Transcatheter Mitral Valve Repair and Replacement

A review article by

AbdelMohsen Mostafa Abdou Aboualia

Al-Azhar University

Faculty of Medicine

Trancatheter Mitral Valve Repair and Replacement

I-Introduction

Transcatheter approaches to mitral valve disease have reached a turning point after many years of research studies. Transcatheter edge-to-edge repair, approved in the United States since the spring of 2013 and performed in more than 75,000 patients to date worldwide, has become an accepted therapy for patients with primary (degenerative) mitral regurgitation who are at high risk for surgical repair or replacement. In the setting of functional mitral regurgitation, where surgical therapy has not been proven nor embraced, the prospective, randomized COAPT trial recently demonstrated that transcatheter edge-to-edge repair, when combined with maximally tolerated guideline directed medical therapy, reduces recurrent heart failure hospitalization and decreases mortality compared with optimal guideline-directed medical therapy alone although previous trial MITRA-FR showed no much added benefit rather than optimal medical therapy, this introducing the term proportionate and disproporniate mitral regurgitation to suggest the indication which can benefit from it . Mitral valve abnormalities in those who had malfunctioning biological valve or mitral valve ring open the innovation to the transcatheter mitral valve replacement over the horizon to treat those difficult-to-treat and highly co-morbid patients. Transcatheter mitral valve replacement has been challenging due to particular anatomic aspects and device profiles with encroachment on left ventricular outflow tract (LVOT).

II-Anatomy of mitral apparatus

The healthy mitral valve is a complex apparatus that functions as a 1-way conduit from the left atrium to the LV. The mitral apparatus is composed of the mitral annulus, leaflets, commissures, chordae tendinae, posterior left atrium, LV free wall, and papillary muscles, which work in a coordinated fashion to allow frictionless passage of blood through the left side of the heart. Dysfunction of any component can lead to mitral valve pathology, including MR (Figure 1) (Maréchaux et al., 2014).

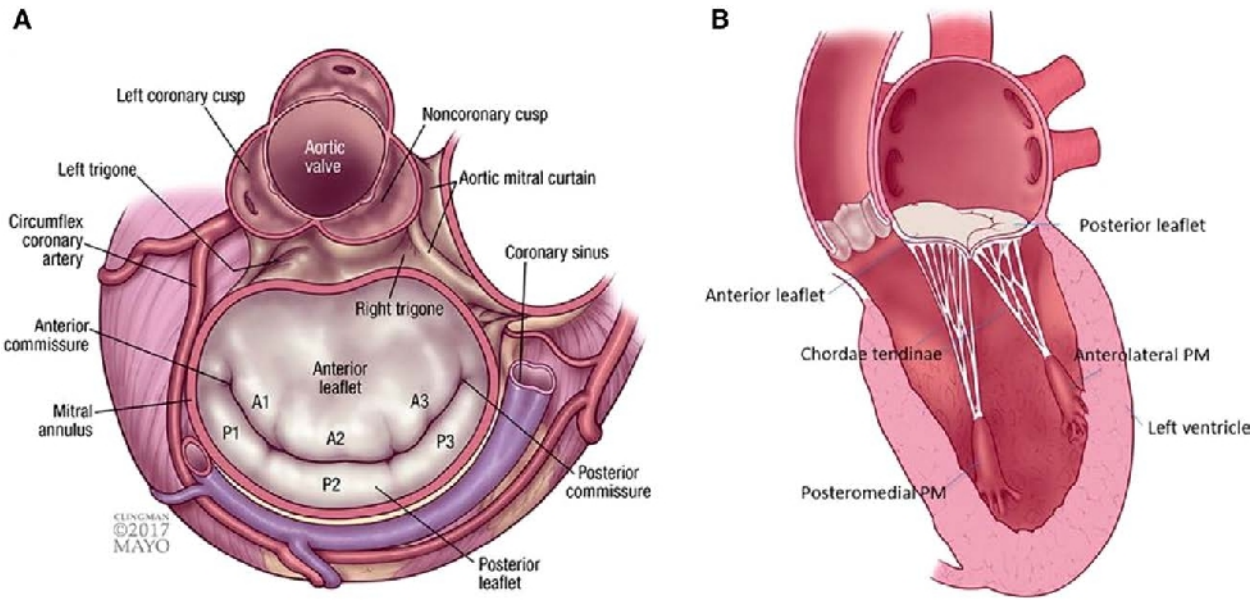


Figure 1. Atrial and sagittal views of mitral valve. A, Schematic representation of the mitral valve and surrounding structures from the atrial view. Note the 2 fibrous trigones and structures posterior to the mitral valve (coronary sinus and left circumflex artery). Note the mitral leaflet scallops; P1-A1 is anterolateral, P3-A3 is posteromedial. B, Sagittal view showing subvalvular supporting structures. A indicates anterior; P, posterior; and PM, papillary muscle (Quoted from Maréchaux et al., 2017).

A-Mitral annulus

Historically, the mitral annulus (MA) is defined by the junction of the left atrium, left ventricle (LV), and mitral leaflets, resulting in a 3-dimensional (3D) saddle-shaped configuration with anterior and posterior peaks, the former being (Levine et al., 1987).

The junction of the left atrium (LA), LV, and PML insertion typically forms a well-defined, distinct fibrous structure. In contrast, the anterior annulus is more difficult to define, having various perspectives among specialties and imaging modalities, primarily due to the continuous transition of the AML into the intervalvular fibrosa, also referred to as the "aortomitral curtain" or "continuity." Surgeons tend to exclude the intervalvular fibrosa from their MA definition as they can visually identify the distal margin of left atrial myocardium along the aortomitral curtain intraoperatively. However, the intervalvular fibrosa is often included in cardiac imaging, likely due to the lack of a distinct border on both computed tomography (CT) and echocardiography (Figures 2 and 3). Importantly, the anterior MA does not correspond to the hinge point of the AML, as the latter is located further toward the ventricle, usually below the fibrous trigones (Bothe et al., 2013).

B-MV leaflets

The two MV leaflets are referred to as "anterior" and "posterior." However, due to the oblique orientation of the mitral apparatus, relative to the anatomical axes, the leaflets are oriented in a more anterosuperior and posteroinferior position. The leaflets are asymmetrical in shape, with the AML being rounded and occupying a third of the annular circumference, whereas the radially narrower PML occupies the other two-thirds. The coaptation line approximates a semilunar arc, with each end referred to as a "commissure." Importantly, the anterolateral and

posteromedial commissures do not extend to the annulus, often lacking a distinct separation of both leaflets. The PML is indented by folds or clefts, creating 3 frequently unequal scallops, with the middle scallop being typically the largest (Theriault-Lauzier, et al., 2014). Carpentier's nomenclature describes the most lateral, anterosuperior segment as P1, the central segment as P2, and the most medial, posteroinferior segment as P3. Although the indentations can be well visualized on echocardiography, they are not as discrete on CT, owing to partial volume averaging. Thus, on CT the PML can be routinely subdivided into 3 equal partitions, P1, P2, and P3. The AML is curtain-like and lacks distinct scallops, although similar labeling (A1, A2, and A3) is applied to the lateral, middle, and medial segments, respectively (Carpentier et al., 1995).

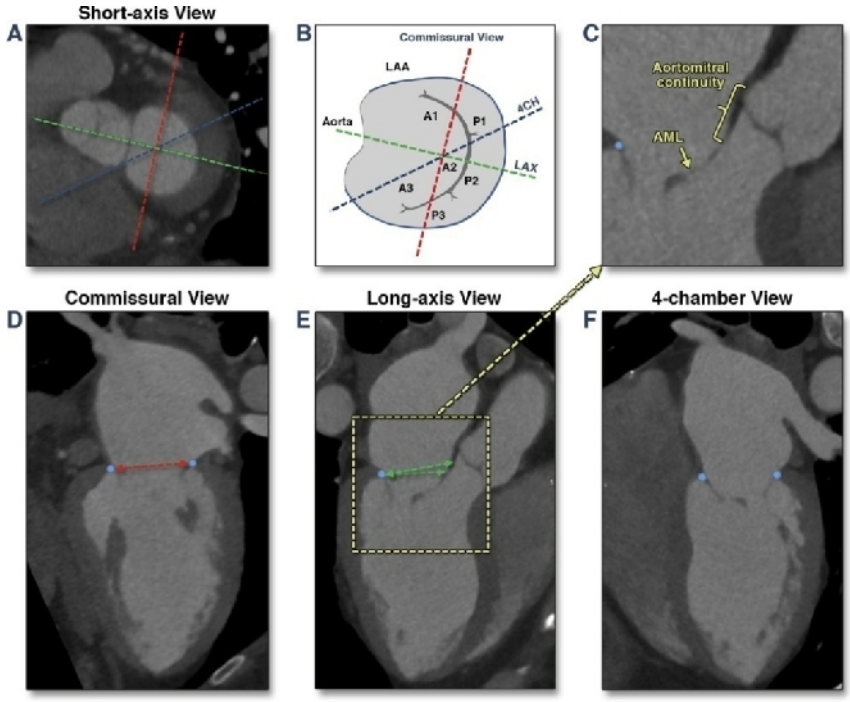


Figure 2. 2D Multiplanar Cardiac CT Views. Short-axis view of the MA region **(A)** and schematic of the leaflet scallops **(B)** with **dashed lines** indicating the orientation of the views in **D** to **F**. **(D)** Commissural view transecting at P1-P3 (major MA diameter). **(E)** Long-axis view transecting through A2-P2, oriented perpendicularly to the commissural view. The long-axis view is lacking a distinct MA landmark at A2, resulting in variable measurements **(C, inset)**. **(F)**

Four-chamber view with a diagonal orientation (not recommended for 2D measurements). 2D = two-dimensional; CT = computed tomography; LAA = left atrial appendage; LAX = long-axis; MA = mitral annulus (quoted from Blanke et al., 2015).

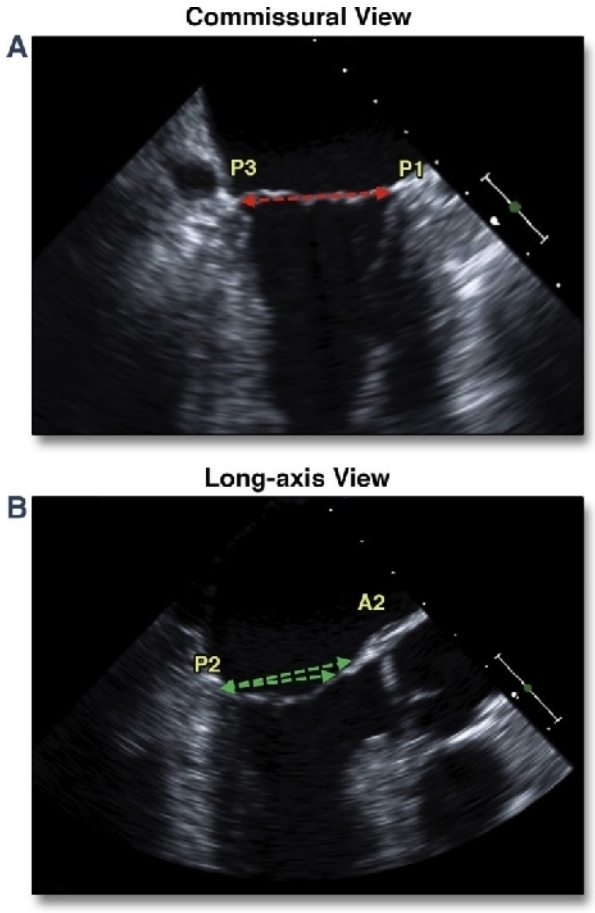


Figure 3. 2D Cardiac Views and MA Measurements in TEE. Commissural view transecting the annulus at P1-P3, typically yielding the major MA diameter **(A)**. Perpendicular long-axis view transecting at A2-P2 **(B)**, yielding the minor MA diameter. In contrast to P1-P3, there is no distinct landmark at A2 defining the anterior annulus. TEE = transesophageal echocardiography (quoted from Blanke et al., 2015).

III-Pathophysiology and natural history of mitral regurgitation

Mitral regurgitation is classified based upon the acuity and the underlying mitral valve structure. The Carpentier classification is a helpful tool to standardize the mitral valve pathologies (Figure 4). Functional MR differs from degenerative (primary) MR in that the mitral valve apparatus is normal, but ventricular

remodeling provides the substrate for mitral valve dysfunction. Ventricular remodeling from any cause (ischemic cardiomyopathy or nonischemic cardiomyopathy), as well as left atrial dilatation due to AF (and subsequent annular dilatation), leads to progressive annular dilatation and leaflet malapposition. This begins a cycle of further LV pressure and volume overload from the regurgitant volume, leading to further LV remodeling with progressive LV dilation and dysfunction. Functional MR is an independent predictor of adverse prognosis and mortality. The sequelae of LV remodeling includes a cycle of neurohormonal activation and irreversible damage and fibrosis, resulting in poor cardiac output, heart failure, and ultimately death. Furthermore, invasive hemodynamic studies had shown an elevation in left atrial mean pressure, left atrial V-wave pressure, left atrial mean pressure index, left atrial V-wave pressure index, increased pulmonary capillary wedge pres- sure, pulmonary arterial pressures, and right atrial and tricuspid annular dilatation, all of which are risk factors of recurrent hospitalizations (Fuster et al., 2017). Chronic MR can be divided further into 3 stages. In stage 1 (compensated phase), long-standing MR results in LV volume overload/enlargement, eccentric hypertrophy with normal systolic function. Enlargement of left atrium due to compliance keeps the left atrial pressures and thus pulmonary arterial pressures within normal limits in the initial compensatory phase (stage 1) of MR. Left atrial enlargement is the first sign that MR is worsening. In stage 2 (transitional phase), there is mild LV dysfunction; however, it is reversible following correction of the regurgitant lesion. In stage 3 (decompensated phase), the LV dilates, wall stress increases, and may cause irreversible myocardial damage. As this occurs, LV contractility may decline, with a reduction in LV stroke volume and ejection fraction (Fuster et al., 2017).

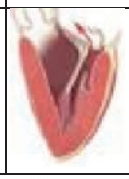
Carpentier's classification				
	Organic			**Functional**
	Type I (normal leaflet movement)	Type II (excessive leaflet movement)	Type IIIa (restrictive leaflet movement in diastole)	Type I/Type IIIb (restrictive leaflet movement in systole)
Non-Ischemic	Endocarditis (perforation); degenerative (annular calcification); congenital (cleft leaflet)	Degenerative (billowing/flail leaflets); endocarditis (ruptured chordae); traumatic (ruptured Chord/PM); rheumatic (acute RF)	Rheumatic (chronic RF); iatrogenic (radiation/drug); inflammatory (lupus/anticardiolipin, eosinophilic endocardial disease, endomyocardial fibrosis)	Cardiomyopathy; myocarditis; left-ventricular; dysfunction (any cause)
Ischemic	**Organic**	Ruptured PM		Functional ischemia
				
MR- Mitral regurgitation, PM- Papillary muscle, RF- Rheumatic fever				

Figure 4. Carpentier classification. PM indicates papillary muscle; and RF, regurgitant fraction (Quoted from Fuster et al., 2017).

IV- Trancatheter mitral valve repair

Catheter-based mitral interventions target mitral valve pathologies ranging from leaflet dysfunction (prolapse and rupture) to annulus dilation to subvalvular problems (ventricular dilation, ruptured chordae, or papillary muscles). Mitral valve replacement focuses on all these pathologies. Alternatively, repair options focus only on an individual pathology.

The field of transcatheter MV therapy is quickly evolving, and the clinical need for safe and effective devices is still largely unmet. Currently, 13 different transcatheter MV devices are used in humans (CE Mark and/or FDA approved, CE Mark trial

and/or FDA pivotal trial, first-in-human studies), of which five devices have CE Mark and/or FDA approval for routine clinical use in patients who are at prohibitive risk for surgery (Figure 5 and Table 1). These devices are the MitraClip, Cardioband, PASCAL, NeoChord and Carillon. Of these, the clinical evidence and experience are most extensive for the MitraClip and the NeoChord systems. All approved devices should be used in patients with high operative risk or inoperable status (Figure 5).

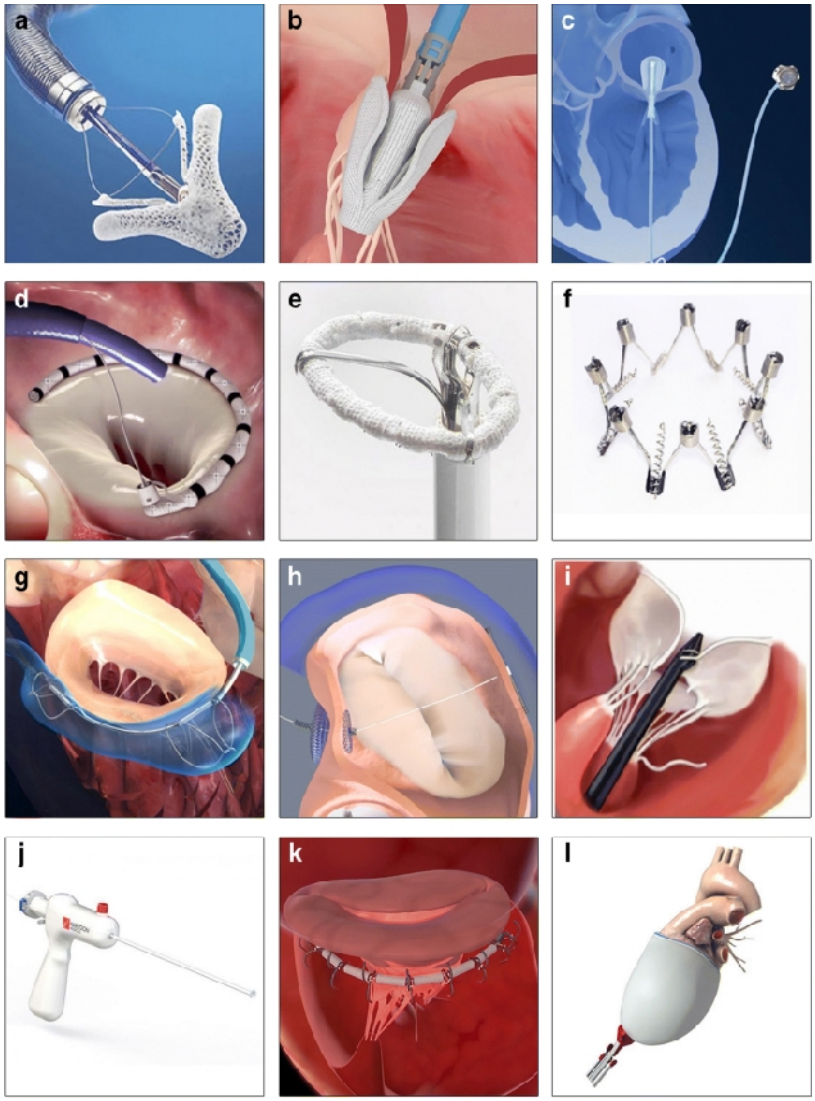


Figure 5 :In-human used transcatheter mitral valve repair devices. a MitraClip. b PASCAL. c Mitra-Spacer. d Cardioband. e Amed. f IRIS. g Carillon. h ARTO. i NeoChord. j Harpoon. k AccuCinch. l VenTouch (Quoted from Noack et al., 2020).

Based on the need for less invasive treatment options and the history of success of transcatheter aortic valve replacement, several transcatheter MV repair techniques have been developed over the past decade to treat MR. These techniques can be categorized as coaptation devices, annuloplasty devices, chordal replacement devices and LV remodelling devices (Figure 6) (Noack et al., 2020).

