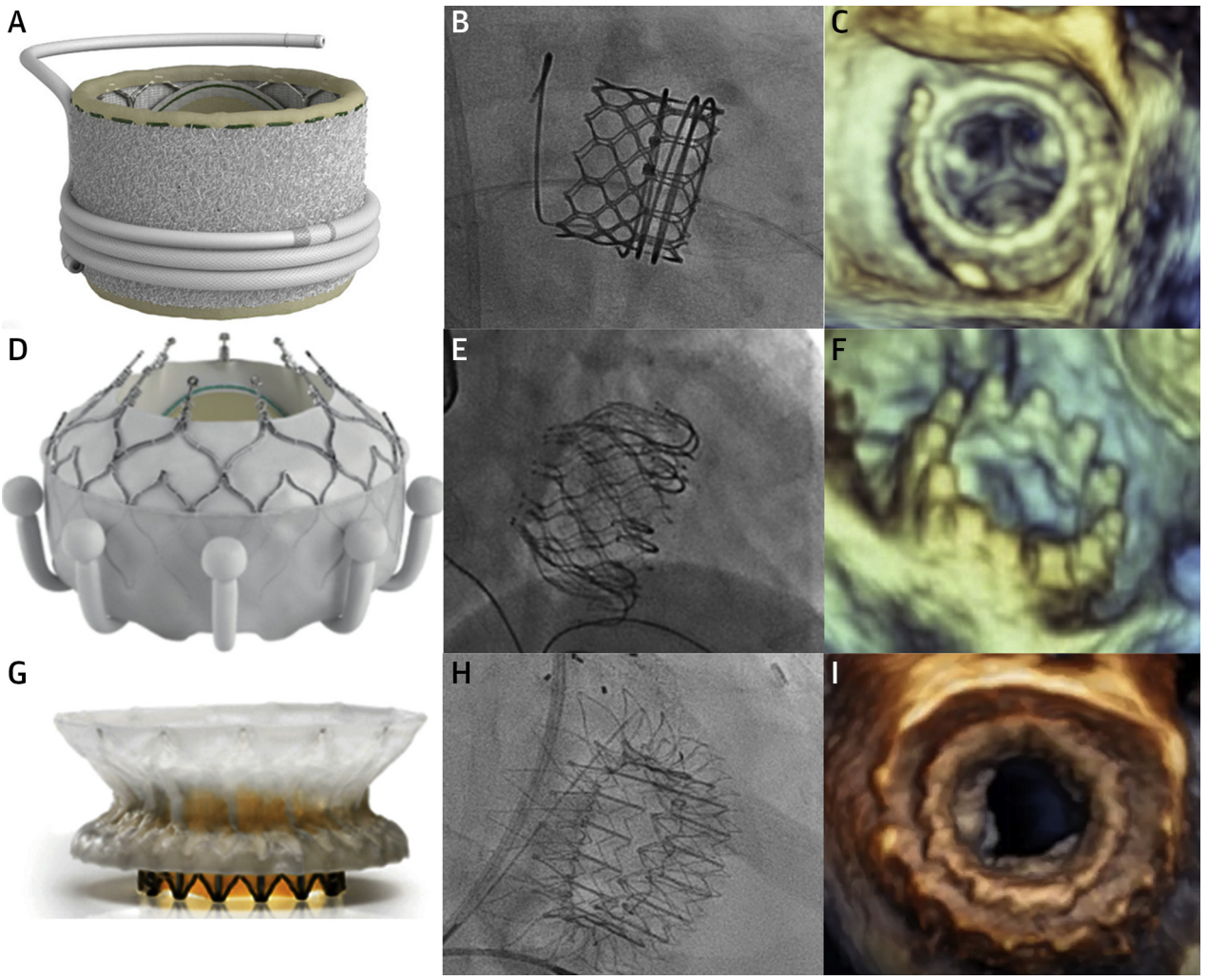
Clinical results. Webb et al. (53) reported the results of the first clinical experience with the M3 valve including 10 patients (**Table 4**). Technical success was achieved in 9 patients (90%), and 30-day outcomes revealed no mortality and optimal valve function in all valves implanted (the case with failed implantation was due to pericardial effusion during dock placement). Further evaluation of this valve system is ongoing in an early feasibility study in United States and Canada, and the results of the first 35 patients included in this study revealed a technical success rate of 88.6%, with no procedural-related deaths and a 30-day stroke incidence of 8.6% (54).

Future perspectives. The ongoing ENCIRCLE trial for the Sapien M3 valve will help to further determine the early and midterm outcomes of this device (NCT04153292) (**Table 6**).

EVOQUE. Device description. The EVOQUE system (Edwards Lifesciences) is the latest iteration of the previous CardiAQ valve (Edwards Lifesciences) (**Figure 5, Table 3**). The valve consists of a self-expanding nitinol frame, 3 bovine pericardial leaflets, and a fabric skirt. The valve uses a specific anchoring mechanism involving the subvalvular apparatus. Briefly, the system "captures" the mitral leaflets and subvalvular chordae with the aid of ventricular anchors. It is currently available in 44- and 48-mm sizes. The EVOQUE delivery system is 28 F and is compatible with both valve sizes.

Procedural aspects. The delivery system allows for 3 planes of motion, which facilitates crossing of the interatrial septum and the coaxial alignment within the mitral valve (monitored by TEE during implantation). An independent depth control allows precise positioning at the level of the mitral annulus while maintaining coaxial alignment. The system is secured in a stabilizer stand during implantation. After crossing the mitral valve annulus with the device, the ventricular outflow portion of the valve is partially expanded by withdrawal of an outer restraining capsule. Further expansion of the outflow portion results in the ventricular anchors capturing the mitral leaflets and subvalvular apparatus. The atrial inflow portion of the valve with its sealing skirt is subsequently expanded.

FIGURE 5 Transfemoral TMVR Systems



(A) M3 valve and dock. **(B)** Fluoroscopic view of M3. **(C)** Three-dimensional echocardiography (surgical view) of M3. **(A to C)** Reprinted from Webb et al. (53) with permission from Elsevier. **(D)** Evoque valve. **(E)** Fluoroscopic view of Evoque. **(F)** Three-dimensional echocardiography of Evoque system. **(D to F)** Reprinted from Webb et al. (55) with permission from Elsevier. **(G)** Cephea valve. **(H)** Fluoroscopic view of Cephea. **(I)** Three-dimensional echocardiography of Cephea. **(G and H)** Reprinted from Alperi et al. (56) with permission from Elsevier. Abbreviation as in Figure 1.

Clinical results. The results of the initial 14 patients treated with this valve system (special access Canadian program + U.S. early feasibility) were recently reported (55) (Table 4). Technical success was achieved in all patients but one, which required conversion to open heart surgery. At 30-day follow-up, 1 death was observed (noncardiovascular cause), and the rates of any-stroke and major/life-threatening bleeding were 14.3% and 21.4%, respectively. Hemodynamic valve performance was optimal (there were no cases of PVL and all patients exhibited ≤ mild MR grade).

Future perspectives. The Evoque EFS is ongoing and actively recruiting (NCT02718001). A new iteration of the system, allowing for complete valve recapture and retrieval, will be available in the upcoming months.

CEPHEA. Device description. The Cephea TMVR system (Abbott, Menlo Park, California) consists of a self-expanding nitinol double-disc structure and a central bovine trileaflet valve (Figure 5, Table 3). The prosthesis has a multilevel conformability design, making the valve capable of adapting to various anatomies, and it anchors on the mitral annulus by

means of axial compression forces. The atrial disc is positioned at the floor of the left atrium, the center column provides a stable platform for leaflet support, and the ventricular disc anchors into the subannular region. This modular architecture isolates the prosthesis from external deformation. The valve is deployed using a dedicated transfemoral delivery system using the transfemoral approach, and a single valve size (36-mm central waist) is available for clinical use to date.

Procedural aspects. The ventricular disc is deployed starting at the level of the distal portion of the AML and, once the ventricular disc is fully opened and in contact with the annulus, the atrial disc is progressively deployed resulting in complete apposition of the valve into the mitral annulus.

Clinical results. A total of 4 TMVR cases have been published with the use of Cephea valve (56,57), all of them in patients with organic MR (**Tables 4 and 5**). The 4 valves were successfully implanted (technical success rate of 100%) with optimal immediate valve function. At follow-up, all patients experienced an improvement in functional class, no valve-related complications were observed, and valve positioning and function (evaluated with both CCT and echocardiography) were excellent.

Future perspectives. An early feasibility study of the Cephea valve will start in the United States and Canada in 2021.