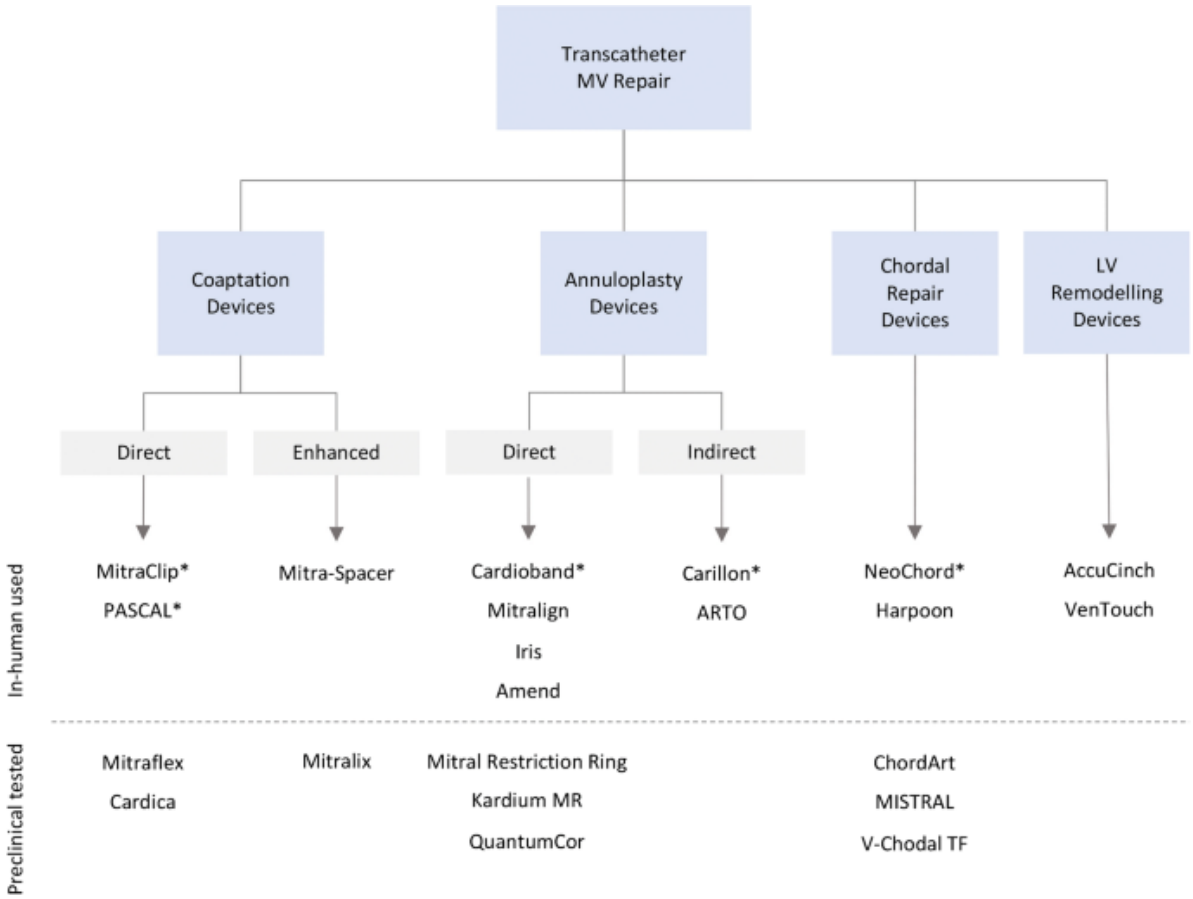


Figure 6: Classification of transcatheter mitral valve repair devices according to their anatomic target and mechanism. Status of development is given. LV, left ventricle; MV, mitral valve. "*" means CE Mark and/or FDA approval. (Quoted from Noack et al., 2020).

A summary with key characteristics of each transcatheter MV repair device is given in Table 1.

Table 1 Overview of in-human used and investigated transcatheter mitral valve repair devices

Device type	Device name	Description	Status
Coaptation devices			
Direct	MitraClip (Abbott Vascular)	• Transvenous, transseptal approach (24 Fr) • Based on Alfieri edge-to-edge technique • V-shaped clip • 3rd-generation device available in two sizes: XTR and NTR • Indication in patients with severe MR and prohibitive risk for MV surgery	• CE Mark approval gained • FDA approval
	PASCAL Mitral Repair System (Edwards Lifesciences)	• Transvenous, transseptal approach (22 Fr) • Based on Alfieri edge-to-edge technique • Two paddles, one spacer, two clasps • Indication in patients with severe MR and prohibitive risk for MV surgery	• CE Mark approval gained • US pivotal trial under way
Enhanced	Mitra-Spacer (Cardiasolutions)	• Transapical approach (18 Fr) • Fluid-filled balloon positioned between the mitral leaflets to improve MV coaptation	• First-in-human study under way
Annuloplasty devices			
Direct	Cardioband (Edwards Lifesciences)	• Transvenous, transseptal approach (25 Fr) • Adjustable annuloplasty band, anchored by nitinol screws on the atrial side of posterior mitral annulus (from lateral to medial trigone) • Designed to reduce annulus size and MR • Indication in patients with severe, secondary MR and prohibitive risk for MV surgery	• CE Mark approval gained • US pivotal trial under way
	Mitralign (Mitralign, Inc.)	• Transfemoral, transventricular approach (14 Fr) • Plication of mitral annulus by two pledgets placed on ventricular side of mitral annulus	• CE Mark trial completed • US pivotal trial planned
	IRIS (Millipede Medical)	• Transvenous, transseptal approach • Complete, semirigid annuloplasty ring fixed by multiple anchor elements on atrial side of mitral annulus	• First-in-human study under way

Device type	Device name	Description	Status
	Amend (Valcare Medical)	• Transapical approach • Complete, semirigid, D-shaped annuloplasty ring fixed by 12 anchors on atrial side of mitral annulus	• First-in-human study under way
Indirect	Carillon (Cardiac Dimensions)	• Transjugular approach • Curvilinear segment with two self-expanding anchors placed in coronary sinus	• CE Mark approval gained • US pivotal trial under way
	ARTO (MVRX, Inc.)	• Transvenous approach • Suture with two anchors, one anchor placed in coronary sinus and one anchor on atrial septum	• First-in-human study under way
Chordal repair			
	NeoChord (NeoChord, Inc.)	• Transapical approach • PTFE suture is anchored on free edge of the mitral leaflet and LV apex • Indication in patients with leaflet prolapse	• CE Mark approval gained • FDA approved
	Harpoon (Edwards Lifesciences)	• Transapical approach (14 Fr) • Adjustable PTFE chord anchored by knot on mitral leaflet and LV apex • Indication in patients with leaflet prolapse	• CE Mark trial under way
LV remodelling			
	AccuCinch (Ancora Heart)	• Transfemoral, transventricular approach • Cable with series of nitinol anchors is placed subvalvularly below the MV • Tension on the cable reduces LV dimensions • Indication in patients with dilated LV and secondary MR	• First-in-human study under way
	VenTouch (Mardil Medical)	• Left-sided mini-thoracotomy • Bladder placed around RV and LV • Bladder reduces LV dimensions by inflation of specific localized LV pads • Indication in patients with dilated LV and secondary MR	• First-in-human study under way
	BACE (Phoenic Cardiac)	• Slim polyester belt loops and secured at the base of the heart	• Early feasibility

Device type	Device name	Description	Status
		• Inbuilt balloons are connected to subcutaneous ports • Inflation of the system leads to reduction of mitral annular size and secondary MR • Indication in patients with dilated LV and secondary MR	trial completed

CE, certification mark; FDA, Food and Drug Administration; Fr, French; LV, left ventricle; MR, mitral regurgitation; MV, mitral valve; PTFE, polytetrafluoroethylene; RV, right ventricle; US, United States (Quoted from Noack et al., 2020).

A-Coaptation devices

Coaptation devices can be categorized as direct or enhanced devices.

1-Direct coaptation devices

Direct coaptation devices are inspired by the Alfieri stitch, a surgical MV repair technique for anchoring the free edge of the mitral leaflet to the corresponding free edge of the facing leaflet (the edge-to-edge technique). The correction results in a double orifice that improves coaptation and reduces the regurgitant orifice area with reduction of MR. This surgical technique stimulated the development of the first clinically used transcatheter MV repair system, the MitraClip system (Abbott Vascular, Santa Clara, CA, USA). Currently, two types of devices are routinely used, the MitraClip system and the PASCAL mitral repair system (Edwards Lifesciences, Irvine CA, USA) (Maisano et al., 2011).

a-**MitraClip®**

The MitraClip system is the most frequently implanted and best-investigated transcatheter MV repair system worldwide. It consists of a polyester-covered cobalt-chromium V-shaped clip. Using a 24-Fr transvenous, transseptal system, one or more clips are used to approximate the anterior mitral leaflet with the

posterior mitral leaflet. Currently, the third generation of the MitraClip system is available in two sizes: the larger XT*R* and the normal NT*R*. The MitraClip device is safe, can be used in primary and secondary MR and can be performed with a high rate of procedural success (reduction of MR to ≤2+). The in-hospital mortality rate, reported mostly in high-risk patients, is 2 to 3%. The rate of technical success is about 90% (Sorajja et al., 2017).

The MitraClip system was evaluated initially in the EVEREST-I (Endovascular Valve Edge-to-Edge Repair Study) and EVEREST-II trials. The final 5-year results of the EVEREST-II trial showed that MitraClip treatment was safe but was less effective in reducing MR than surgical repair in surgical candidates, mainly those with primary MR. Advantages were observed in patients aged ≥70 years and those with secondary MR (Feldman et al., 2011).

The latest two randomized clinical trials, the COAPT (Clinical Outcome Assessment of the MitraClip Percutaneous Therapy) and MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) trials, compared the efficacy of MitraClip treatment with that of guideline-directed medical therapy (GDMT) in patients with functional MR. The COAPT trial found lower rates of hospitalization for heart failure and lower all-cause mortality at 24 months in the group treated with MitraClip than in the group treated with GDMT alone (Stone et al., 2018). The MITRA-FR trial found no significant differences between patients who underwent percutaneous MV repair with MitraClip in addition to receiving GDMT and those who received GDMT alone (Obadia et al., 2018). These controversial results stimulated a discussion about selection of patients for MitraClip therapy and the prognostic impact of LV dysfunction in patients with functional MR and heart failure. Both

studies differ in the following aspects, which could possible explain the main differences:

1.Study design and GDMT: COAPT includes only patients with maximally tolerated GDMT at baseline with few major changes during follow-up vs. HF medication in baseline with allowed variable adjustments during follow-up in the MITRA-FR group;

2. Effective regurgitation orifice area (EROA) and left ventricular end-diastolic volume (LVEDV): EROA was 41±15 mm^2 in COAPT vs. 31±10 mm^2 in MITRA-FR as well as LVEDV was 135±35 mL/m^2 in COAPT vs. 101±34 mL/m^2 in MITRA-FR;

3. Procedural success: MR≥3+ in COAPT vs. MITRA-FR at discharge 5% vs. 9% and at 12 months 5% vs. 17%, respectively.

So, EROA was higher and LVEDV was lower in COAPT in comparison with MITRA-FR. Patients in COAPT showed a higher procedural success as MITRA-FR. Besides these main differences between the baseline data and treatment of MR in both cohorts, the new conceptual framework of proportionate and disproportionate functional MR may explain further the differences between the results of the two randomized clinical trials, but further investigations are needed (Grayburn et al., 2011).

b-**PASCAL mitral repair system**

The PASCAL (PAddles Spacer Clasps ALfieri) implant consists of a 10-mm central spacer that is attached to the MV leaflets by two paddles and clasps. The paddles and clasps are wide and should allow load across the surface areas of the inserted leaflets; the convex curvature of the tips of the paddles aims to reduce tension on the MV leaflets. The clasps can be operated simultaneously or

independently, which allows an optional separate grasping of each mitral leaflet. One or more devices can be implanted using a 22-Fr transvenous, transseptal system. A multicentre, prospective, observational, first-in-human study demonstrated the feasibility of the PASCAL system with a high rate of technical success and reduction of MR. The 30-day mortality was 13% in this high-risk cohort (Praz et al., 2017).

Third and fourth edge-to-edge repair devices are undergoing preclinical testing: the Mitraflex system (TransCardiac Therapeutics, Atlanta, GA, USA) and the Cardica Mitral Repair system (AesDex, LLC, Palo Alto, CA, USA) (Figure 5).

2-Enhanced coaptation devices

Enhanced coaptation devices reduce MR by occupying space in the MV orifice and increasing native leaflet coaptation.

a-**Mitra-Spacer**

One device is the Mitra-Spacer (Cardiosolutions, Inc., West Bridgewater, MA, USA). The transapical implanted (18 Fr) Mitra-Spacer is a fluid-filled balloon that is positioned between the two mitral leaflets. The balloon is made of Elast-Eon (AorTech, Weybridge, Surrey, UK), a non-thrombotic polymer, and is apically anchored by a HeartPad (B. Braun, Melsungen, Germany). The balloon has a subcutaneous port for later adjustment by fluid retrieval or filling. During the first-in-human implantation, the Mitra-Spacer was successfully technically implanted, and MR was reduced to moderate. Despite anticoagulation, thrombi developed around the device, and the valve was replaced at 8 months (Silaschi et al., 2017).

B-Annuloplasty devices

Transcatheter annuloplasty devices imitate surgical annuloplasty by ring or band. The annuloplasty device should reduce the size of the dilated mitral annulus to normal or prevent annular enlargement. Transcatheter annuloplasty devices can be categorized as direct and indirect devices. The most extensive clinical experience is with the Cardioband (Edwards Lifesciences, Irvine, CA, USA) and Carillon (Cardiac Dimensions, Kirkland, WA, USA) systems (Noack et al., 2020).

1-*Direct annuloplasty devices*

Direct percutaneous annuloplasty devices use anchors or sutures to implant the device on the atrial or ventricular side of the mitral annulus. The devices reduce the size of the mitral annulus, improving mitral coaptation and reducing MR.

a-**Cardioband mitral system**

The Cardioband mitral system is a direct annuloplasty system for the treatment of secondary MR. It is delivered via a transvenous, transseptal approach. The Cardioband is an open adjustable Dacron band, anchored by 6-mm-long multiple nitinol screws from the lateral to the medial trigone. After implantation, the Cardioband is cinched to reduce annular dimensions and MR (Noack et al., 2020).

In a feasibility trial in 31 patients with functional MR, transcatheter mitral annuloplasty with Cardioband was effective in reducing MR and was associated with improvement in heart failure symptoms and demonstrated a favourable safety profile. The anteroposterior diameter was reduced by >30% from 3.7±0.5 cm at baseline to 2.5±0.4 cm after 1 month and 2.4±0.4 cm after 6 months. The residual MR grade was ≤2 in 86.3% of patients at 6-month follow-up (Maisano et al., 2016). In a single-arm, prospective multicentre trial in 60 symptomatic patients, the rates of functional, technical device and procedural success, based on Mitral Valve Academic Research Consortium (MVARC) criteria, were 97%, 72% and

68%, respectively. At 1 year, the rates of overall survival, survival free of readmission for heart failure and survival free of reintervention were 87%, 66% and 78%, respectively. There were one stroke, two coronary artery complications, one tamponade and 10 anchor disengagements (all but one in the first half of the population), resulting in device inefficacy in five patients and leading to device modification halfway through the study to mitigate this issue (Messika-Zeitoun et al., 2019).

b-**Mitralign**

The Mitralign system (Mitralign, Tewksbury, MA, USA) is a percutaneous 14-Fr transfemoral, transventricular annuloplasty system. A pair of pledgets are plicated and locked on the ventricular side of the mitral annulus to reduce annular dilatation and MR. The feasibility and safety of the system were demonstrated in a first-in-human study. Echocardiographic analysis at 6 months showed MR reduction in 50% of treated patients (Nickenig et al., 2016).

c-**IRIS transcatheter annuloplasty ring**

The IRIS annuloplasty system (Millipede Medical, Santa Rosa, CA, USA) is a semirigid complete adjustable ring with a nitinol frame, which is placed on the atrial side of the mitral annulus by multiple anchor elements. The system is placed via a transvenous, transseptal approach. The first-in-human implantation was announced in May 2017 (Rogers et al., 2018).

d-**Amend™**

The Amend system (Valcare Medical, Herzliya Pituah, Israel) is a complete, semirigid, D-shaped mitral annuloplasty ring. The annuloplasty ring is fixed by 12 anchors on the atrial side of the mitral annulus via a transapical approach. First-in-human implantation was reported (Gerosa et al., 2016).

Several other transcatheter direct annuloplasty devices are under preclinical testing: Mitrals Restriction Ring (Cardiac Implant Solutions, Jacksonville, FL, USA), Kardium MR (Kardium, Burnaby, BC, Canada) and QuantumCor (QuantumCor, Lake Forest, CA, USA).

2-*Indirect annuloplasty devices*

Indirect annuloplasty devices are placed by sutures or anchors on the left atrium or coronary sinus in close proximity to the mitral annulus.

a-**Carillon® mitral contour system**

The Carillon mitral contour system (Cardiac Dimensions, Kirkland, WA, USA) consists of two self-expanding nitinol anchors connected by a nitinol curvilinear segment. The system is delivered transjugularly in the coronary sinus and indirectly reduces the annular dimensions. A feasibility trial in patients with secondary MR showed safety with significant reduction of MR from the EROA from 0.23±0.07 cm^2 to 0.12±0.08 cm^2 at 1-year follow-up. Comparison of treated patients with a pseudocontrol consisting of patients without implants showed improvement of functional and performance status in the treated group (Lipiecki et al., 2016). Randomized clinical trials comparing the Carillon system with sham procedure or GDMT are under way. Despite the clinical improvement in patients treated by Carillon, the system has several limitations: the efficiency of the system depends on the anatomy of the coronary sinus and mitral annulus. Further, there is

a risk of coronary obstruction that may preclude patient eligibility (Noack et al., 2020).

b-**ARTO™ system**

The ARTO system (MVRX, San Mateo, CA, USA) consists of a suture connected to two anchors. During the transvenous procedure, one anchor is placed in the interatrial septum and the second anchor is placed in the coronary sinus. Tension on the suture reduces the annular anteroposterior diameter, resulting in improvement of coaptation and reduction of MR. The first-in-human Mitral Valve Repair Clinical (MAVERIC) trial in 11 patients with symptomatic heart failure and secondary MR demonstrated safety and meaningful efficacy (Rogers et al., 2015).

C-Chordal replacement devices

Chordal replacement devices should restore coaptation and MV function by artificial chordal replacement and are mainly used in patients with primary MR. The largest experience is with the NeoChord device (NeoChord, St. Louis Park, MN, USA).

1-NeoChord DS1000

The NeoChord DS1000 is an echo-guided, transapical, catheter-based device for implantation of adjustable polytetrafluoroethylene (PTFE) sutures for treatment of primary MR. The PTFE suture is fixed on the free edge of the mitral leaflet and is adjusted in real time under echocardiographic control. After adjustment of the length of the PTFE suture, the suture is fixed at the apex of the LV by pledgets. Multiple implantation of PTFE sutures in addition to leaflet pathology is possible (Noack et al., 2020).

The safety and feasibility of the NeoChord DS1000 were demonstrated in the Transapical Artificial Chordae Tendinae (TACT) feasibility trial. The efficacy and durability depended on the complexity of MV leaflet morphology. Patients with a wide P2 and/or P3 prolapse were identified as most suitable (94%) for the composite end point (mortality, MR recurrence, mitral surgery, rehospitalisation and stroke at 1 year). Bileaflet or commissural pathologies decreased the rates of success and durability to 82% and 63% (for the composite end point at 1 year), respectively. Successful implantation of the NeoChord leads to improvement of clinical status with good mid-term durability (Kiefer et al., 2018).

2-Harpoon TSD-5

The Harpoon TSD-5 device (Edwards Lifesciences, Irvine, CA, USA) is a 14-Fr, echo-guided, transapical chordal replacement device, which allows the implantation of multiple and adjustable PTFE chordae. The mitral leaflet is anchored by a preformed knot (instead of free-edge leaflet fixation with NeoChord), which should improve long-term durability. Safety and feasibility were demonstrated in the initial feasibility trial in 30 patients with severe degenerative MR. At 1 month, MR was mild or less in 89% of patients and moderate in 11% of patients. At 6 months, MR was mild or less in 85% of patients, moderate in 8% of patients and severe in 8% of patients (Gammie et al., 2018).

3-ChordArt™

The ChordArt device (Coremedic GmbH, Tuebingen, Germany) uses an antegrade transvenous, transseptal approach for implantation of premeasured artificial chordae. The distal parts of the chordae are fixed by an anchor directly to the papillary muscle. The device is in preclinical validation, and a first-in-human trial

is planned for 2019. The ChordArt system overcomes the limitations of the transapical devices (e.g. bleeding) (Noack et al., 2020).

The technical success, efficacy and durability of transcatheter chordal replacement devices clearly depend on patient selection, which remains the critical point of this technique. Based on the experience with surgical MV repair in patients with primary MR, it is questionable whether the durability of this technique is comparable with that of surgical MV repair in the absence of ring or band annuloplasty. One possible solution for the future could be a combination of transcatheter chordal replacement and annuloplasty devices in patients with MV prolapse (Taramasso et al., 2018).

D-LV remodelling devices

LV remodelling devices address the reduction of LV dimension in the presence of secondary MR caused by ischemic or non-ischaemic cardiomyopathy. These devices should reduce the distance from the LV wall and papillary muscle to the mitral annulus and leaflets, which should improve MV competence.

1-AccuCinch®

The AccuCinch system (Ancora Heart, Santa Clara, CA, USA) consists of a cable with a series of nitinol anchors that are implanted subvalvularly on the ventricular side of the MV, using a transfemoral, retroaortic approach. The tension on the cable results in a ventriculoplasty, leading to MR reduction. The AccuCinch system is under investigation in early first-in-human studies (Gooley et al., 2015).

2-VenTouch™

The VenTouch system (Mardil Medical, Minneapolis, MN, USA) consists of a bladder that is placed via a left-sided mini-thoracotomy around the left and right ventricles. The inflation of specific LV pads should reduce LV and mitral annular dimensions, resulting in improvement of mitral leaflet coaptation (Sorajja et al., 2017). A first-in-human study has been initiated.

3-BACE

The BACE (Basal Annuloplasty of the Cardia Externally) device (Phoenix Cardiac Devices, Cary, NC, USA) is implanted by means of slim polyester belt loops, and secured at the base of the heart. This device can be adjusted remotely under echocardiographic guidance, by inflating the inbuilt balloons that are connected to subcutaneous ports. The inflation of balloons by saline leads to a reduction of dilated mitral annulus and LV dilatation with subsequent reduction of MR. An early feasibility trial in 11 patients demonstrates the safety of a beating-heart reduction of secondary MR and sustained benefit in preventing HF progression (Padmanabhan et al., 2017).

Decision-making and device selection should be performed by a multidisciplinary heart valve team according to current guidelines and recommendations. Shared decision-making for the selection of transcatheter MV therapy should performed by a multidisciplinary heart valve team with interventionalists, mitral surgeons, imaging experts, anaesthesiologists, valve experts and a nurse care team. Aetiology and severity, symptoms, LV function, associated conditions (e.g. atrial fibrillation, coronary artery disease), comorbidities, risk assessment and functional status should be evaluated before the heart valve team selects a patient for transcatheter MV repair therapy or enrolment in a clinical trial. For device selection, the feasibility of transcatheter MV repair devices in patient-specific pathoanatomical

characteristics of the MV complex should be proven. Because of the great anatomic variability of MR, interventionalists will likely need to develop interventional expertise with more than one transcatheter MV repair device and with advanced imaging techniques such as two-dimensional/three-dimensional echocardiography, computed tomography (CT)–based planning, fluoroscopy and imaging fusion techniques (Testa et al., 2016).

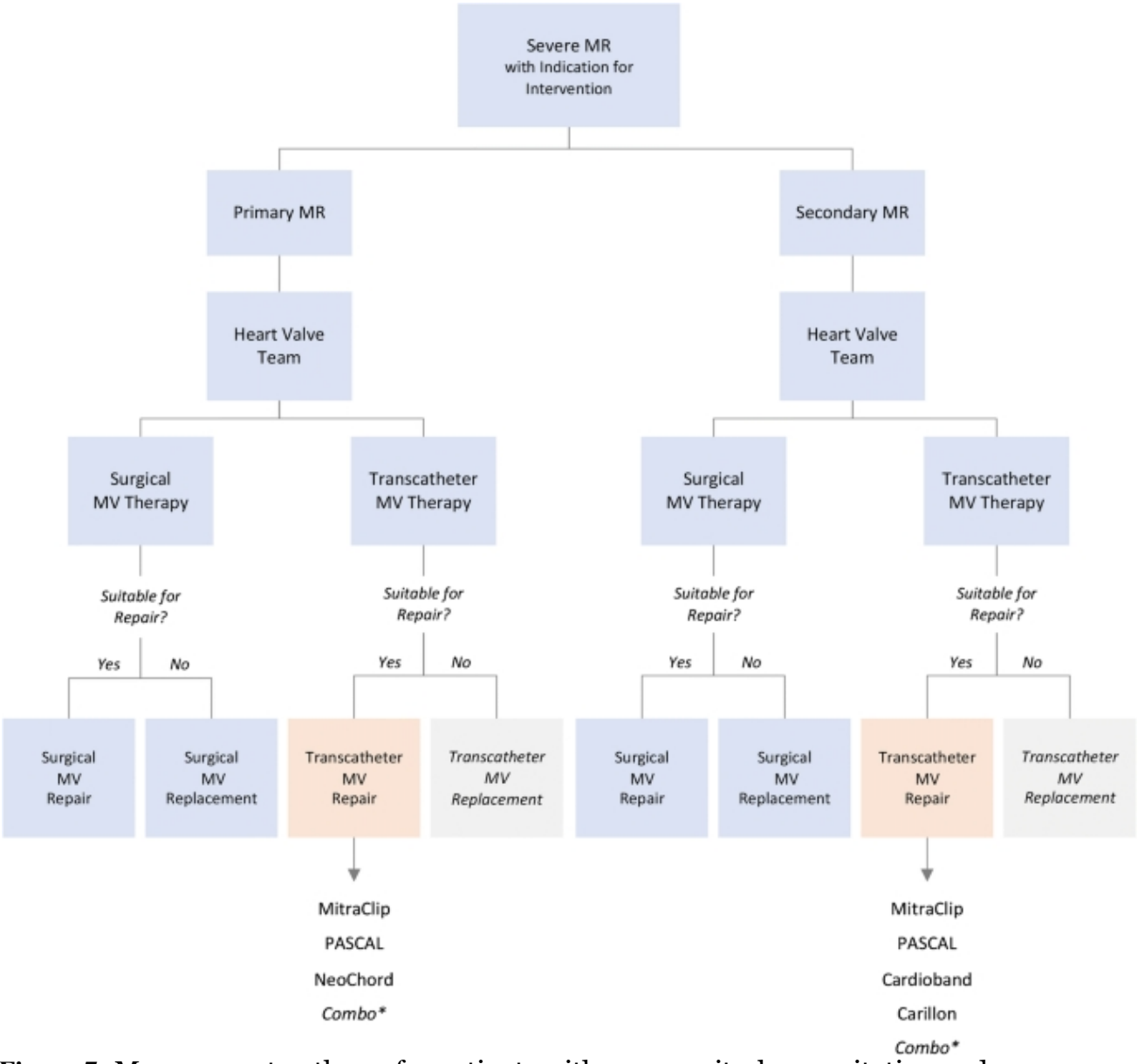


Figure 7: Management pathway for patients with severe mitral regurgitation and indication for intervention. Only transcatheter mitral valve (MV) devices with CE Mark and/or FDA approval are given. MR, mitral regurgitation. "*" means combination of two different CE Mark and/or FDA approved transcatheter mitral valve repair devices (Quoted from Noack et al., 2020).

V-Transcatheter mitral valve replacement

Transcatheter mitral valve replacement (TMVR) may propose benefits over MV repair devices. Due to the complex structure of the MV creating a MV repair device that is tailored to all anatomical disparities can present several issues. This is where TMVR devices pose the opportunity to create a 'one valve fits all' ideal, with more predictable MR reduction, and less technically demanding procedures. Though, TMVR procedures pose a greater risk of injury as complications can become more catastrophic and less forgiving. MV repair devices allow for a greater safety profile, as there is less change to the native valve anatomy and physiology. Further development of TMVR systems needs to be done (Goode et al., 2020).

A-Design Challenges & Criteria

When comparing the TMVR intervention to the transcatheter aortic valve replacement (TAVR) intervention, there are substantially more design challenges that need to be addressed. These challenges are what has hampered the development of TMVR, as the complexity has proved to be cumbersome. In addition to challenges, certain design criteria are ideal for successful implantation. After thorough studies into the physiological and anatomical components of the mitral valve, along with studying designs in clinical and preclinical stages, we can outline a criterion for the transcatheter MV design. The specific criteria chosen for the designs are as follows:

- *The design must be able to be crimped*. For the catheter-based insertion, it is crucial to have a design that can conform to a low profile to aid in the ease of insertion for the surgeons. The lower the profile, the more ideal.

- *The design must have an anchoring system*. The development of an anchoring system that can withstand the dynamic pressures felt within the heart during systolic and diastolic pressures is important. The valve must stay in place after final placement, without any migration, for optimal performance.
- *The design must not have Left Ventricular Outflow Tract (LVOT) obstruction*. Minimizing obstruction and allowing for the maximum amount of blood flow through the left ventricular outflow tract is vital for the patients' health.
- *Reduction of stagnation flow*. Optimizing proper blood flow washout to prevent stagnation flow and resulting thrombosis (blood clot) initiation is imperative to design success.
- *Maximize mitral annulus sealing*. Improved sealing around the mitral annulus from proper conformation prevents leakage and resultant turbulent blood flow which can cause thrombosis initiation.
- *Maximize mitral orifice shape*. Closely matching the natural MV orifice shape will allow for optimal valve performance like a healthy native MV.
- *Made for established TMVR surgical approaches* The design should be made to utilize surgical methods and approaches that are familiar to the surgeons performing the transcatheter procedures.
- *Readjustment during intervention*. A design that can be fully retracted and readjusted during procedure will aid the surgeons and allow for the ideal placement of the valve.

Designing these TMVR prosthetic devices with these certain aspects in mind will lead to designs with high technical implantation success along with superior performance (Goode et al., 2020).

1-Valve Fixation and Sealing

Valve fixation techniques cannot exclusively rely on radial forces similar to TAVR due to the usual absence of calcification and a shorter annular region, so more advanced anchoring techniques must be utilized. A variety of different anchoring techniques have been proposed: using tethers to achieve counteracting axial forces; native leaflet grasping to fixate the prosthesis in place; docking systems to allow radial forces sufficient enough for fixation; atrial and ventricular flanges to grasp the MV annulus and leaflets; atrial cages that use the full anatomy of the left atrium to prevent valve migration; subannular hooks that pierce the native MV tissue; cork-like effects that produces radial forces to aid in the anchoring of the prosthesis; and partial replacement devices that affix to the MV annulus. Some studies suggest that supra-annular fixation with an apical tether shows promising results when compared to sub-valvular fixation techniques. The MV is subjected to high pressures (~ 120 mmHg) during the systolic phase when the valve is closed, so late migration of the TMVR device is of concern. Additionally, the dynamic motion over the cardiac cycle should be considered as a newly protruding anterior MV leaflet due to the implanted TMVR device may create LVOT obstruction, or device dislodgement if the system utilizes leaflet capturing, under the high systolic pressures (Flynn et al., 2018). Examples of TMVR anchoring mechanisms can be seen in Figure 8.

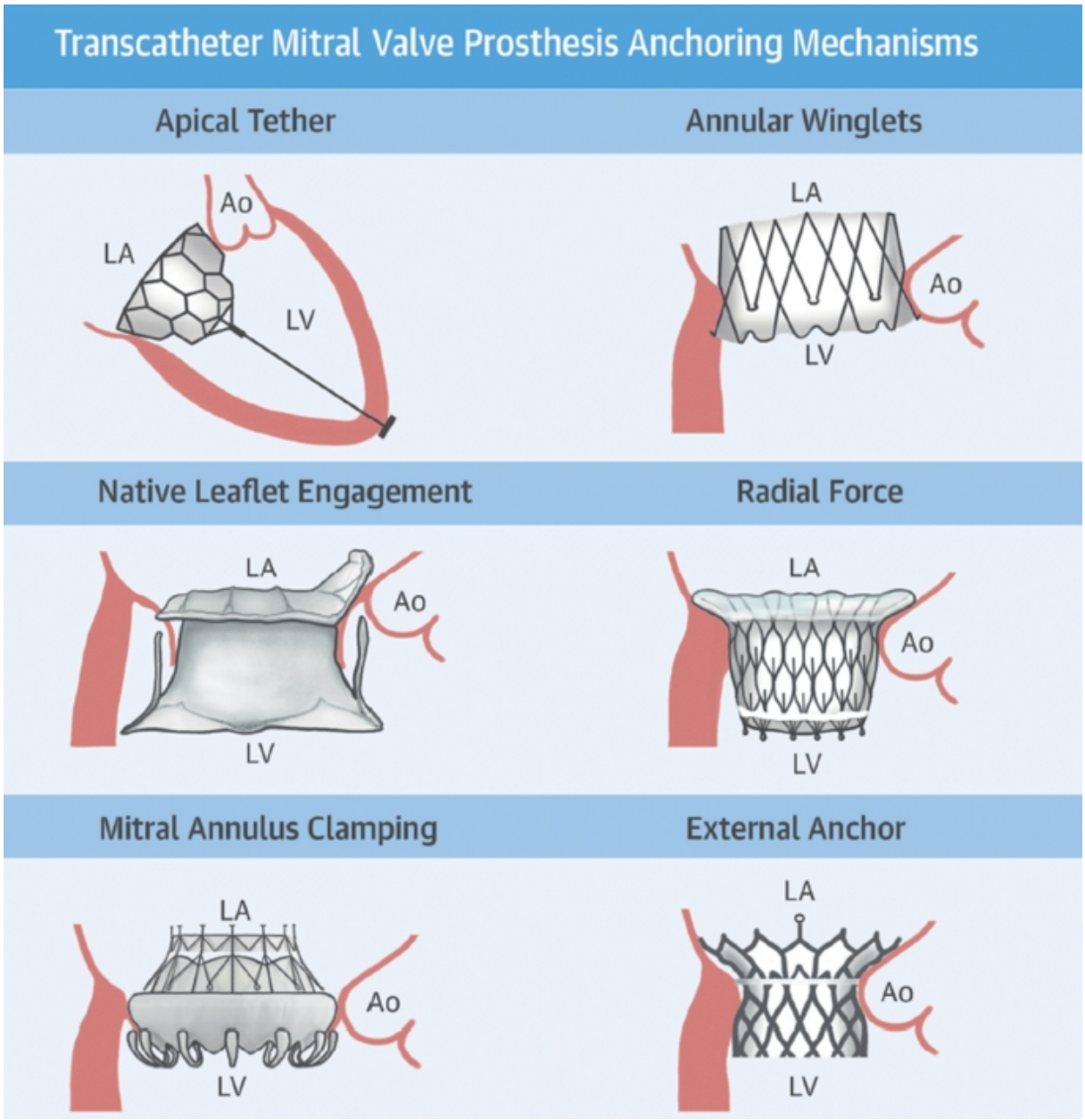


Figure 8 : Examples of transcatheter mitral valve prosthesis anchoring mechanisms (Quoted from Goode et al., 2020).

When compared to TAVR, which implants to a hardened stenotic AV that is a tubular shape providing radial reaction forces that are sufficient to seat the prosthesis into place, TMVR devices are implanted to treat MR, needing the designs to be seated to a noncalcified construct that is both dynamic and D-shaped

in one plane and saddle-shaped overall. On top of proper anchoring, TMVR devices need to conform to the native MV annulus to apply proper sealing required to prevent leakage through the interface of the valve stent and the native annulus, also known as paravalvular leakage (PVL). It has been seen that D-shaped TMVR stents have produced better PVL results than circular shaped TMVR stents, as expected. Though better sealing with a circular TMVR stent is plausible when the stent is oversized for the MV annulus, as the discrepancy between oversized D-shaped stents compared to circular stents is far less than the discrepancy between stents that are not oversized (Pierce et al., 2019).

There should be careful consideration when it comes to the oversizing of TMVR stents, as other potential challenges may become more apparent. Additionally, to achieve oversizing of TMVR stents, circular stents create larger septal-lateral forces and smaller inter-commissural forces when compared to the D-shaped stent. As for D-shaped stents, studies show that they expand more along a possibly less compliant inter-commissural axis than circular stents, and less along a possibly more compliant septal-lateral axis. Furthermore, radial expansion forces are significantly less uniform for D-shaped stents than circular stents. TMVR devices that generate sealing from contact between native tissue and a straight tubular section, radial force is not the primary determinant of sealing. D-shaped stents sealing stems from its ability to better reach commissural features of the MV annulus, which supports the concept of the use of fabric casing the whole region of potential stent-leaflet contact (Goode et al., 2020). Stents that expand and conform to the MV annulus seem to be more effective than stents that have circumferentially uniform forces against the MV annulus, though further studies should be conducted to validate this concept(Goode et al., 2020).

2-Left Ventricular Outflow Tract Obstruction

LVOT is the region of the left ventricle between the anterior cusp and the ventricular septum that blood passes through to enter the aorta through the aortic valve. There have been cases of a decrease in LVOT following surgical implantation of annuloplasty rings and prostheses, and reports of LVOT obstruction following surgical mechanical MV replacement. With the larger prosthetic size of the TMVR, in addition to being anatomically close to the LVOT, LVOT obstruction is a large design hurdle to overcome (Grayburn et al., 2019). To produce a TMVR prosthesis that does not encroach upon the LVOT, many factors need to be taken into consideration: The TMVR device protrusion into the left ventricle, and subsequently projection into the LVOT; the prosthesis flaring created from the anchoring method may extend into the LVOT; the angle between the aortic and mitral valve annular planes, also denoted as the aortomitral annular angle, will determine if the prosthesis extends into the LVOT; septal bulging can create narrowing of the LVOT, especially when a TMVR prosthesis juts from the other side creating a bottleneck effect. When compared to the native LVOT, the new altered LVOT can be greatly reduced in size. This newly altered LVOT can be described as a “neo-LVOT” (Blanke et al., 2017). The listed factors are illustrated and can be seen in Figure 9.