CLINICAL PERSPECTIVES

SCREEN FAILURE. One of the main reasons supporting the development of percutaneous TMVR systems has been the possibility of treating a wider range of anatomies and valve failure mechanisms with the use of a single technique. However, an important number of patients referred for TMVR are ultimately rejected, and this high screen failure rate (usually >50%) is partially related to anatomic and sizing issues, particularly mitral annuli too large or small for a specific valve size and an excessive risk of LVOT obstruction (29,33,56,58). Importantly, many studies reporting on early clinical experience with novel TMVR systems failed to provide data on screen failure rates. It would be important to systematically detail the rate and reasons for screen failure in future TMVR reports in order to provide a real picture of the global applicability of this technology and to permit the evaluation of the changes related to different valve iterations over time. A broader range of valve sizes is expected to be available over the upcoming years for most TMVR systems. This fact, along with the development of lower valve profiles enabling minimal interaction with the LVOT, will certainly help to reduce screen failure rates.

OVERVIEW OF THE CLINICAL RESULTS. To date, most TMVR cases worldwide have been performed through a retrograde transapical approach, as early-generation dedicated TMVR systems were mostly designed to be implanted transapically. The transapical access facilitates a more direct implant as it minimizes the distance between the introducer and the mitral valve. However, several studies in the TAVR field have shown the detrimental effects associated with a transapical access (59,60), likely related to the inherent myocardial injury and the need for longer in-hospital recovery periods after a left thoracotomy. In addition, the negative impact of the transapical access on frail and highly comorbid populations, like those patients ultimately undergoing TMVR, might be even higher. The design of lower profile delivery systems with the ability to bend and properly track the guiding guidewire after transeptal crossing has been one of the greatest engineering challenges in this field. Following several iterations, a growing number of successful implants have been achieved with multiple TMVR devices using the transfemoral approach. The main early outcomes after TMVR evaluated according to access (**Table 4**) demonstrated that technical success rates were quite similar in both transfemoral and transapical strategies, whereas procedural mortality rates were slightly lower in the transfemoral approach. It should be noted that most patients undergoing transapical TMVR had functional MR, therefore likely presenting with a lower ejection fraction and a more advanced heart disease. However, these findings are encouraging, and if these preliminary results are confirmed in larger series, a fully percutaneous transfemoral-transeptal approach will likely become the default strategy (as in the TAVR field). In addition, the switch from transapical to transfemoral TMVR would be associated with a more rapid postprocedural recovery and a shorter length of stay. On the other hand, the transfemoral access poses the clinical dilemma of whether to close the remaining iatrogenic interatrial communication after valve deployment. The rationale underlying septal closure is the avoidance of right ventricular and pulmonary volume overload. A recently published trial that randomized patients to interatrial defect closure or conservative treatment 1 month after TEER failed to demonstrate better outcomes (6-min walk test, N-terminal pro-B-type natriuretic peptide, heart failure, and mortality) with the interventional strategy (61). However, this trial was based on a small cohort (n = 80), and

therefore, each patient should be evaluated individually until gathering more robust data. Both procedural refinement and technological iterations (e.g., transeptal TMVR devices enabling partial/full valve recapture and retrievability) are key for improving TMVR clinical results in the near future.

Stroke has been one of the most dreadful complications associated with structural heart procedures, and its impact on early mortality has already been demonstrated (62,63). For current TMVR recipients, the early stroke rate was approximately 4%, which was higher compared with TEER series (64,65), and similar to that reported in TAVR series (66). Although these results may be partially related to the learning curve process along with the use of first-generation devices and delivery systems, further efforts are required to decrease the risk of cerebrovascular events during TMVR procedures. Of note, embolic protection devices were not used (or its use was not reported), in the TMVR field. Previous data suggested that the use of cerebral protection systems during TEER was feasible, and its use associated with a high rate (almost 100%) of material being captured within the filter during the intervention (67). The safety and effectiveness of these systems for TMVR remains unknown and requires further investigation. Also, the optimal anticoagulation level during the procedures and the type of antithrombotic regimen in the periprocedural period remain to be determined.