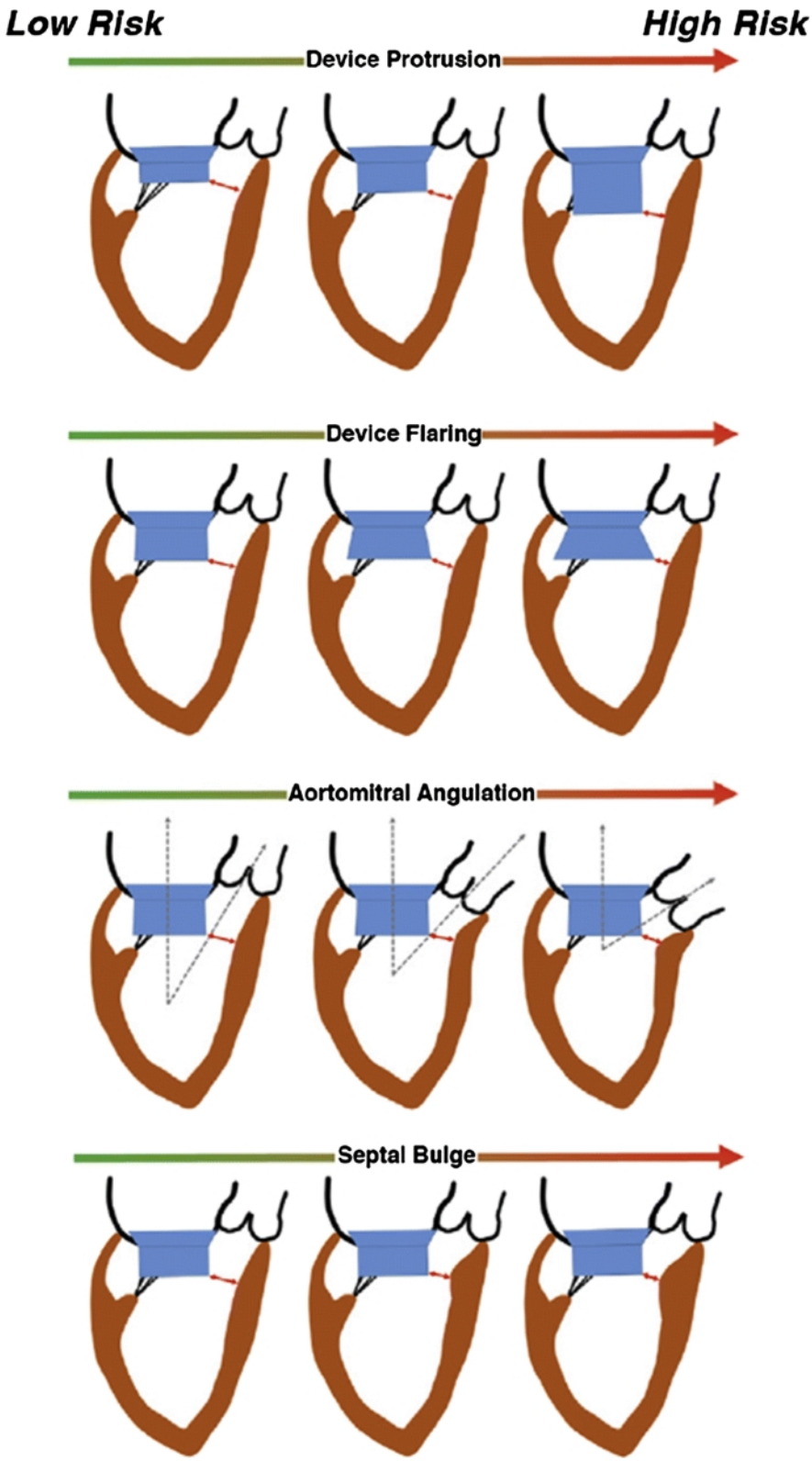


Figure 9 : Anatomical and device related factors that result in the narrowing of the neo-LVOT dimension which develop low to high risk of LVOT obstruction (Blanke et al., 2017).

When predicting the neo-LVOT on pre-procedural time-resolved computed tomography (CT) with the risk factors, observational registries suggest a simulated neo-LVOT area of under 170 to 190 mm^2 predicts a high risk of LVOT obstruction. These factors can be described as fixed obstruction as the anterior MV leaflet is pushed towards the interventricular septum, or the septum bulging towards the anterior MV leaflet. The neo-LVOT can also be subjected to a dynamic obstruction, as the anterior MV leaflet can be drawn towards the interventricular septum during systole from generated Bernoulli forces (Khan et al., 2019). A long anterior MV leaflet with redundant chordae is a risk factor, while additionally, a long anterior MV leaflet may prolapse back into the TMVR valve, obstructing the valve from properly closing and initiating acute valve failure. LVOT obstruction is identified as an LVOT gradient of ≥ 30 mmHg and can be deemed a severe obstruction if the pressure gradient is greater than 50 mmHg. The LVOT gradient can be determined by taking the variance between peak systolic left ventricle pressure and the peak central aortic pressure (Alharbi et al., 2017). The emergence of the intentional laceration of the anterior MV leaflet to prevent LVOT obstruction (LAMPOON) technique has proved to be a feasible means of increasing neo-LVOT, decreasing LVOT gradients and preventing LVOT obstruction. Furthermore, utilizing the LAMPOON technique for TMVR procedures has proven to be a sufficient means of preventing LVOT obstruction. TMVR designs should consider the possible neo-LVOT area created due to the implanted prosthesis, along with utilizing the LAMPOON technique to further increase the neo-LVOT area and decrease LVOT gradients (Krishnan et al., 2006).

3-Delivery Method

TAVR procedures have the option to utilize a transfemoral approach that provides a minimally invasive method that would be ideal to use for TMVR procedures, but due to the location of the MV, exclusively transaortic implantation is difficult. TMVR designs are currently restricted to four approaches: a transapical approach, which is a puncture through the apex of the heart giving access to the left ventricle, and a direct shot to the MV; a transseptal approach, which is a puncture through the atrial septum and is most often accessed *via* a transfemoral approach to the right atrium; a transatrial approach, also known as a left atriotomy, which is a puncture through the left atrium to give access to the MV; a transaortic approach, where a minimally invasive surgical incision into the aorta is made to insert the device. Current TMVR delivery approaches are illustrated in Figure 10. The transapical approach has been an alternate for TAVR procedures due to the short distance of travel along with good alignment with the implantation location. However, there have been reports of suboptimal results with the transapical access for TAVR implantation when compared to the transfemoral approach, which can be related to the harmful effects of a thoracotomy in high-risk patients, and to a greater degree of myocardial injury (Gillespie et al., 2013).

Though, in the early stage development of TAVR larger bores were used, along with a learning curve to conduct the TAVR surgery. Additionally, first generation TAVR devices were larger in size, making them unsuitable for transfemoral insertion, leaving the transapical approach as the only means of insertion. These components may have led to suboptimal performances. Early TMVR designs have utilized the transapical approach, but next-generation devices have had a push towards employing the transseptal approach to avoid similar issues with myocardial injury and the harmful effects of a thoracotomy on high-risk patients.

Careful design modifications will must be considered to employ the transseptal approach, due to the increased travel length, and a higher amount of turns (Goode et al., 2020).

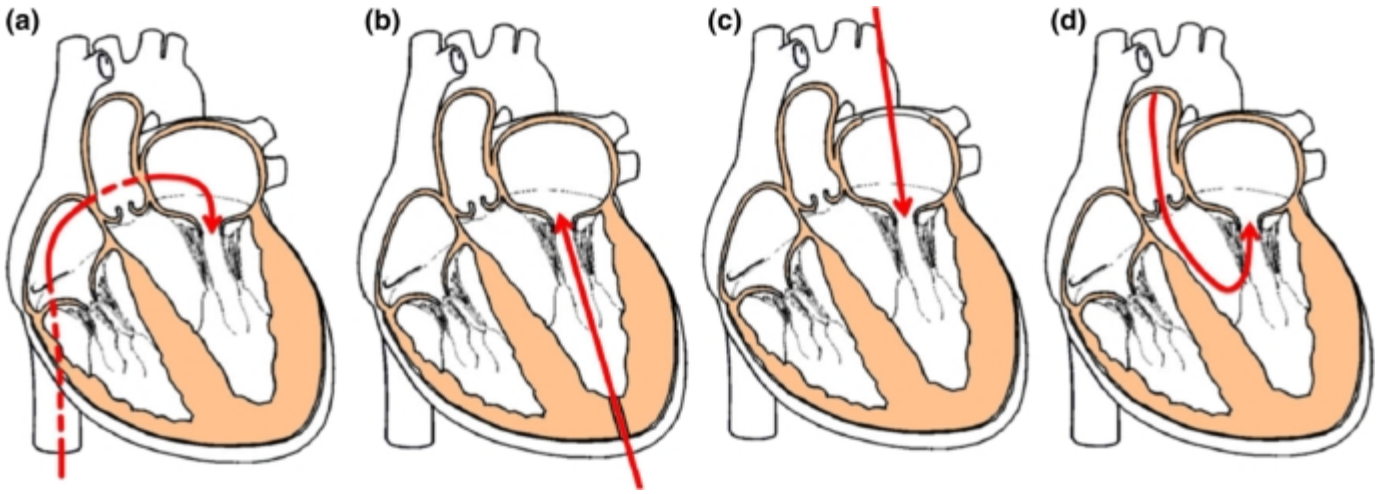


Figure 10: Transcatheter mitral valve delivery methods: (a) transseptal, (b) transapical, (c) left atriotomy, and (d) transaortic (Quoted from Goode et al., 2020).

4-Hemodynamics

TMVR devices are employed to operate during both systole and diastole. Furthermore, an aspect to consider is for the TMVR devices to create the largest effective orifice area (EOA) possible during diastole to refrain from mitral stenosis initiation. Additionally, a mitral pressure gradient ≥ 5 mmHg is deemed to be a characteristic of mitral stenosis (Jolobe, 2016).

Thrombosis (blood clot) initiation in TMVR devices is also of concern, as there have been reports and cancellation of trials due to thrombosis presence. In the vicinity of prosthetic valves where blood flow maintains a very slow velocity in a relatively small circulation zone, the possibility for blood to clot increases. One of the main reasons for clot formation is an intensified exposure time of red blood cells to large variants in shear stresses, even if shear stress values are not

significant. It has been evidenced that pulsation in blood flow is substantial in the regulation of stagnation areas and also blood clot formation (De Backer et al., 2014). Moreover, blood clotting is proven to be triggered from both jet-like velocity where turbulent shear stresses are high, i.e., Reynolds number being high, as well as stagnation regions. Factors that are known to be overriding in the triggering of blood clot formation are listed in Table 2.

Table 2 Blood clot factors.

Factor	Triggering criteria for blood clots
Cavitation	Water hammer and squeeze flow
Cardiac output	Slow movement of leaflets (A low cardiac output will cause a reduction in the movement of the leaflet. This will promote the potential for the formation of blood clots by reducing the washout and dilution of the activated platelets)
Stagnant flow	If occurring adjacent to prosthetic valves, can promote the deposition of damaged blood elements, leading to thrombus formation on the prosthesis
Vortex shedding	Yields repeated vortex pairing within the wake, which is responsible for the formation of larger platelet aggregates
Recirculation	Allows many platelets to be trapped
Pressure drop	A larger pressure drop means that the heart with the MHV prosthesis has to work harder,72 thereby reducing cardiac output. In fact, heart must maintain the cardiac output and does not lower it in order to keep the output up to the required level and thus is strained harder

(Goode et al., 2020).

The procedure of blood clotting starts with activated platelets aggregating to an injured blood element. The level of platelet activation and red blood cell lysis are considerably linked to the level and length of the applied shear stress, also known as the residual time (Goode et al., 2020).

In particular, TMVR clots form between the native leaflet and the valve due to blood stagnation or lack of wash out. It is well known that a certain amount of shear stress or wall shear stresses must be provided in the vicinity of prosthetic heart valve to avoid blood stagnation or blood clot formation which could happen behind the leaflets in TMVR or around the hinges in mechanical heart valve prostheses. Regarding TMVR, the vortex created in the left ventricle during the diastolic phase can be translated into a kinetic energy resource for assisting propulsion and redistribution of blood flow in the systolic phase. In fact, diastolic dysfunction resulting from the design of prosthetic devices may be characterized by breakdown of the vortex with amplified dissipation of the stored energy which may take away the positive effects of vortex formation. In other words, the shape and mechanical design of prosthetic devices for the mitral position plays an important role and may cause non-physiological hemodynamics within the valve and/or in the left ventricle which is not desirable (Goode et al., 2020).

5-Prosthetic Valve Leaflet Degeneration

A factor when it comes to TMVR development is the focus on the valve tissue composition. Conventional surgical and transcatheter bioprosthetic valves utilize animal tissues such as bovine or porcine pericardium, treated by glutaraldehyde. Durability data for TMVR valves do not exist currently, but there are certain factors that need to be taken into consideration when contemplating the possibility of valve leaflet degeneration. The first being that surgical bioprosthetic valves for the mitral position have a higher chance of suffering early structural valve degeneration when compared to surgical bioprosthetic for the aortic position. Secondly, surgical bioprosthetic valves have a higher rate of failure in younger patients than that in elderly patients (Pierce et al., 2019). Though TMVR for younger patients is of less concern for now, as the technology develops, more

thought needs to be put into place towards valve durability for patients with long life expectancies. New insights on durability and structural valve deterioration learned from TAVR and surgical bioprosthetic valves will be beneficial for TMVR device development due to the use of the same materials. Surgical bioprosthetic valves are shown to have good durability towards the 10-year follow-up mark with a greater increase of incidence thereafter, while TAVR devices have shown good durability towards the 5-year follow-up with limited data at the 10-year follow-up. There needs to be careful monitoring of patients undergoing TMVR over the next several years, to collect consistent valve durability data to provide developers more insight on the longevity of their devices (Goode et al., 2020).

6-Readjustment & Re-Capturability

Going forward with the design of the TMVR devices, the ability to design a device that can be readjusted during implantation can plausibly improve the technical success of the procedure. Due to the multiple recorded events of early death in patients due to TMVR malposition and failed deployments, the ability to readjust and recapture the device after it has been implanted and had post-implantation performance tests conducted can prove to be a valuable asset. Despite these challenges and restrictions, many TMVR systems have been designed and have had positive first-in-human implantations and are currently in further clinical assessments, while other designs are in research stages (Fröhlich et al., 2015).

B-Clinical Evaluation in trials

FORTIS (Edwards Lifesciences, Irvine, USA)

The Edwards FORTIS (Figure 11A) is composed of a circular cloth-covered (to promote endothelization) self-expanding nitinol frame, with a trileaflet bovine

pericardial valve. The non-recapturable frame includes an atrial flange and two opposing paddles that fold out at the base and capture the native mitral leaflets to the frame (anatomical anchoring system). During the deployment, surgeons align the paddles to the A2 and P2 sections of the MV leaflets under transesophageal echocardiography (TEE) direction. Once the paddles are discharged, they secure the native mitral leaflets for valve attachment (Goode et al., 2020).

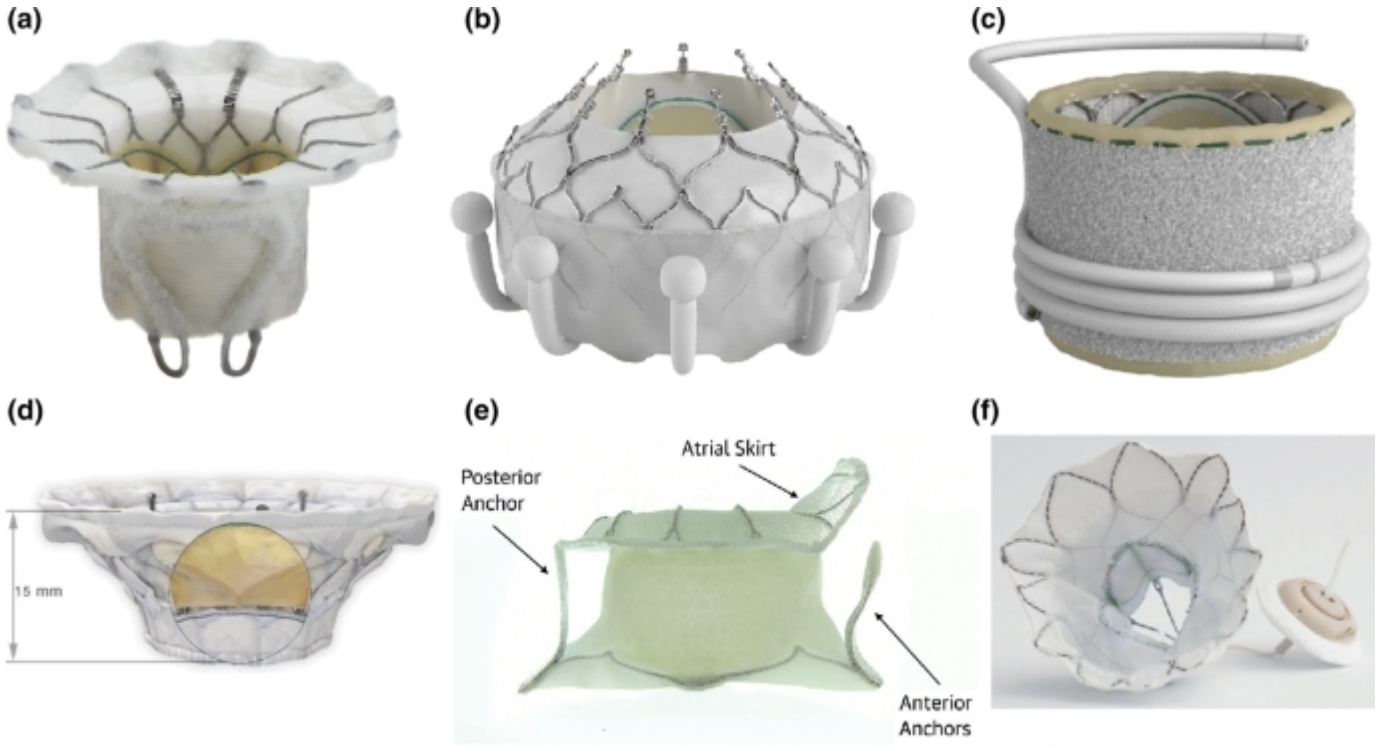


Figure 11A : TMVR systems in clinical evaluation (a) FORTIS. (b) EVOQUE TMVR System. (c) Sapien M3 System. (d) Cardiovalve TMVR System. (e) Tiara TMVR System.(f) Tendyne Mitral Valve System (Goode et al., 2020).

The first-in-human implant of the FORTIS device was performed in 2014 by Bapat's team from London, UK, and had excellent technical and initial clinical outcomes. Overall, there were 13 cases of very high-risk patients performed on with an implant success of 10/13 (76.9%), though the all-cause 30-day mortality

was reported to be 5/13 (38.5%). Due to reports of valve thrombosis, the clinical trial was stopped at the end of 2015 ((Goode et al., 2020).

This system has a good novel anchoring system but the leaflet capturing techniques may have led to thrombosis initiation from created stagnation flow areas. Additionally, the circular stent design does not conform to the natural MV annulus. Certain components of the valve could be utilized for future designs, but with reports of valve thrombosis, certain issues need to be evaluated before any further iterations of this system are created (Bapat et al., 2014).

1-CardiAQ-Edwards TMVR System (Edwards Lifesciences, Irvine, USA)

This first generation of the CardiAQ-Edwards TMVR system had the first success in terms of implantation of a TMVR apparatus in a clinical setting. Søndergaard *et al.* delivered the valve transseptally in 2012. The CardiAQ-Edwards TMVR system is a non-recapturable, self-expanding, foreshortening nitinol frame, trileaflet bovine pericardial valve, with two sets of circumference-oriented anchors; one on the ventricular side and one and the atrial side. The ventricular anchors sit behind the valve leaflets and sub-valvular device, using the leaflets for support while also conserving the chords. The principal body of the prosthesis is located in the left atrium, denoted as a supra-annular position, allowing for minimal LVOT obstruction. The circular/symmetric design requires no rotation to conform to the natural mitral annulus. Additionally, the frame is enclosed in a polyester fabric skirt which aids in the reduction of paraprosthetic leakage. A second generation of the CardiAQ-Edwards TMVR system was developed with improved delivery for the transapical approach, and good technical success in implantation in 2015 (Sondergaard et al., 2015).

Early clinical trials (RELIEF) results showed a technical success of 12/13 (92.3%) and all-cause 30-day mortality of 7/13 (53.8%). Though the RELIEF trial began in 2016, it was put on hold in early 2017 to reevaluate the device design. Enrollment was reinitiated in 2018 with transseptal access being the sole delivery mode (Sodhi and Zajarias, 2018).

This system is one of the more prominent valves in the industry. The design offers effective anchoring through its MV annulus clamping technique but poses a possibility of LVOT obstruction with its large ventricle profile. Furthermore, the device utilizes a circular stent design and does not conform to the MV annulus. This may reduce the device's PVL performance, though proper oversizing of the device may allow for sufficient results. The move to sole transseptal delivery should improve clinical results (Goode et al., 2020).

2-EVOQUE TMVR System (Edwards Lifesciences, Irvine, USA)

In December 2018, Bernard J. Zovighian unveiled a second-generation valve, named the EVOQUE TMVR system (Figure 11A). This valve utilizes designs from the FORTIS system and the CardiAQ-Edwards TMVR system, with a similar aesthetic look to the CardiAQ-Edwards TMVR system. The EVOQUE TMVR system has a unique anchoring mechanism that preserves the native MV anatomy while also utilizing the MV annulus, leaflets, and chords. The system provides a low profile for both the atrial and ventricular sides to aid in the reduction of procedural complications. The system comes in a 44 mm size or a 48 mm size that is compatible with a single size delivery system and features an intra-annular sealing skirt and frame that allows for the minimization of PVL. The transseptal delivery system has a low profile of 28 Fr, that the Edwards team believes may reduce the need for septal closure (Hansson et al., 2016).

Early feasibility studies of the EVOQUE TMVR system are currently recruiting and estimated study completion date of December 2024. It is believed that Edwards Lifesciences is going forward with its focus on the EVOQUE TMVR system and the SAPIEN M3 system.

As the EVOQUE TMVR system is a combination of two prominent TMVR designs, the best components of each system were funneled into this valve. The system, similar to the CardiAQ-Edwards valve, using MV annulus clamping as its anchoring technique and has a large LV profile which again poses a threat to cause LVOT obstruction. Additionally, the circular stent design can also impede PVL performance. It'll be interesting seeing how the clinical trial goes with this new design (Goode et al., 2020).

3-SAPIEN M3 System (Edwards Lifesciences, Irvine, USA)

The Edwards SAPIEN M3 system (Figure 11A) is an adaptation of the SAPIEN 3 system that is utilized for the aortic position. The valve includes a shape memory nitinol stent with a trileaflet bovine pericardial valve, much like the SAPIEN 3 system. The SAPIEN M3 valve has an addition of a polyethylene terephthalate (PET) skirt to minimize paravalvular leakage, and the SAPIEN M3 system has an additional shape memory nitinol dock which encloses the native mitral leaflets to anchor and seals the valve into place (Goode et al., 2020).

In March 2018 and June of 2019, John Webb, MD, presented the early feasibility results at both the Cardiovascular Research Technologies (CRT) 2018 Conference and the 2019 TVT Structural Heart Summit, which included 10 patients. All patients were hemodynamically stable throughout the procedure, all had the device successfully implanted, and none had LVOT obstruction (Webb et al.,

2019). Additionally, there was no mortality observed at 30 days. Raj Makkar, MD, at the Transcatheter Cardiovascular Technologies (TCT) 2018 scientific symposium in September 2018, showcased the SAPIEN M3 system and displayed results from 15 patients. He showcased the system having high technical success (13/15, 86.7%), 14/15 (93.3%) reduction in MR to 0 or 1 + and no death, LVOT obstruction and hemolysis. Edwards Lifesciences plans to continue the early feasibility study with a plan to initiate a U.S. pivotal trial in late 2019 (Webb et al., 2019).

The early feasibility results for the SAPIEN M3 system is very promising, proving that alterations to TAVR devices with an addition of a docking system are a feasible means of TMVR. As the anatomical structure of the MV is far more complex than the AV, adding a docking system may not be enough to overcome the TMVR design hurdles. The design solely uses radial forces, which it will be interesting to see how repeated cyclic systolic forces applied to the closed valve will affect the implantation position. As the design has a docking system, the circular stent seems to be sufficient when it comes to PVL performance. The docking system does have the possibility of impeding on the LVOT. Above all, this is a system to watch closely, especially with its promising early feasibility results (Goode et al., 2020).

4-Cardiovalve TMVR system (Cardiovalve Ltd., Or Yehuda, Israel)

The Cardiovalve TMVR system (Figure 11A) is a trileaflet valve that includes two frames; an atrial frame and a ventricular frame. The valve is fixed into the mitral annulus by employing over 24 central “sandwiching” sites, utilizing a symmetrical design that foregoes the need for rotational alignment (Regueiro et al., 2017).

The valve has a crimped height of 32 mm and the deployed valve protrudes approximately 12 mm into the left ventricle. The system is implanted using a transfemoral/transseptal approach and comes in three different size variations ranging from 40 to 50 mm. The valve is deployed using a three-step procedure; first is grasping the mitral valve leaflets which is followed by the atrial flange delivery, and finally a full release of the valve to seat it into place. The first five in-human cases of implantation had perfect technical success (5/5, 100%) along with no LVOT obstruction, and no mitral regurgitation. The first 30 days after implantation had a mortality of 3/5 due to access site bleeding, retroperitoneal bleeding, and deep vein thrombosis (Maisano et al., 2015).

The Cardiovalve TMVR system offers a low-profile device to avoid LVOT obstruction, along with no need for rotational alignment. This circular approach may prove to have greater complications with sealing, as it doesn't conform to the natural MV annulus. The sandwich anchoring system allows for the low-profile and may prove to be a suitable means of fixating the valve into place. Both the European and USA early feasibility trials should be monitored closely, to evaluate the technical success of the device, along with patient selection (Goode et al., 2020).

5-Tiara TMVR System (Neovasc Inc., BC, Canada)

The Tiara TMVR system (Figure 11A) is a D-shaped device, consisting of three bovine pericardial leaflets with a self-expanding nitinol frame. On the ventricular side, the valve boasts three anchors (2 anterior and 1 posterior). The ventricular anchors are fit to secure the valve against the fibrous trigone anteriorly and posterior shelf of the MV annulus (Cheung et al., 2014). On the atrial side, the valve has an atrial skirt that helps fix the valve into the atrial segment of the mitral

annulus. The valve comes in two sizes: the 35 mm valve has internal diameter dimensions of 30 and 35 mm (area: 6.3 cm^2 to 9.0 cm^2), and the 40 mm valve has internal diameter dimensions of 34.2 and 40 mm (area: 9.0 to 12.0 cm^2), implying that the valve has a tapered shape with minimum and maximum diameters and cross sectional areas. The Tiara TMVR system is delivered through a transapical approach (Regueiro et al., 2017).

The first-in-human implantation of the Tiara TMVR system was reported in early 2014. The early feasibility trial named TIARA I (started in December 2014) and additional cases, totaling 33 cases, were performed with a 90% implant success and an early mortality rate of 12%. A multicenter international feasibility trial named TIARA II is now ongoing and recruiting with a target of 115 patients and an estimated study completion date of January 2025(Coffey et al., 2016).

One of the intriguing design elements of the Tiara TMVR system is that it takes on a D-shape, to aid the device in conforming to the natural MV annulus. For sealing purposes, this may be the most optimal approach to prevent PVL. The device has effective ventricular anchors, with right positioning, but may have issues with protruding into the LVOT. Furthermore, the device is only designed for the transapical approach, which increases the chances of surgical complications. The development of this device to be able to be delivered *via* the transseptal approach would be of great value to this system. The TIARA II trial will be a suitable test and provide good data on if the system is good enough for commercial applications (Goode et al., 2020).

6-Tendyne Mitral Valve System (Abbott Laboratories, Illinois, USA)

The Tendyne mitral valve system (Figure 11A) utilizes a 30Fr transapical delivery casing for their self-expanding double frame device and adjustable tether with a trileaflet porcine pericardial valve. The outer stent is D-shaped to conform to the natural mitral annulus while the inner stent is a circular shape. The outer stent can come in a variety of sizes, while the interior stent is a singular size to preserve an EOA of greater than 3.2 cm^2 (Regueiro et al., 2017).

The system has an atrial cuff to aid in anchoring and prevent the valve from entering the ventricle when the tether is under tension, along with providing sealing to prevent paravalvular leaking during diastole. The left ventricular apical tether system has an apical pad that affixes the apparatus to the apex of the heart and helps promote apical closure (Goode et al., 2020).

With the success of the first-in-man implantation of the Tendyne mitral valve system in February 2013 and October of 2014, an initial feasibility study between November 2014 and November 2017 was performed on 100 patients, and reported with a technical success of 96 (96%), 30 day all-cause mortality of 6, and 1 year all-cause mortality of 26. Due to the success of the global feasibility study, a U.S. approval (SUMMIT) trial was approved with a target of 1010 patients and began recruiting in June of 2018, with an estimated primary completion date of June 2022, and an estimated study completion date of June 2026. The SUMMIT trial is currently being redesigned to address the control arm for functional MR and to include mitral annular calcification. The mitral annular calcification feasibility study began in October 2018 with a goal of 30 patients at 10 sites. The first implantation occurred in November of 2018 (Sorajja et al., 2019).

The tethering system utilized for the Tendyne MV system is quite novel, and though the device is only delivered *via* the transapical approach, the apical pad allows for a reduction of surgical issues and aids in the sealing of the access puncture. Additionally, this system utilizes a D-shaped stent to conform to the natural MV annulus, which should prevent PVL. The device does limit itself to patient selection with only having the transapical approach as an option, but due to the design of the device, there aren't other delivery options available. Furthermore, the tethers may contribute to hemodynamic and flow changes within the LV. Though, one component that this device has over its competitors is the fact that it can be fully retrieved even after surgery, as the tether aids in grasping the device and removing it at a later date if necessary. This system is one of the furthest along regarding clinical trials and will be interesting to watch how the SUMMIT trial will go, especially with the addition of mitral annular calcification for implantation options (Goode et al., 2020).

7-INTREPID TMVR System (Medtronic, Minnesota, USA)

The INTREPID TMVR system (Figure 11B) was first named the TWELVE TMVR system from Twelve Inc. until Medtronic purchased the company and renamed the valve. The system employs a dual nitinol self-expanding stent design, which contains an individual annular fixation structure with a suspended circular valve stent. The system includes a 27 mm trileaflet bovine pericardial valve in the circular stent, and the outer stent which is fixated to the sub-annular apparatus by means of cleats comes in three sizes (43, 46, and 50 mm). Due to the system being circular with no paddles or anchors, the valve does not need to be oriented to the natural mitral valve annulus. The outer stent also includes a flexible atrial brim to facilitate visualization under echocardiography. The valve takes on a 'champagne cork-like' configuration (narrow neck and wider body) to oppose valve migration

during high systolic pressures. The design is meant to preserve and leverage the native leaflets along with the chordae to seal around the device. The device is delivered transapically and new design iterations have made the system to be recapturable up to the point of final release. The system length was increased for larger patients to enhance ease of use and changed the sheath aesthetics and hub design to improve hemostasis and usability (Loger et al., 2018).

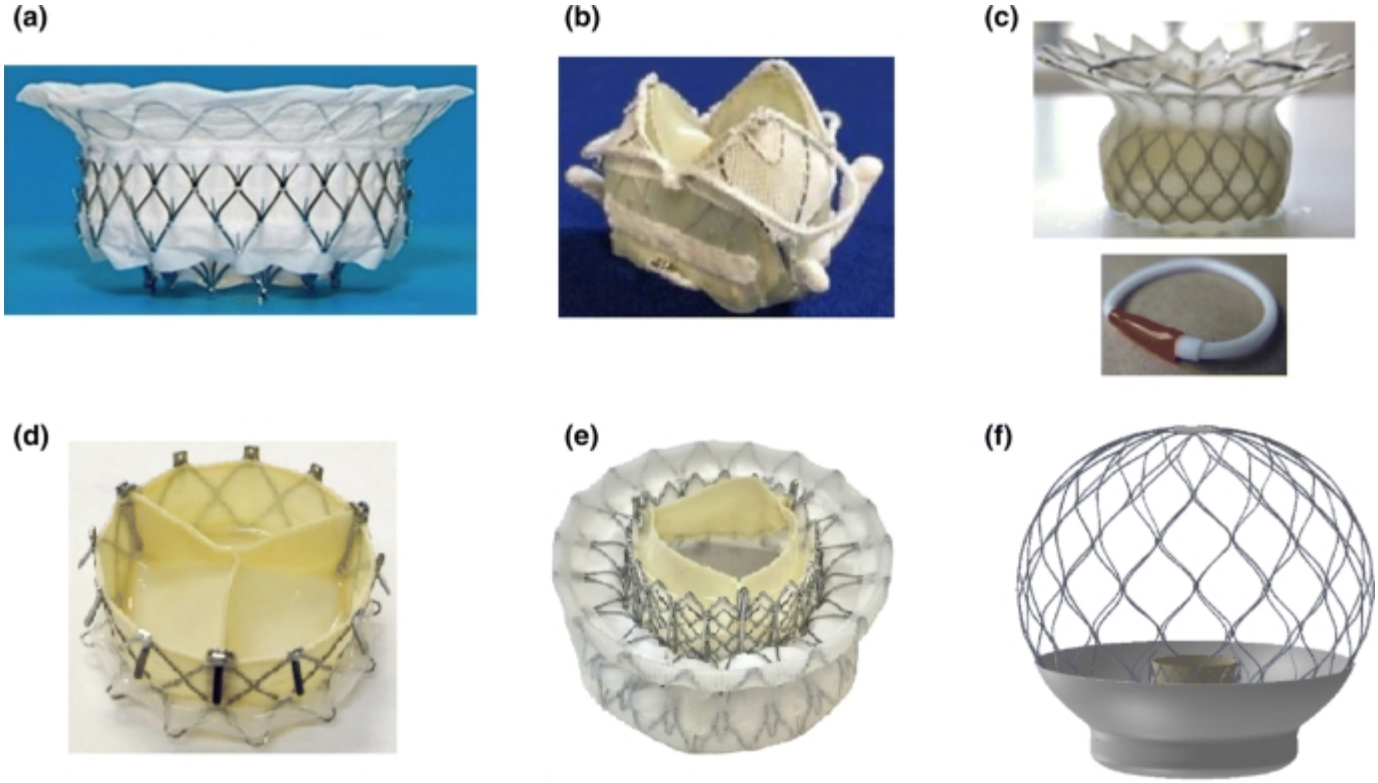


Figure 11B : TMVR systems in clinical evaluation. (a) Intrepid TMVR System. (b) Caisson TMVR System. (c) HighLife TMVR System. (D) NAVI System. (e) Cephea TMVR System. (f) AltaValve TMVR System (Quoted from Goode et al., 2020).

Bapat *et al*.(2018) outlined the early experience with the INTREPID TMVR system describing the first 50 patient's implantation along with 30-day follow-ups. One patient did not undergo implantation due to apical site bleeding complications, while 48 of the other 49 had successful implantations resulting in a reduction of MR to mild or none at all. 7 deaths occurred within the first 30-days; 3 deaths

related to apical site bleeding at or immediately after the initial implantation, 1 due to malposition of the valve, and 3 others due to refractory heart failure early after the procedure (< 30 days). There were 4 additional patients that died between days 54 and 122, but there were no deaths after 4 months. The secondary clinical trial, the APOLLO trial, is currently recruiting with an enrollment goal of 1380 patients with an estimated primary completion date of October of 2021 and estimated study completion date of October of 2025.

The INTREPID TMVR system is another device that is far along regarding clinical trials. The device needs no rotational alignment and utilizes a combination of radial and axial forces to anchor the device into place. With the device being delivered transapically and seeing the early feasibility results, it is safe to say that redesigning the device for a transseptal approach would be of great value. Also, the device doesn't conform to the natural MV annulus, which puts it at risk of PVL (Goode et al., 2020).

8- Caisson TMVR system (LivaNova PLC, London, United Kingdom)

The Caisson TMVR system (Figure 11B) was originally created by Caisson Interventional, LLC, but was purchased by LivaNova PLC in 2017 to aid in LivaNova's entry into the TMVR space. The Caisson TMVR system consists of a two-stage deployment system; the anchor component and the valve. The anchor component is made of a self-expanding nitinol frame and is D-shaped to fit the mitral annulus. The anchor component has four ventricular sub-annular anchoring feet that provide axial fixation onto the mitral annulus, while the three atrial grasping components interact with the atrial surface of the MV annulus. Once the anchor component is deployed, the trileaflet pericardial tissue nitinol-based valve stent is positioned and deployed within. The valve stents additional anchors to

provide further fixation, minimizing PVL. The system is deployed using a transseptal approach and both the anchor and valve stent components are repositionable and fully recapturable. The Caisson TMVR system is an atrially-biased system to prevent LVOT obstruction and the 3-leaflet circular valve provides an EOA of greater than 3.0 cm^2 (Regueiro et al., 2017).

The Caisson TMVR early feasibility study (PRELUDE) began in June of 2016 and was completed in August of 2018. The study had 23 patients enrolled, with 18 patients getting the system implanted, 4 converting to surgery and 1 being retrieved. There were two deaths during the first 30 days post-surgery; one due to septicemia and the other due to drug-induced hypotension. Due to the success of the PRELUDE trial, the LivaNova team moved forward with its European approval trial (INTERLUDE), which is currently active, but not recruiting. A total of 30 patients have been enrolled in the INTERLUDE and PRELUDE studies showing encouraging results, with current work being done on improving the ease of use of the system. INTERLUDE has an estimated study completion date of August 2025. The protocol is currently being finalized for its US approval trial (ENSEMBLE) (Goode et al., 2020).

With the Caisson TMVR system being atrially-based, the possibility of LVOT obstructions is greatly reduced. Additionally, the D-shaped stent conforms better to the native MV annulus and should provide acceptable PVL performance. The ventricular anchoring feet may provide sufficient anchoring to the MV apparatus with good performance. The attributes that the device is repositionable and fully recapturable are intriguing and very beneficial for surgeons. The complexity of implantation is detrimental to the technical success of the device. As Liva Nova

looks to improve upon the ease of use of the system, this device is a device to watch (Goode et al., 2020).

9-HighLife TMVR system (HighLife Medical, Paris, France)

The HighLife TMVR system (Figure 11B) consists of two components; a sub-annular implant ring that acts as a docking system, and a prosthetic valve that sits inside the ring. The sub-annular implant consists of a polymer tube covered in a polyester graft with nitinol hooks for ring closure, to create a single definite ring length of 31 mm. This sub-annular implant is deployed using a transfemoral transaortic method, placing it around the prosthesis which hinders any displacement of the device into the left ventricle. The prosthetic valve consists of a 31 mm nitinol frame with a trileaflet bovine pericardial tissue valve and can be delivered *via* a transapical or transseptal approach. The valve is circular, allowing it to self-center and align, and includes a pre-formed indentation in the annular section to allow for the sub-annular implant to interact with the valve for satisfactory sealing and fixation. The native valve leaflets sit between the prosthetic valve and the sub-annular implant to minimize PVL. The device is non-recapturable once it is deployed (Barbanti et al., 2017).

The HighLife TMVR system study began in July of 2017 and is currently recruiting patients with a goal of 20 patients. In October of 2017, Dr. Nicolo Piazza outlined the first 11 patient implants. The results included 9 successful implantations, with one causing LVOT obstruction resulting in an in-hospital death. The two other patients were converted to surgery due to chordal entanglement, one ending in an in-hospital death, and the other having greater than 12 months follow up. The estimated study completion date is for December of

2023, with a new generation transseptal delivery system to undergo clinical study around quarters 2 and 3 of 2019 (Peruzz et al., 2019).