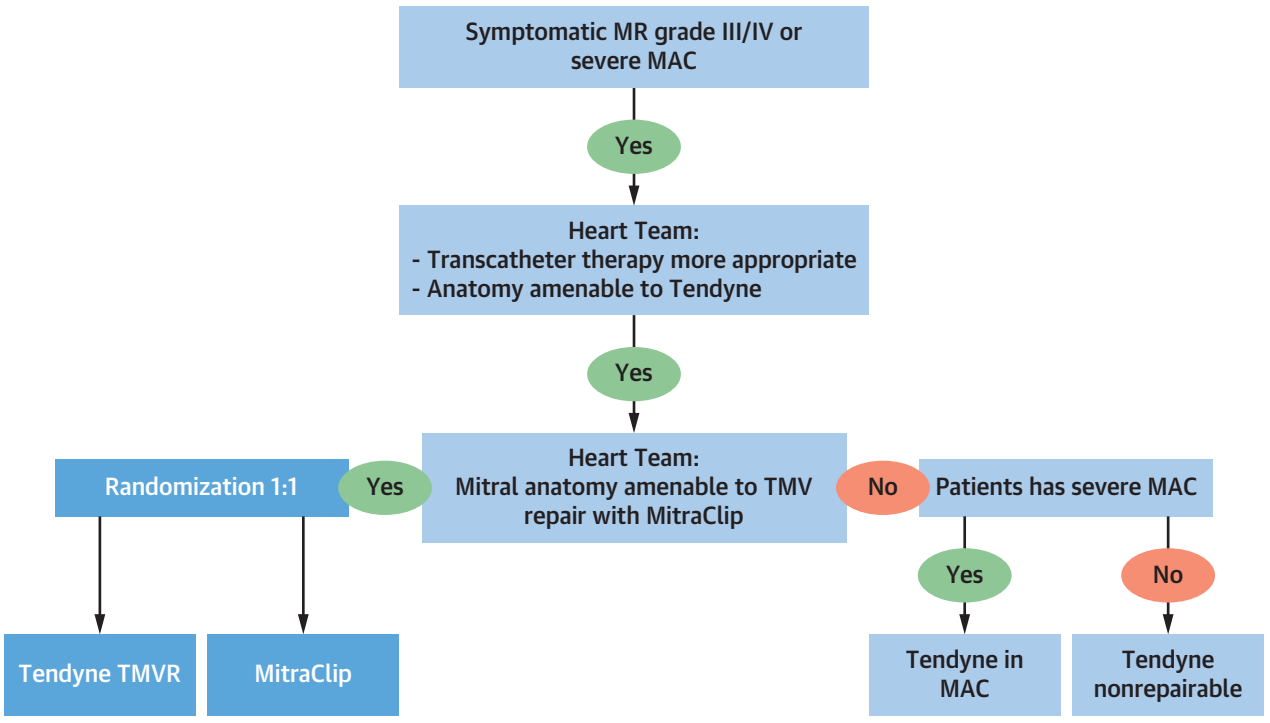
One of the major pitfalls since the beginning of the TMVR experience has been the high incidence of early major or life-threatening bleeding events. Although these events could be partially explained by the use of intense anticoagulant therapy in patients with increased bleeding risk, the routine use of large-bore catheters for both transapical and transfemoral accesses has also played a significant role. In fact, one of the largest TMVR studies evaluating a transapical TMVR system reported that the rates of reoperation at 30 days due to bleeding issues related to the transapical access were as high as 10% (41). After a comprehensive review of the initial clinical experience with current TMVR systems, the rates of 30-day major/life-threatening bleeding were quite similar between transapical and transfemoral interventions. However, it should be outlined that these results reflected the very early experience for most of the transfemoral devices, whereas larger series have been reported for transapical systems (a 5-fold number of patients have been treated with transapical TMVR compared with transfemoral). Therefore, an important learning-curve effect should not be discarded as a major factor impacting these early results. Larger studies are needed to gain further knowledge on this subject.

The risk of LVOT obstruction after TMVR has been an important factor likely limiting a more rapid expansion of the technique. This complication was reported in a low number of TMVR cases (<1%) (45,55), likely due to the accurate anatomic inclusion process leading to a highly selected population (excluding patients at risk for LVOT obstruction). Post-procedural immediate TEE will be of vital importance with the implementation of partially/fully recapturable and retrievable transfemoral systems. It helps to determine the presence of LVOT obstruction early after the valve is positioned and before final release. However, it must be considered that the hemodynamic state of the patient (general anesthesia, likely hypovolemic) will change after the procedure, and, therefore, a comprehensive assessment should be repeated in the hours following the implantation.