The HighLife TMVR system provides a surgically complex anchoring system that may be cumbersome for surgeons. Though the device is circular and does not conform to the native MV annulus, the sub-annular implant allows for satisfactory valvular sealing to prevent PVL. Additionally, the sub-annular implant provides effevtive anchoring for the system. LVOT obstruction will be a question with this design, as the device protrudes into the LV. The use of the LAMPOON technique may prove to be beneficial for this device (Goode et al., 2020).

10-NAVI System (NaviGate Cardiac Structures Inc., Lake Forest, USA)

The NAVI system (Figure 11B) is comprised of a circular self-expanding nitinol stent-frame that takes the shape of a truncated cone with a height of 21 mm. The system utilizes a trileaflet pericardial tissue valve, and the catheter implantation system has a diameter of 30 Fr at the distal end, and 18 Fr at the level of the catheter shaft. Implantation can be done *via* the transatrial, transapical and transseptal approaches. The system anchors using annular winglets to secure the valve to the mitral annulus (Regueiro et al., 2017).

The first-in-human implantation was done in October of 2015 using the transatrial approach, with a reduction to zero MR. The NaviGate team received approval to implant the NAVI system from the Krakow, Poland, Ethics Committee in July of 2016 and planned to perform a 30 patient transatrial feasibility study. No further information has been posted regarding the NAVI system, though the development of the NaviGate team's GATE system for the tricuspid valve position has been progressing with the first-in-human procedure done in April 2017, and with

excellent leaflet mobility and valve function at the one year mark. The NAVI system and the GATE system take on the same design features but are meant for their respected annulus locations (Naim et al., 2015).

The NAVI system utilizes annular winglets to anchor the device to the MV annulus and thus does not protrude into the LV which reduces chances of LVOT obstruction. The stent is circular and does not conform to the native MV annulus, which may cause PVL. It'll be interesting to see how the device handles the dynamic systolic pressures in the LV and how robust the annular winglets anchoring is. The movement to the tricuspid valve application may be due to the dynamic systolic pressures in the LV (Goode et al., 2020).

11-Cephea TMVR System (Cephea Valve Technologies, San Jose, California)

The Cephea TMVR system (Figure 11B) utilizes a self-expanding double disk assembly that seats the trileaflet bovine pericardial valve. The system boasts a low-profile frame structure to allow for minimal LVOT obstruction and sparing sub-valvular anatomy. The structure has a multilevel conformity design that isolates the leaflets from non-circular distortions, which allows for scaling of the valve sizes with a single valve core. The center column of the prosthesis creates leaflet support by providing a stable platform, to allow the valve to adapt to diverse anatomies. The prosthesis is delivered using an antegrade (transatrial or transseptal) approach and is seated with the atrial disc secured to the floor of the left atrium, while the ventricular disc is anchored to the sub-annular region (Regueiro et al.,2017) .

The first-in-human was set to begin in the first quarter of 2018. The early procedural experience with the Cephea TMVR system has shown favorable results,

allowing the strategy for the early feasibility study to be in development (Mohammadi et al., 2019).

Though the Cephea TMVR system does not conform to the natural MV annulus, the double disk design may prevent it from PVL. Additionally, the low-profile design will be beneficial in decreasing LVOT obstruction, though careful monitoring of the system will need to be conducted. The use of the LAMPOON technique may be beneficial for this device if LVOT obstruction occurs (Goode et al., 2020).

12-AltaValve TMVR system (4C Medical Technologies, Inc., Minnesota, USA)

The AltaValve (Figure 11B) has a spherical shaped nitinol stent design that encompasses the entire left atrium. The system applies a supra-annular and atrial anchoring mechanism to seat the device into place, which provides acceptable paravalvular sealing with the PET skirt that interacts with the native supra-annular apparatus. The stent comes in multiple sizes to fit the left atrium and is made to be compliant with the left atrium anatomy. The device is comprised of a 27 mm diameter trileaflet bovine pericardial tissue valve and is implanted using transseptal or transapical approaches by way of a 34 or 32 Fr catheter, respectively. Due to the exclusive supra-annular placement of the device and the minimized annular ring, there is total sub-annular preservation, leading to no LVOT obstruction and total preservation of the native MV (Goel et al., 2014).

Animal studies have produced remarkable results, with a total of 45 animals receiving implantations. The device has good endothelization along the stent, with

full attachment to the atrial roof, along with no evidence of thrombosis or damage to the sutures or valve tissue (Rodriguez-Gabella et al., 2017).

The first-in-human implantation was showcased at TCT 2018 and utilized the transapical approach with good technical success, and no postoperative complications. 7-month follow up showed great improvement for the patient, along with great improvements from the patients' baseline statistics. An AltaValve early feasibility study for up to 30 patients has been approved to begin in the second half of 2019 and will be performed in Canada, the United States, and in Japan (Goode et al., 2020).

The supra-annular and atrial anchoring that the AltaValve TMVR system employs is quite novel and could be the answer to LVOT obstruction. The sealing of the stent does come into question, as though the device is exclusively supra-annular, the interaction between the device and the MV annulus is important. Because the device is circular fit into the MV annulus, there may be PVL issues. Better conforming to the MV annulus could be a possible solution if PVL arises. Monitoring on the AltaValve will be interesting to see how the device interacts over the long term to the atrial wall of the LA. Even though the pressures felt in the LA are less than the LV, LA flow dynamics will also need to be monitored and evaluated (Goode et al., 2020).

C-Preclinical Evaluation

Preclinical evaluations include systems under preclinical animal studies, along with systems in research stages. Devices with plans of the first-in-human implantation with no updates are also included in this section.

1-AccuFit TMVR system (Sino Medical Sciences Technology Inc., Tianjin, China)

The AccuFit TMVR system (Figure 12A) is a self-expanding, circular, self-centering valve with a nitinol frame. The system comprises of an atrial flange and ventricular flange with annulus support. The ventricular flange has a maximum height of 14 mm, with an added covering on the ventricle commissural tips and an added protective suture layer on the left ventricle anchors. The annulus support has an annular clipping space that is between the atrial flange and a ring of anchors that extend radially. The valve is composed of three bovine pericardial leaflets in a tubular shape to avoid central leakage. The Sino Medical team attempted an initial design with reversed leaflets, but have since abandoned that design and gone with the conventional leaflet design. The valve is implanted with a 38-F caliber system *via* the transapical approach (Abdelghani et al., 2015).

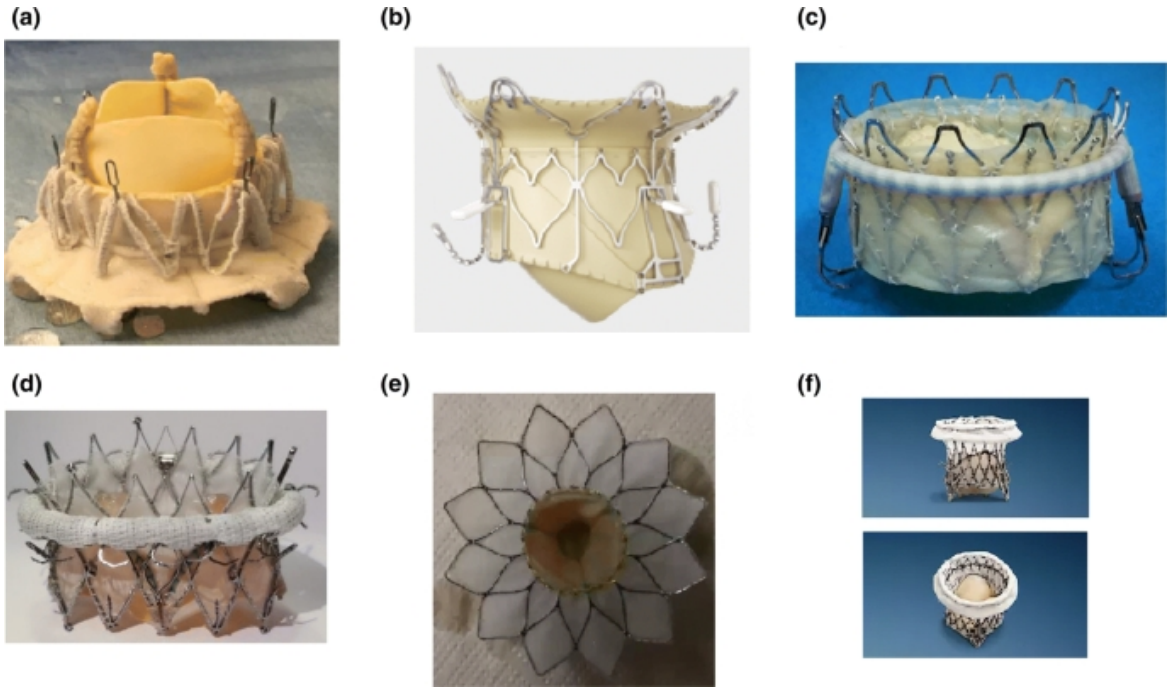


Figure 12A : TMVR systems in preclinical evaluation (a) AccuFit TMVR System. (b) Epygon TMVR System. (c) Saturn TMVR Technology. (d) Corona Mitral Valve Replacement System. (e) MValve System. (f) Permavalve TMVR System (Goode et al., 2020).

Preclinical animal (LYD cross-breed Yorkshire swine) studies were done on 87 acute and 32 sub-chronic and chronic animals. For 30 sub-chronic and chronic implantations, the success rate was 80% with a procedure range from 7 to 15 min. PVL occurred in 7 cases, with greater than mild PVL in one case, along with LVOT obstruction in a single case. Out of 23 pathological studies, 21 cases (91%) resulted in non-traumatic anchorage with complete sealing and 9 cases (39%) of injury to chordae (Goode et al., 2020).

2-Epygon TMVR system (Affluent Medical SA, Paris, France)

The EPYGON TMVR system (Figure 12A) consists of a monoleaflet pericardial tissue that is combined with a D-shaped annular ring. The asymmetric stent shape allows for a minimization of LVOT obstruction due to the protrusion towards the aortic valve, along with a reduction in interference with the left ventricle wall. The D-shaped monoleaflet is designed to cope with the left ventricle shape providing optimal fitting to the valve stent and having a large coaptation surface against the prosthetic posterior wall. The system is anchored by way of an atrial flange that seats the valve into position, and the left ventricle engagement arms that maintain traction over the papillary muscles to prevent any left ventricle sphericity. The anchors capture and block the anterior leaflet, allowing for no LVOT obstruction. The system is implanted using the transapical approach and is designed to create similar flow dynamics than that of the native MV, creating a rotary flow (vortex) that minimizes energy loss and propels blood toward the LVOT (Goode et al., 2020).

Preclinical trials performed on 14 sheep models assessed the flow dynamics within the left ventricle and showcased that vortex properties were unchanged, other than the intensity that decreased. Technical success for the preclinical trials was greater than 90%, and the system produced excellent hemodynamics with no prosthetic migration, no LVOT obstruction, no left ventricle to aorta pressure gradients, and no intra or paravalvular thrombosis initiation. The implant also had low atrio-ventricular gradients (1-2 mmHg) while only having traces of PVL (Goode et al., 2020).

3-Saturn TMVR Technology (InnovHeart SRL, Milan, Italy)

The Saturn technology (Figure 12A) consists of an annular structure that encircles the MV to aid in both the anchoring sealing of the prosthetic valve. The device is implanted using a three-step procedure that includes insertion of the annular structure by way of guidewires for the first two steps, then the connection to the self-expanding central valve body. The annular structure also prevents LVOT obstruction by holding the native MV leaflets in place, along with the low profile of the prosthesis. The central valve body utilizes a trileaflet pericardial tissue valve, and InnovHeart states that the system provides surgical-like anchoring to the annulus (Goode et al., 2020).

Good laboratory practice *in vivo* preclinical trial was started in the first quarter of 2018 for the transapical approach, while the transseptal approach is still under development. To date, no trial results have been released.

4-Corona Mitral Valve Replacement System – (ValCare Medical, Tel Aviv, Israel)

The Corona Mitral Valve Replacement System (Figure 12A) is a complementary approach that utilizes the AMEND percutaneous annuloplasty ring developed by

ValCare Medical. The AMEND ring is a closed ring that takes on a D-shape, is semi-rigid, and provides roughly 15-25% septal-lateral reduction. The AMEND ring is used to offer a solid landing zone for the Corona valve. The Corona valve is a dedicated D-shaped self-expanding stent-based valve with a 4-pericardial-leaflet concept. The bioprosthesis can be crimped to a small profile (21 Fr) and boasts a short stature (27 mm) which provides minimal protrusion into both the left atrium and left ventricle, and thus targeted to produce little to no LVOT obstruction. The system can be implanted using both the transseptal and transapical approaches while preserving the native valve geometry. Due to the Corona valve being fitted to the AMEND ring, the combined systems allow for minimal PVL. The Corona valve is meant to be implanted either utilizing a one-stage approach, meaning the AMEND ring and Corona valve are implanted in a single procedure with two steps or a two-stage approach that uses the AMEND ring to reduce MR with the Corona valve being implanted at a later date if there is a late occurrence of MR (Goode et al., 2020).

The AMEND ring has shown good initial clinical experience on a total of 16 cases utilizing the transapical approach. The transseptal approach is undergoing final validation, with plans of being in clinical use later in 2019. The Corona valve is currently undergoing chronic preclinical trials, with no results posted to date(Goode et al., 2020).

5-MValve System (MValve Technologies Ltd., Herzliya, Israel)

The first generation of the MValve system is a docking system for the mitral position, to allow other transcatheter prostheses to be implanted and anchored. The system allows for a true chordal-sparing as it preserves the native leaflets' function and is inserted using a transapical approach. The system is designed to be

accordant to several commercially available transcatheter valves. The device is able to be recaptured along with being fully retrieved after full deployment(Goode et al., 2020).

The first-in-human implantation of the MValve system was performed in September of 2015, with acceptable technical success. There were no complications, good valve positioning resulting in no residual MR. The MValve Technologies company first planned to begin their first-in-human trial, titled DOCK 1, in the 4th quarter of 2016. but the development of the second generation of the MValve system (Figure 12A) but those plans on hold. The second-generation system has leaflets sewn to the dock, providing single-step implantation, along with adjusting for the transseptal approach with a 22-24 Fr delivery profile. The group planned to complete final long term durability testing on the newly enhanced device, with plans to start DOCK 1 at approved centers in the EU and South America in the 4th quarter of 2017. There are no updates to date (Regueiro et al., 2017).

6-Permavalve TMVR system (Micro Interventional Devices, Inc., Pennsylvania, USA)

The original name of the Permavalve TMVR system (Figure 12A) was the Endovalve and was renamed after the purchase of Endovalve Inc. in April of 2011 by Micro Interventional Devices Inc. The Permavalve TMVR system comes with PolyCor anchors to fix the device to the native mitral annulus. Micro Interventional, Inc. also states that the Permavalve is the first and only TMVR system that has an active fixation, which is achieved by the PolyCor anchors. Dacron cloth is used for the stent skirt that includes integral billows that ensure biological integration while also eliminating PVL. The device is

delivered *via* a transapical approach with a 28 Fr delivery system. The Permavalve utilizes the Permaseal system developed at Micro Interventional Devices, Inc. which aids in the sealing of the transapical access point by way of soft-tissue anchors and advanced biocompatible elastomers (Min Yun et al., 2014).

7-MitrAssist Device (MitrAssist Medical Ltd., Misgav, Israel)

The MitrAssist device (Figure 12B) is a valve-in-valve approach to treating MR, meaning rather than full replacement of the native MV, the system aids the native MV and increases functionality. The device comes with a nitinol frame with a pericardial tissue in an asymmetrical bileaflet design. Because the system works in uninon with the native MV there is a reduced risk of valve migration, LVOT obstruction, and the system preserves the natural MV functionality. The device is anchored to the papillary muscles to further help MitrAssist work in uninon with the MV, as the papillary muscles move in synchrony with the MV apparatus(Goode et al., 2020).

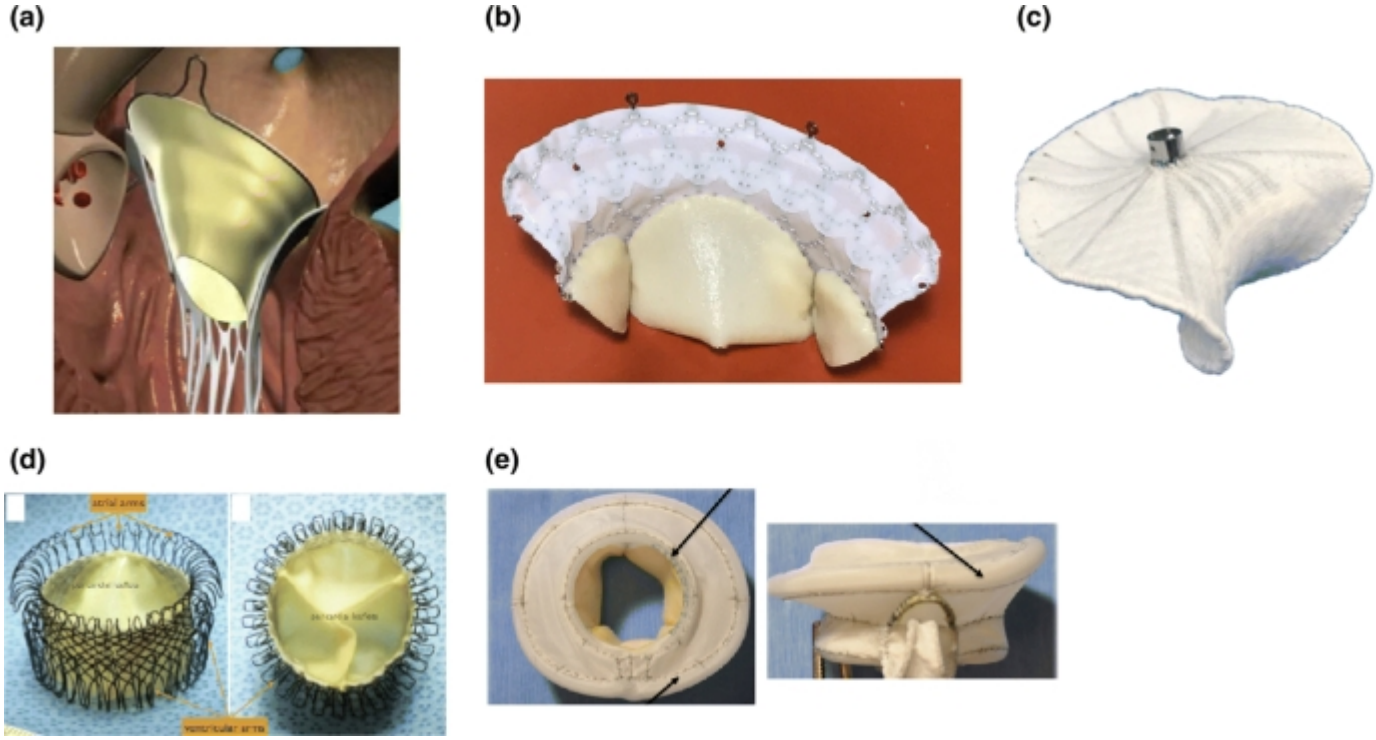


Figure 12B : TMVR systems in preclinical evaluation. (a) MitrAssist Device. (b) Sutra TMVR system. (c) Polares. (d) Gorman TMVR System. (e) Direct Flow TMVR System(Goode et al., 2020).

Preclinical animal trials have shown promising results, with no trauma to leaflets, no thrombosis initiation and no leaflet adhesion.

8-Sutra TMVR system (Dura Biotech, Connecticut, USA)

The Sutra TMVR system (Figure 12B) is a hemi-valve concept, meaning it targets replacing only one of the mitral valve leaflets, more specifically the posterior leaflet. The systems ideology is to take the benefits from both valve replacement and valve repair to create a seamless device. The system has a crescent-shaped stent frame, allowing it to be crimped to a small profile, have no LVOT obstruction and allows normal anterior leaflet function. The leaflet is comprised of a trileaflet design, emulating the scallops on the native posterior leaflet, which improves coaptation with the native anterior leaflet and reduces leaflet stress to enhance

durability. The system is anchored using a dual-guiding-fixation method that is deployed from the left atrium, securing the system to the annulus with cinching capabilities (Stone et al., 2018).

The Sutra TMVR system has shown adequate early preclinical results at 120 days post-implantation with good leaflet coaptation, no central MR, and no PVL. Currently ongoing is the accelerated wear testing at over 200 million cycles, and the 28 Fr transseptal delivery system development with the next goals of *in vivo* implantation into chronic animals (Latib et al., 2015).

9-Polares (Polares Medical, Inc., Ecublens, Switzerland)

Polares (Figure 12B) stands for **po**sterior **l**eaflet **a**ugmentation and **res**toration, denoting it focuses on the partial replacement of the posterior mitral valve leaflet. The Polares device has an anchoring base with leaflet extension curving into the left ventricle. The technology is targeting restoring coaptation for both primary and secondary MR. The Polares device is implanted exploiting a transfemoral transseptal approach and is anchored with primary and secondary anchors. The primary anchor fastens the hemi-valve to the supra-annular apparatus of the MV, with four secondary anchors further securing the system. The system is fully repositionable and retrievable while preserving options for further TMVR implantations in the future. The ventricular hemodynamics are preserved providing no impingement on the LVOT, while also preserving the MV annulus and causing no damage to the MV leaflets (Preston-Maher et al., 2015).

10-Gorman TMVR system (Gorman Cardiovascular Research Group, Pennsylvania, USA)

The Gorman TMVR system (Figure 12B) is part of the Annulon startup company that the Gorman Cardiovascular Group founded to focus on catheter-based technologies used for the replacement of the mitral valve. The device is comprised of a supporting frame and the tissue valve mechanism. The frame is a self-expanding nitinol wire woven into a three-dimensional shape. The frame provides a radial expansion force, along with a grasping force, while still providing a casing for the valve mechanism. The system produces the grasping forces by way of the ventricular arms that collect the posterior and anterior leaflets of the native MV onto the bulk of the device. The atrial arms seat the valve in the atrial space while collecting the supra-annular tissue centrally. The device uses a trileaflet pericardial tissue valve and is designed for both transseptal and transatrial approaches. The system provides no LVOT obstruction, with a good perivalvular seal (Greenbaum et al., 2018).

The sutureless device has shown good preclinical results, and the Annulon team is working to bring their devices to clinical practice.

11-Direct Flow TMVR system (Direct Flow Medical, Inc., Santa Rosa, USA)

The Direct Flow TMVR system (Figure 12B) is an adaptation from their existing TAVR device. The TAVR device is a non-metallic double ring design, that is inflated with saline that allows the device to be seated into place with good sealing (Khalighi et al., 2017). Once the functionality is achieved the saline is removed and replaced with a high strength polymer. The design utilizes a bovine pericardial trileaflet within the inflatable stent. Initial implantations of the TAVR device with minor alterations for the mitral position were performed to showcase

feasibility. Further adaptations for the mitral position provided a conforming anatomical atrial sealing flange that is additionally inflated with saline for sealing. The flange provides a smooth surface for sealing and is fully retractable and repositionable during the procedure. The device is implanted using either a transseptal or transaortic approach with a short valve height. The first-in-human implantation with the newest adaptation was planned to be done in late 2016, but due to the main financial lender for Direct Flow Medical, Inc. refusing to extend their funding arrangement, the company had to shut down. There are no updates on whether the TAVR and TMVR devices will be picked up and further developed (Khalighi et al., 2017).

12-MitraCath TMVR system (Emory University, Atlanta, USA)

The MitraCath TMVR system is a self-expanding stent docking system that allows for the implantation of circular aortic and pulmonary catheter-based valves to be implanted into the non-circular D-shaped MV annulus. Due to the lack of information and updates, it is unsure if the MitraCath TMVR system is being further developed (Goode et al., 2020).

VI-General Principles of Device Implantation

A-Intraprocedural Imaging

Intraprocedural imaging is performed with TEE and fluoroscopy (table 3). The location of the ventricular puncture can be confirmed on TEE by “poking” the LV with a finger at the intended cannulation site (Figure 13), ideally using standardized views, comparable to the previous CT simulation, aiming at following the MA trajectory but staying away from the papillary muscles, septum, and right

ventricular apex. Continuous imaging of the guidewire is performed to determine the correct placement across the MA and positioning in the right pulmonary vein, using fluoroscopy and TEE. To ensure that the wire does not pass through the chordae, an inflated balloon catheter may be advanced into the left atrium and pulled back under TEE, fluoroscopic, and tactile surveillance. At this stage, C-arm angulation already provides either a SL/A2-P2 or a compromise view along the optimal viewing curve, as proposed by prior CT-analysis, allowing for a coplanar depiction of the delivery system if aligned with the MA trajectory. The delivery system is introduced under both fluoroscopic and TEE guidance, again confirming free passage from the apex to the left atrium and excluding entanglement of the device in the subvalvular apparatus by moving the device in the MV orifice (Blanke et al., 2015).

Depending on device design, device unsheathing and unfolding begins either above or at the annular level. Centering of the delivery system in the mitral orifice at A2-P2 is guided by TEE, using either a 3D en face surgical view or a multiplane 2D view, such as simultaneous long-axis and commissural views, or deep gastric short-axis views, especially if 3D views are suboptimal. The x-plane function is most useful for centering and determining the degree of advancement with respect to the annulus, whereas the en face 3D view is helpful for judging rotational alignment, although in practice, both functions are often interchanged rapidly. Unfolding of the atrial flange/skirt is monitored on both fluoroscopy and echocardiography. Continuous monitoring of the orientation with appropriate rotational adjustment can be performed throughout the deployment process, ensuring alignment of the flat portion of D-shaped devices or specific anchoring mechanism with the mitral apparatus (Lutter et al., 2014).

Table 3. Role and Contribution of Imaging Modalities in the Context of TMVI

Plan	TTE	2D TEE/X-Plane 3D-	3D TEE	CT	Fluoroscopy
Pre-procedural planning					
Quantification of MR	+++	++	+++	NA	+
Annular dimensions	+	+	++	+++	NA
Leaflet morphology	++	+++	+++	++	NA
Annular and leaflet calcifications	++	++	+	+++	+
Chordae	++	++	++	+	NA
Papillary muscle anatomy	++	++	++	+++	NA
LV Size and function	+++	++	NA	++	++
LVOT anatomy	+	++	+++	+++	NA
Periprocedural imaging					
Localization of ventricular puncture	NA	+++-	+	NA	+
Guidewire advancement and positioning	NA	++-	+++†	NA	++
delivery system advancement and positioning	NA	+++-	+++	NA	++
Device deployment	NA	+++-	+++	NA	++
Rotational alignment	NA	+§	+++†‡	NA	+
Device anchoring	NA	+++-	++	NA	+
Post-TMVR					
Valvular competency/para-valvular regurgitation	++	++	+++‖	+	+
Trans-mitral gradient	+++	+++	NA	NA	NA
LVOT anatomy	++	++	+++	+++	NA
LVOT gradient	+++	++	NA	NA	+++#
Device apposition/seating	++	++	+++	+++	NA
Device stability	+++	+++	++	++	+++
Leaflet mobility/thrombus	+	+++	++	+++	NA
Stent fracture	NA	NA	NA	+	+++

LV = left ventricle; LVOT = left ventricular outflow tract; MR = mitral regurgitation; NA = not applicable; TMVI = transcatheter mitral valve implantation. X-plane mode. † Live 3D mode. ‡ Zoom 3D mode. § Transgastric view. ‖ Color 3D and vena contracta area. # Catheter-based direct gradient measurement. (Quoted from Blanke et al., 2015).

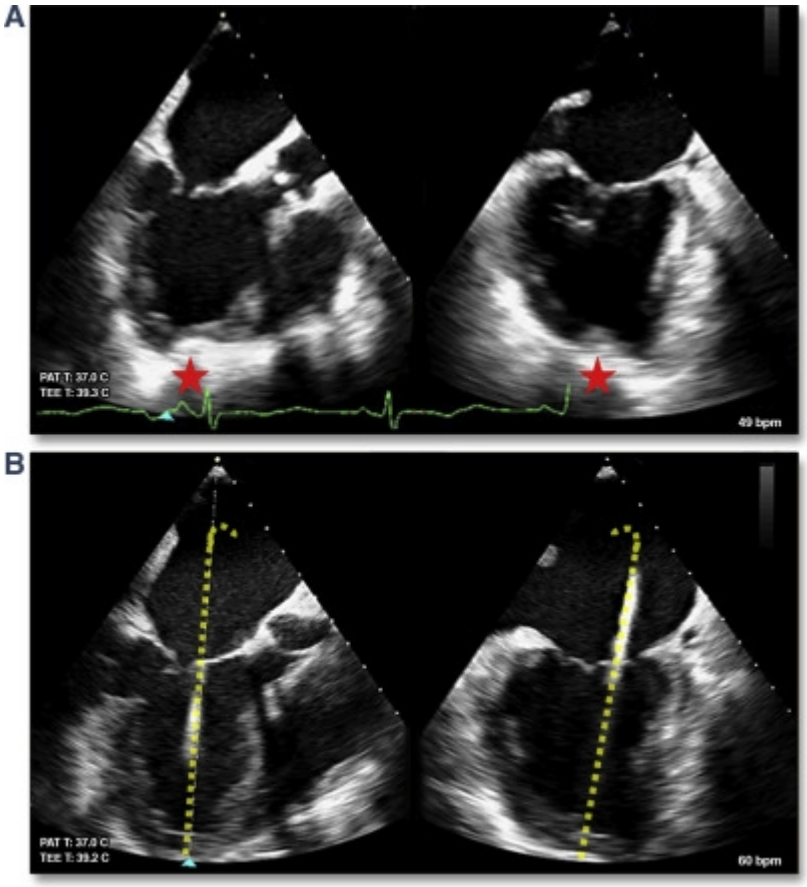


Figure 13. Localizing the Apical Cannulation Site. **(A)** Simultaneous multiplane image showing the surgeon's finger **(red star)** poking the intended cannulation site. **(B)** Initial wire path **(yellow dotted line)** (Quoted from Blanke et al., 2015).

A coronary sinus wire may aid estimation of the device's position in relation to the annular plane on fluoroscopy by mentally integrating the distance of the coronary sinus to the MA plane from prior CT analysis. Furthermore, fluoroscopy can show changes in the atrial skirt configuration, when the partially unfolded device is lowered toward the annular plane, supported further by tactile feedback. Atrial skirt apposition to the atrial wall is documented on TEE, typically using the x-plane mode with the long-axis view as the primary view and the commissural view as the secondary view. These views and the ability to change the orientation of the secondary view may allow rapid imaging of anchoring mechanisms prior to release of the device. Devices anchoring to the MV leaflets with paddles require

synchronous capture of the AML and PML at A2 and P2 before the main body is unsheathed. Correct paddle orientation and centered position at A2-P2 must be confirmed on x-plane or 2D transgastric short-axis views. Appropriate leaflet capture and paddle insertion are confirmed on the long-axis view. Finally, further unsheathing of the main body is monitored on both TEE and fluoroscopy (Bapat et al., 2014). (intraprocedural examples are shown in Figure 14 and 15).

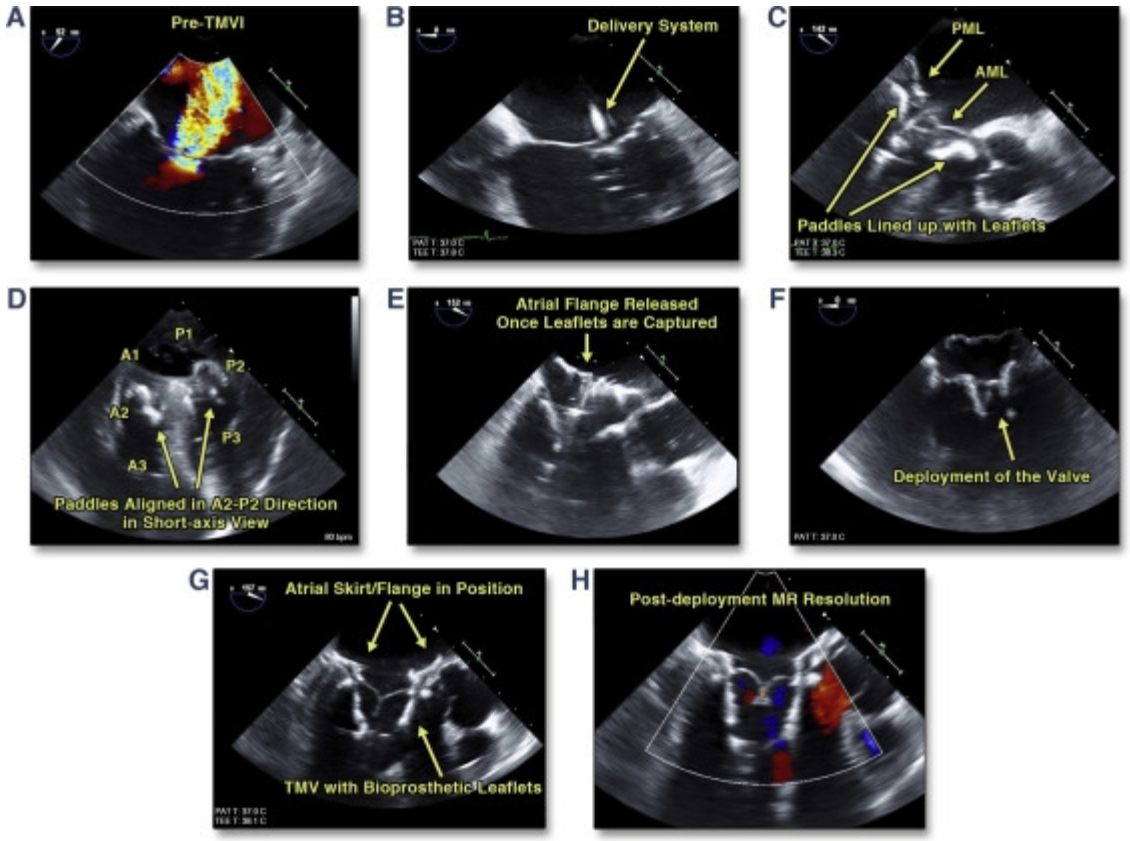


Figure 14. Periprocedural TEE Imaging During TMVI With the Fortis Device. The treatment of severe mitral regurgitation (A) with TMVI (B-G). Anchoring paddles are initially positioned outside the leaflets (C), aligned at A2-P2 using a short-axis gastric view **(D)**. Leaflets are captured between the paddles and valve body, and the atrial flange is released **(E)**, followed by deployment of the valve and sealing of the atrial skirt **(F and G)**, leading to resolution of mitral regurgitation **(H)** (Blanke et al., 2015).

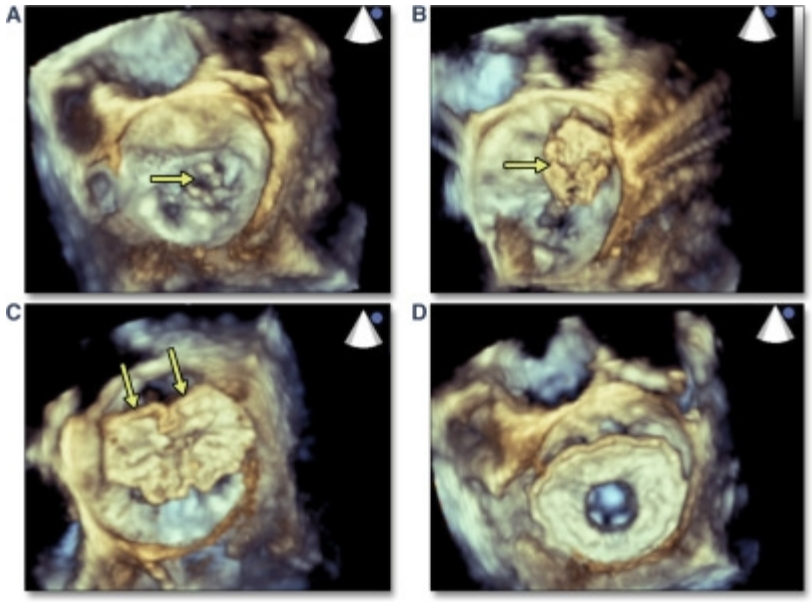


Figure 15. Deployment of Tendyne Valve Using 3D Zoom Surgical Views. **(A)** Sheath **(arrow)** is seen in the LA above native leaflets. **(B)** Valve flange **(arrow)** is released and begins to appear in LA. **(C)** Valve flange is rotated, aligning the flat part of the D-shaped mitral annulus with the aortic-mitral curtain **(arrows)**. **(D)** Flange is fully opened, and the bioprosthesis is seen in the center (Blanke et al., 2015).

B-Post-TMVI Echocardiographic Assessment

Immediately following deployment, 2D and 3D imaging confirm appropriate seating, stability, radial orientation, relationship to the captured leaflets, and prosthetic valve function. Comprehensive 2D and 3D assessments of the LVOT are performed by using color, pulsed and continuous wave Doppler to exclude potential LVOT obstruction. The transgastric window can be used to measure LVOT velocities (del Valle-Fernandez et al., 2009).

Color Doppler is used to assess central or paravalvular mitral regurgitation (Figure 16). Qualitative and semiquantitative methods of assessing paravalvular mitral regurgitation have been reported previously. Assessment may be complicated by device-related acoustic shadowing and irregular or atypical regurgitant jets. Here, TEE is likely to be more sensitive than TTE. However, adjudication

of paravalvular mitral regurgitation severity may be difficult due to the variability and complexity of orifice geometry and absence of a true gold standard. Therefore, incorporation of other methods, such as pulmonary venous flow pattern ("systolic blunting/reversal") and LVOT-to-transmitral velocity time integrals ratio (as a surrogate for mitral regurgitant volume) may be helpful. Although data are presently lacking, assessment of paravalvular mitral regurgitation severity by 3D vena contracta area seems likely to have an increasing role (Blanke et al., 2015).

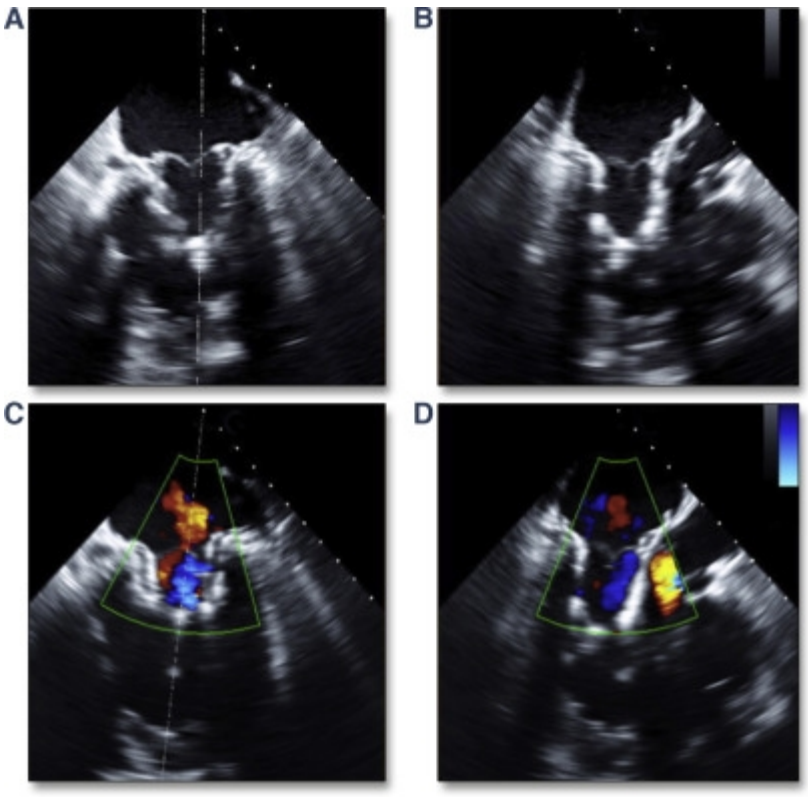


Figure 16. TEE Images Immediately After Implantation of Tendyne Valve. X-plane view shows mid-commissural **(A)** and long-axis **(B)** views. Valve leaflets are in closed position (mid-systole). Color Doppler images in same views showing LVOT preservation and no paravalvular leakage **(C and D)** (Blanke et al., 2015).