Some promising preventive and bail-out techniques have been proposed for TMVR recipients at high risk for or with postprocedural presence of clinically significant LVOT obstruction, such as septal alcohol ablation, radiofrequency septal ablation, kissing-balloon (aortic valvuloplasty balloon inflation at the LVOT level simultaneously to mitral valve deployment), or TAVR after TMVR (68–70). However, these techniques require further validation, and their used cannot be currently recommended. The intentional percutaneous laceration of the AML to prevent outflow obstruction (LAMPOON) technique merits further consideration. This fully percutaneous technique comprises 2 arterial accesses to perform, by means of a 0.014-inch guidewire and 2 guiding catheters, a laceration of the AML, ultimately splitting this structure in half. It aims to facilitate left ventricular emptying after TMVR by minimizing LVOT obstruction dependent on the apical displacement of the AML. It was first reported in 2017, and a feasibility trial has demonstrated its safety with a success rate of 100% in 30 patients (71,72). Although further validation and a larger experience is needed, this approach seems promising, especially for patients within the upper range of AML length and redundancy. However, it should be noted that some dedicated TMVR systems (e.g., Evoque) are purposely designed to capture the mitral valve leaflets during deployment, thereby embedding them into the stent frame. The LAMPOON technique has no place in this particular setting.

VALVE PERFORMANCE. Currently available data show that TMVR significantly reduces the MR grade

FIGURE 6 SUMMIT Randomized Clinical Trial



Study design chart for the SUMMIT trial. Abbreviation as in Figure 1.

when the valve is adequately implanted. In fact, leaving aside unsuccessful procedures (e.g., device malposition or impossibility for device deployment) there has been a very low rate of cases with more than mild MR after TMVR. Moreover, the mean residual gradient has been low (mean 2 to 3 mm Hg) for all TMVR valve systems.

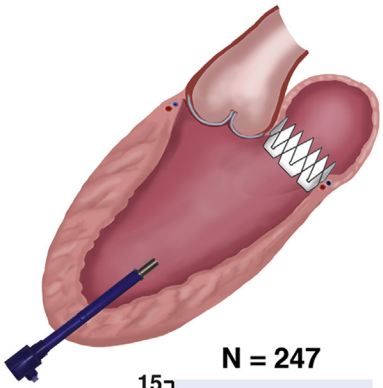
However, the rates of valve thrombosis at 30-day and 1-year follow-up (approximately 2.0% and 3.5%, respectively) are of concern (33,55), and raise the issue of antithrombotic management for these patients. In fact, an important rate of valve thrombosis was observed among the first 35 Tendyne recipients in the early feasibility trial (6 of 35, 17.1%) when oral anticoagulation was not yet mandatory per study protocol. Thereafter, under required antivitamin K therapy, no more device-related thrombotic events were found (33). In the early experience with current TMVR devices, a strategy comprising at least 3 to 6 months of oral anticoagulation with vitamin K antagonist was common (33,41,53,56), although some Evoque patients (23.1%) received new oral anticoagulants (55). Of note, the use of antiplatelet therapy was variable among studies reporting on it, with rates of concomitant single antiplatelet treatment ranging between 53% and 100% for Evoque (55) and Intrepid (41) recipients, respectively.

The results regarding valve performance are encouraging, although a competitive risk effect accounting for these positive findings should also be considered. Long-term clinical and echocardiographic data are warranted. Meanwhile, anticoagulation therapy for several months should probably be administered following TMVR (irrespective of the presence of atrial fibrillation). The type and level of anticoagulation and the role of adding antiplatelet therapy will need to be determined.

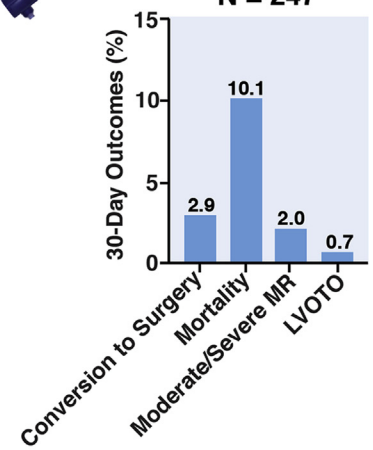
TEER VERSUS TMVR. Current data suggest the superiority of TMVR versus TEER regarding valve performance and the presence of residual MR. Significant MR recurrence following TEER has been reported in about 6% of cases (73), and its appearance is a well-known predictor of poorer clinical outcomes. On the other hand, TMVR lies way behind TEER in terms of procedural safety and major adverse cardiovascular events. Albeit TMVR might be more effective regarding complete MR resolution ("surgical-like"

CENTRAL ILLUSTRATION **Presence and Future of Transcatheter Mitral Valve Replacement**