Mitral valve orifice area can be quantified by direct planimetry or by using Doppler and the continuity equation (usually by TTE), which is preferred in the absence of significant mitral regurgitation. Although a significantly prolonged

pressure half-time may indicate valve stenosis, this method has limitations, given the potential impact of variable LV and LA compliance on the pressure decay slope and should not be used to report valve areas (del Valle-Fernandez et al., 2009).

C-Follow-up Echocardiographic Imaging

TTE is convenient for evaluation of TMVI devices over time. Apical views allow assessment of LV volumes, LVEF, and global longitudinal strain and strain rate to assess reverse remodeling and improvement of LV systolic function after TMVI. They also allow accurate assessment of mitral valve gradients and calculation of the LVOT/mitral inflow VTI ratio. In contrast, TTE imaging of the left atrium may be challenging due to acoustic shadowing, making it difficult to evaluate changes in LA volumes or paravalvular leaks, especially from the apical windows (Blanke et al., 2015).

VII-References

Abdelghani M, Onuma Y, Zeng Y, Soliman OI, Ma J, Huo Y, Guidotti A, Nietlispach F, Maisano F, Serruys PW.(2015): The Sino Medical AccuFit transcatheter mitral valve implantation system. *EuroIntervention* **11 Suppl W**: W84-85.

Alharbi Y, Lovell NH, Otton J, Muller D, Al Abed A, Dokos S.(2017): Image-based fluid dynamics analysis of left ventricle outflow tract pressure gradient after deployment transcatheter mitral valve. *Annu Int Conf IEEE Eng Med Biol Soc* **2017**: 4223-4226.

Bapat V, Buellesfeld L, Peterson MD, Hancock J, Reineke D, Buller C, Carrel T, Praz F, Rajani R, Fam N et al.(2014): Transcatheter mitral valve implantation (TMVI) using the Edwards FORTIS device. *EuroIntervention* **10 Suppl U**: U120-128.

Barbanti M, Piazza N, Mangiafico S, Buithieu J, Bleiziffer S, Ronsivalle G, Scandura S, Giuffrida A, Popolo Rubbio A, Mazzamuto M et al.(2017): Transcatheter Mitral Valve Implantation Using the HighLife System. *JACC Cardiovasc Interv* **10**: 1662-1670.

Blanke P, Naoum C, Dvir D, Bapat V, Ong K, Muller D, Cheung A, Ye J, Min JK, Piazza N et al.(2017): Predicting LVOT Obstruction in Transcatheter Mitral Valve Implantation: Concept of the Neo-LVOT. *JACC Cardiovasc Imaging* **10**: 482-485.

Blanke P, Naoum C, Webb J, Dvir D, Hahn RT, Grayburn P, Moss RR, Reisman M, Piazza N, Leipsic J.(2015): Multimodality Imaging in the Context of Transcatheter Mitral Valve Replacement: Establishing Consensus Among Modalities and Disciplines. *JACC Cardiovasc Imaging* **8**: 1191-1208.

Bothe W, Miller DC, Doenst T.(2013): Sizing for mitral annuloplasty: where does science stop and voodoo begin? *Ann Thorac Surg* **95**: 1475-1483.

Carpentier AF, Lessana A, Relland JY, Belli E, Mihaileanu S, Berrebi AJ, Palsky E, Loulmet DF.(1995): The "physio-ring": an advanced concept in mitral valve annuloplasty. *Ann Thorac Surg* **60**: 1177-1185; discussion 1185-1176.

Cheung A.(2018): Early experience of TIARA transcatheter mitral valve replacement system. *Ann Cardiothorac Surg* **7**: 787-791.

Coffey S, Cairns BJ, Iung B.(2016): The modern epidemiology of heart valve disease. *Heart* **102**: 75-85.

De Backer O, Piazza N, Banai S, Lutter G, Maisano F, Herrmann HC, Franzen OW, Sondergaard L.(2014): Percutaneous transcatheter mitral valve replacement: an overview of devices in preclinical and early clinical evaluation. *Circ Cardiovasc Interv* **7**: 400-409.

del Valle-Fernandez R, Jelnin V, Panagopoulos G, Ruiz CE.(2009): Insight into the dynamics of the coronary sinus/great cardiac vein and the mitral annulus: implications for percutaneous mitral annuloplasty techniques. *Circ Cardiovasc Interv* **2**: 557-564.

Feldman T, Foster E, Glower DD, Kar S, Rinaldi MJ, Fail PS, Smalling RW, Siegel R, Rose GA, Engeron E et al.(2011): Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med* **364**: 1395-1406.

Flynn CD, Wilson-Smith AR, Yan TD.(2018): Novel mitral valve technologies-transcatheter mitral valve implantation: a systematic review. *Ann Cardiothorac Surg* **7**: 716-723.

Frohlich GM, Baxter PD, Malkin CJ, Scott DJ, Moat NE, Hildick-Smith D, Cunningham D, MacCarthy PA, Trivedi U, de Belder MA et al.(2015): Comparative survival after transapical, direct aortic, and subclavian transcatheter aortic valve implantation (data from the UK TAVI registry). *Am J Cardiol* **116**: 1555-1559.

Fuster V, Harrington RA, Narula J, Eapen ZJ.(2017): Hurst's the Heart, 14th Edition: Two Volume Set. New York, NY:McGraw Hill Professional.

Gammie JS, Bartus K, Gackowski A, D'Ambra MN, Szymanski P, Bilewska A, Kusmierczyk M, Kapelak B, Rzucidlo-Resil J, Moat N et al.(2018): Beating-Heart Mitral Valve Repair Using a Novel ePTFE Cordal Implantation Device: A Prospective Trial. *J Am Coll Cardiol* **71**: 25-36.

Gerosa G, Besola L, Manzan E, Bizzotto E, Zucchetta F, Pittarello D, Tarantini G, Meerkin D, Colli A.(2016): First-in-Human of Catheter-Delivered Annuloplasty Ring to Treat Functional Mitral Regurgitation. *JACC Cardiovasc Interv* **9**: e211-e213.

Gillespie MJ, Minakawa M, Morita M, Vergnat M, Koomalsingh KJ, Robb JD, Kondo N, Shuto T, Takebe M, Shimaoka T et al.(2013): Sutureless mitral valve replacement: initial steps toward a percutaneous procedure. *Ann Thorac Surg* **96**: 670-674.

Goel SS, Bajaj N, Aggarwal B, Gupta S, Poddar KL, Ige M, Bdair H, Anabtawi A, Rahim S, Whitlow PL et al.(2014): Prevalence and outcomes of unoperated patients with severe symptomatic mitral regurgitation and heart failure: comprehensive analysis to determine the potential role of MitraClip for this unmet need. *J Am Coll Cardiol* **63**: 185-186.

Goode D, Dhaliwal R, Mohammadi H.(2020): Transcatheter Mitral Valve Replacement: State of the Art. *Cardiovasc Eng Technol* **11**: 229-253.

Gooley RP, Meredith IT.(2015): The Accucinch transcatheter direct mitral valve annuloplasty system. *EuroIntervention* **11 Suppl W**: W60-61.

Grayburn PA, Roberts BJ, Aston S, Anwar A, Hebeler RF, Jr., Brown DL, Mack MJ.(2011): Mechanism and severity of mitral regurgitation by transesophageal echocardiography in patients referred for percutaneous valve repair. *Am J Cardiol* **108**: 882-887.

Grayburn PA, Sannino A, Packer M.(2019): Proportionate and Disproportionate Functional Mitral Regurgitation: A New Conceptual Framework That Reconciles the Results of the MITRA-FR and COAPT Trials. *JACC Cardiovasc Imaging* **12**: 353-362.

Greenbaum AB, Condado JF, Eng M, Lerakis S, Wang DD, Kim DW, Lederman RJ, Paone G, Neill WWO, Thourani VH et al.(2018): Long or redundant leaflet complicating transcatheter mitral valve replacement: Case vignettes that advocate for removal or reduction of the anterior mitral leaflet. *Catheter Cardiovasc Interv* **92**: 627-632.

Hansson NC, Grove EL, Andersen HR, Leipsic J, Mathiassen ON, Jensen JM, Jensen KT, Blanke P, Leetmaa T, Tang M et al.(2016): Transcatheter Aortic Valve Thrombosis: Incidence, Predisposing Factors, and Clinical Implications. *J Am Coll Cardiol* **68**: 2059-2069.

Jolobe O.(2016): Recognition of the distinction between primary and secondary mitral regurgitation is also important. *QJM* **109**: 699.

Khalighi AH, Drach A, Gorman RC, Gorman JH, 3rd, Sacks MS.(2018): Multi-resolution geometric modeling of the mitral heart valve leaflets. *Biomech Model Mechanobiol* **17**: 351-366.

Khan JM, Babaliaros VC, Greenbaum AB, Foerst JR, Yazdani S, McCabe JM, Paone G, Eng MH, Leshnower BG, Gleason PT et al.(2019): Anterior Leaflet Laceration to Prevent Ventricular Outflow Tract Obstruction During Transcatheter Mitral Valve Replacement. *J Am Coll Cardiol* **73**: 2521-2534.

Krishnan S, Udaykumar HS, Marshall JS, Chandran KB.(2006): Two-dimensional dynamic simulation of platelet activation during mechanical heart valve closure. *Ann Biomed Eng* **34**: 1519-1534.

Latib A, Montorfano M, Agricola E, Castiglioni A, Blasio A, Monaco F, Spagnolo P, Alfieri O, Colombo A.(2015): First-in-Human Implantation of a Direct Flow Medical Valve in a Radiolucent Mitral Annuloplasty Ring. *JACC Cardiovasc Interv* **8**: e105-e108.

Levine RA, Triulzi MO, Harrigan P, Weyman AE.(1987): The relationship of mitral annular shape to the diagnosis of mitral valve prolapse. *Circulation* **75**: 756-767.

Loger K, Lutter G, Huenges K, Frank D, Gross J, Cremer J, Attmann T, Morlock M, Pokorny S.(2018): Transcatheter mitral valve implantation: supra-annular and subvalvular fixation techniques. *Eur J Cardiothorac Surg* **54**: 1013-1021.

Lutter G, Lozonschi L, Ebner A, Gallo S, Marin y Kall C, Missov E, de Marchena E.(2014): First-in-human off-pump transcatheter mitral valve replacement. *JACC Cardiovasc Interv* **7**: 1077-1078.

Maisano F, Alfieri O, La Canna G.(2011): Percutaneous mitral repair with the MitraClip. *Ann Fr Anesth Reanim* **30 Suppl 1**: S33-37.

Maisano F, Reser D, Pavicevic J, Guidotti A, Denti P, Taramasso M, Addis A, Cesarovic N, Emmert MY, Nietlispach F et al.(2015): A translational "humanised" porcine model for transcatheter mitral valve interventions: the neo inferior vena cava approach. *EuroIntervention* **11**: 92-95.

Maisano F, Taramasso M, Nickenig G, Hammerstingl C, Vahanian A, Messika-Zeitoun D, Baldus S, Huntgeburth M, Alfieri O, Colombo A et al.(2016): Cardioband, a transcatheter surgical-like direct mitral valve annuloplasty system: early results of the feasibility trial. *Eur Heart J* **37**: 817-825.

Marechaux S, Illman JE, Huynh J, Michelena HI, Nkomo VT, Tribouilloy C.(2017): Functional anatomy and pathophysiologic principles in mitral regurgitation: Non-invasive assessment. *Prog Cardiovasc Dis* **60**: 289-304.

Marechaux S, Le Goffic C, Ennezat PV, Semichon M, Castel AL, Delelis F, Lemahieu JM, Menet A, Graux P, Tribouilloy C.(2014): Quantitative assessment of primary mitral regurgitation using left ventricular volumes: a three-dimensional transthoracic echocardiographic pilot study. *Eur Heart J Cardiovasc Imaging* **15**: 1133-1139.

Messika-Zeitoun D, Nickenig G, Latib A, Kuck KH, Baldus S, Schueler R, La Canna G, Agricola E, Kreidel F, Huntgeburth M et al.(2019): Transcatheter mitral valve repair for functional mitral regurgitation using the Cardioband system: 1 year outcomes. *Eur Heart J* **40**: 466-472.

Min Yun B, Aidun CK, Yoganathan AP.(2014): Blood damage through a bileaflet mechanical heart valve: a quantitative computational study using a multiscale suspension flow solver. *J Biomech Eng* **136**: 101009.

Mohammadi H, Goode D, Fradet G, Mequanint K.(2019): Proposed percutaneous aortic valve prosthesis made of cryogel. *Proc Inst Mech Eng H* **233**: 515-524.

Naim W, Ganesan P, Sun Z, Liew Y, Qian Y, Lee C, Jansen H, Hashim S, Lim E. (2016): Prediction of thrombus formation using vortical structures presentation in Stanford type B aortic dissection: A preliminary study using CFD approach. A*pplied Mathematical Modelling* **40(4):** 3115-3127.

Nickenig G, Hammerstingl C, Schueler R, Topilsky Y, Grayburn PA, Vahanian A, Messika-Zeitoun D, Urena Alcazar M, Baldus S, Volker R et al.(2016): Transcatheter Mitral Annuloplasty in Chronic Functional Mitral Regurgitation: 6-Month Results With the Cardioband Percutaneous Mitral Repair System. *JACC Cardiovasc Interv* **9**: 2039-2047.

Noack T, Kiefer P, Besler C, Lurz P, Leontyev S, Abdel-Wahab M, Holzhey DM, Seeburger J.(2020): Transcatheter mitral valve repair: review of current techniques. *Indian J Thorac Cardiovasc Surg* **36**: 53-63.

Obadia JF, Messika-Zeitoun D, Leurent G, Iung B, Bonnet G, Piriou N, Lefevre T, Piot C, Rouleau F, Carrie D et al.(2018): Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation. *N Engl J Med* **379**: 2297-2306.

P**admanabhan C, Jagannathan R, Talluri K, Raman J.(2017):** Extracardiac approach to functional mitral regurgitation: a cost-effective approach to addressing heart failure. BMJ Innovations **3:**91–97.

Peruzzo P, Susin FM, Colli A, Burriesci G.(2019): In vitro assessment of pacing as therapy for aortic regurgitation. *Open Heart* **6**: e000976.

Pierce EL, Kohli K, Ncho B, Sadri V, Bloodworth CH, Mangan FE, Yoganathan AP.(2019): Novel In Vitro Test Systems and Insights for Transcatheter Mitral Valve Design, Part II: Radial Expansion Forces. *Ann Biomed Eng* **47**: 392-402.

Praz F, Spargias K, Chrissoheris M, Bullesfeld L, Nickenig G, Deuschl F, Schueler R, Fam NP, Moss R, Makar M et al.(2017): Compassionate use of the PASCAL transcatheter mitral valve repair system for patients with severe mitral regurgitation: a multicentre, prospective, observational, first-in-man study. *Lancet* **390**: 773-780.

Preston-Maher GL, Torii R, Burriesci G.(2015): A Technical Review of Minimally Invasive Mitral Valve Replacements. *Cardiovasc Eng Technol* **6**: 174-184.

Regueiro A, Ye J, Fam N, Bapat VN, Dagenais F, Peterson MD, Windecker S, Webb JG, Rodes-Cabau J.(2017): 2-Year Outcomes After Transcatheter Mitral Valve Replacement. *JACC Cardiovasc Interv* **10**: 1671-1678.

Rodriguez-Gabella T, Voisine P, Puri R, Pibarot P, Rodes-Cabau J.(2017): Aortic Bioprosthetic Valve Durability: Incidence, Mechanisms, Predictors, and Management of Surgical and Transcatheter Valve Degeneration. *J Am Coll Cardiol* **70**: 1013-1028.

Rogers JH, Boyd WD, Smith TW, Bolling SF.(2018): Early experience with Millipede IRIS transcatheter mitral annuloplasty. *Ann Cardiothorac Surg* **7**: 780-786.

Rogers JH, Thomas M, Morice MC, Narbute I, Zabunova M, Hovasse T, Poupineau M, Rudzitis A, Kamzola G, Zvaigzne L et al.(2015): Treatment of Heart Failure With Associated Functional Mitral Regurgitation Using the ARTO System: Initial Results of the First-in-Human MAVERIC Trial (Mitral Valve Repair Clinical Trial). *JACC Cardiovasc Interv* **8**: 1095-1104.

Silaschi M, Nicou N, Eskandari M, Aldalati O, Seguin C, Piemonte T, McDonagh T, Dworakowski R, Byrne J, MacCarthy P et al.(2017): Dynamic transcatheter mitral valve repair: a new concept to treat functional mitral regurgitation using an adjustable spacer. *EuroIntervention* **13**: 280-283.

Sodhi N and Zajarias A (2018): Status of transcatheter mitral valve replacement: an emerging frontier with unique anatomical, technical, and clinical challenges. *Card. Interv. Today* **12(4):**50–53.

Sondergaard L, Ussia GP, Dumonteil N, Quadri A.(2015): The CardiAQ transcatheter mitral valve implantation system. *EuroIntervention* **11 Suppl W**: W76-77.

Sorajja P, Moat N, Badhwar V, Walters D, Paone G, Bethea B, Bae R, Dahle G, Mumtaz M, Grayburn P et al.(2019): Initial Feasibility Study of a New Transcatheter Mitral Prosthesis: The First 100 Patients. *J Am Coll Cardiol* **73**: 1250-1260.

Sorajja P, Vemulapalli S, Feldman T, Mack M, Holmes DR, Jr., Stebbins A, Kar S, Thourani V, Ailawadi G.(2017): Outcomes With Transcatheter Mitral Valve Repair in the United States: An STS/ACC TVT Registry Report. *J Am Coll Cardiol* **70**: 2315-2327.

Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, Whisenant B, Grayburn PA, Rinaldi M, Kapadia SR et al.(2018): Transcatheter Mitral-Valve Repair in Patients with Heart Failure. *N Engl J Med* **379**: 2307-2318.

Taramasso M, Feldman T, Maisano F.(2018): Transcatheter mitral valve repair: review of the clinical evidence. *EuroIntervention* **14**: AB91-AB100.

Testa L, Latib A, Montone RA, Bedogni F.(2016): Transcatheter mitral valve regurgitation treatment: State of the art and a glimpse to the future. *J Thorac Cardiovasc Surg* **152**: 319-327.

Webb JG, Murdoch DJ, Boone RH, Moss R, Attinger-Toller A, Blanke P, Cheung A, Hensey M, Leipsic J, Ong K et al.(2019): Percutaneous Transcatheter Mitral Valve Replacement: First-in-Human Experience With a New Transseptal System. *J Am Coll Cardiol* **73**: 1239-1246.