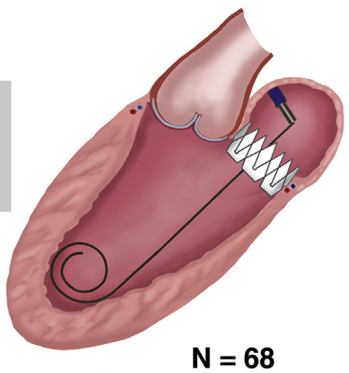
Transapical TMVR



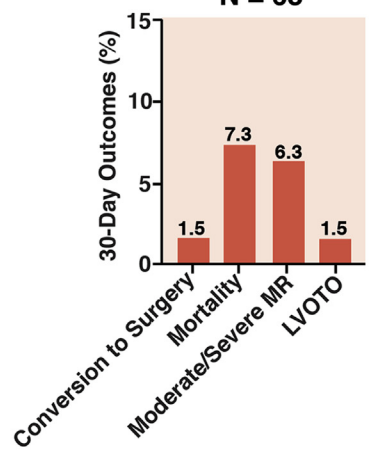
N = 247



Transfemoral TMVR



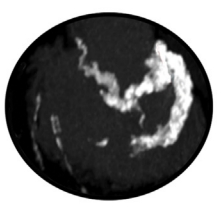
N = 68



Overall technical success rate = 93.7%

Future of the TMVR Field

Ongoing and Future Trials



Clinical applicability in complex anatomies (e.g. MAC)

Device iterations:
- Partial/Fully repositionable TF systems
- More available sizes
- Lower profile devices

Refinement of imaging planning and guidance

Alperi, A. et al. J Am Coll Cardiol. 2021;77(24):3058–78.

Main early results for transapical and transfemoral TMVR approaches **(top)** and future perspectives of the TMVR field **(bottom)**. CCT = cardiac computed tomography; LVOT = left ventricle outflow tract obstruction; MAC = mitral annular calcification; Mod/Sev = moderate or severe; MR = mitral regurgitation; TF = transfemoral; TMVR = transcatheter mitral valve replacement; TMVr = transcatheter mitral valve repair.

result), its use cannot be recommended for patients exhibiting optimal anatomic features for TEER. However, TMVR seems to be a good alternative for high-risk patients with MR not amenable to TEER. For cases lying between the 2 aforementioned scenarios (feasible but not optimal for TMV repair), a great emphasis should be put on the main factors predicting TEER failure and MR recurrence, given that edge-to-edge repair would prevent subsequent TMVR for the vast majority of available systems. It should be highlighted that, although TEER has not demonstrated better clinical outcomes than medical therapy or cardiac surgery for patients with organic MR, its use in functional MR has been shown to reduce both heart failure admissions and mortality (4). Therefore, the etiology of the MR must be a centerpiece in the decision-making process for potential TMVR patients, with TEER favored in doable functional MR cases.

Recently, an electrosurgical clip detachment from the AML has been proposed as an alternative to facilitate TMVR in patients with MR despite prior TEER; however, this technique requires further validation (74). The percutaneous mitral valve treatment toolbox is expanding rapidly and, subsequently, cardiologists, cardiac surgeons, and valvular heart disease physicians will have to deal with a growing number of treatment choices and algorithms. Future trials will shed more light on this topic. Among others, the ongoing SUMMIT randomized clinical trial comparing TMVR versus TEER (**Figure 6**) will help to determine the role of TMVR in the treatment of patients with MR.

CONCLUSIONS

TMVR has emerged as a new approach for the treatment of mitral valve disease, and it may help to overcome some of the limitations associated with TEER and surgical mitral valve repair/replacement (**Central Illustration**). However, several challenges mostly related to the complex anatomy of the mitral valve have impeded a more rapid spread of the technique. Patient selection based on clinical history and imaging-guided suitability is a key step before TMVR. CCT is a prerequisite for anatomic screening, and it allows for optimal annular sizing, calcium assessment, and quantification, as well as risk stratification for specifically procedure-related complications. Currently, 9 TMVR systems are under clinical investigation, and continuous device iterations have led to the possibility of fully percutaneous transfemoral-transeptal implantations with up to 6 different TMVR systems. Transfemoral procedures have demonstrated promising outcomes in their early clinical experience, yielding similar or even slightly better results than their transapical counterparts. However, several concerns remain, like the high rate of major bleeding events, the risk for LVOT obstruction, and the relatively high early mortality rates. Future trials are eagerly awaited to shed more light in this expanding field.

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KEY WORDS **mitral regurgitation, transcatheter mitral valve replacement, valve heart disease**