



Current state of transcatheter mitral valve implantation in bioprosthetic mitral valve and in mitral ring as a treatment approach for failed mitral prosthesis

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With heightened awareness of mitral valve disease and improvement in surgical techniques, the use of mitral valve bioprostheses has increased. There is a large aging population with prior surgical valvular interventions. Limited durability of the prosthesis due to valvular degeneration over time may necessitate the need for repair or replacement of the prior prosthesis in the future. This usually entails another surgical intervention in this population with elevated risk for a reoperation. There is an ongoing clinical need for newer, less invasive options that are feasible and carry a lower complication rate. The advent of transcatheter heart valve (THV) therapies has opened up a wide range of therapeutic options for treatment of a failed bioprosthesis. Their safety and feasibility are now well established. This article serves as a review of the currently available THVs for implantation in the mitral position, the pre-procedural assessment, the challenges associated with implantation, as well as outcomes associated with a mitral valve-in-valve (VIV) and a mitral valve-in-ring (VIR) procedure.

Keywords: Valve-in-valve (VIV); valve-in-ring (VIR); mitral valve bioprosthesis; surgical heart valve; transcatheter mitral valve replacement (TMVR); transcatheter heart valve (THV)



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Introduction

The incidence of valvular heart disease has increased substantially in the past decade. In developing countries, rheumatic heart disease still remains the principal cause of valvular pathology. In industrialized countries, the primary etiology of valvular heart disease is valve degeneration, mainly driven by an aging population (1-3). Mitral regurgitation (MR) is the most common valvular heart disease diagnosed in the United States. In the year 2000, an estimated 2–2.5 million people were diagnosed with significant MR (moderate-to-severe or severe). This number is expected to double by the year 2030 (3). This however

may not be a true reflection of the disease burden as a large number of patients remain underdiagnosed. More recently, epidemiologic studies conducted in Olmstead County, Rochester, MN, USA suggest that mitral valve regurgitation is prevalent in approximately 1.0% of the population, with moderate-to-severe MR accounting for half of those cases (3,4). Given these data, it is apparent that mitral valve disease poses an important public health problem.

The standard of care for most patients with valvular heart disease is either a surgical repair or a surgical replacement if operative risk is favorable. Despite increases in the frequency of mitral valve interventions (5), patients

with mitral valve disease continue to be undertreated. Patients are often not offered surgery due to lack of therapy awareness on the part of the referring cardiologist or because of excessive surgical risk in patients who have had a delayed referral to a surgeon. The frequency of mitral valve surgery in an Olmstead County cohort for patients who met indications for surgery was a mere 15%. The emergence of improved and more standardized imaging, along with the development of novel transcatheter therapies, provides some hope to correct this historical shortcoming.

Mitral valve anatomy

Mitral valve apparatus comprises of the mitral valve annulus, anterior and posterior mitral leaflets, medial and lateral commissure, chordae tendineae and the papillary muscles. These structures work synchronously during systole and diastole to accommodate the stress of the blood flow into the ventricle during diastole and the high closing pressure during systole. Changes in the valvular morphology can disrupt the mechanical integrity and lead to valvular dysfunction that manifests as regurgitation or stenosis.

Surgical therapies include leaflet repair, often accompanied with annuloplasty devices that target the annulus, or complete replacement using surgical prosthetic valves. There are two main types of prosthetic heart valves – bioprosthetic and mechanical valves. The primary benefit of bioprosthetic valves is the ability to avoid anticoagulation. However, their durability remains a potential limitation, particularly in younger patients. The past few decades have seen a steady rise in the usage of bioprosthetic valves compared to mechanical valves, with rates of bioprostheses increasing from 16.7% in 1996 to over 50% in 2013 (5,6). Nevertheless, the increased use of bioprosthetic mitral valves has not necessarily resulted in improved outcomes. In patients under seventy, prosthetic valves have been associated with higher mortality and reoperation rates. Mechanical valves, on the other hand, are associated with higher rates of stroke, and bleeding due to the need for lifelong anticoagulation (7).

As the life span of the average American increases, there has also been an escalation in the incidence of prosthetic valve deterioration in the elderly population. With improvement in operative techniques, the mortality and morbidity associated with reoperation in this elderly population is lower than what was seen in the past, but is still noted to range from 7–15% (8-10). Advanced age (>65 years), renal insufficiency, advanced New York Heart

Association (NYHA) class, and non-elective operations are the main factors that are associated with increased hospital mortality in reoperative surgery. This increased risk associated with reoperation makes transcatheter therapies an appealing option in this population.

Devices for surgical mitral valve repair

Surgical techniques used to repair or replace the mitral valve continue to evolve. Surgical repair can now be performed via right thoracotomy or minimally invasive robotic techniques rather than a full sternotomy in selected patients. Mitral valve repair, rather than replacement, is the preferred therapy for isolated primary MR. Mitral Regurgitation International Database (MIDA) registry, encompassing thirty-five years of data, suggests repairs account for a large majority (89%) of mitral valve surgeries (11). The choice of repair versus mitral valve replacement (MVR) seems to be independent of patient age, as the median age for mitral repair patients was similar to that for MVR patients (65 versus 67, respectively). The strong preference for mitral repair over MVR is supported by the registry data, with repair patients doing far better than their MVR counterparts with degenerative MR. In the MIDA registry, mitral valve repair resulted in both a lower operative mortality and a higher 20-year survival rate. The operative mortality following mitral valve repair was 1.3% compared to 4.7% for MVR. At 20 years, the survival rate for mitral repair patients was nearly twice the survival rate after MVR (46% versus 23%, respectively). This mortality benefit, however, is less apparent in ischemic MR (12). Similarly, the complication rate for mitral repair is lower when compared to MVR, with complications predominantly including stroke, endocarditis and bleeding. However, both mitral valve repair and replacement are similar in terms of recurrent MR, with rates being less than 5%.

Mitral valve repair for degenerative MR often involves resection of the degenerated or redundant leaflet and primary repair of this area. Chordal shortening, chordal transfer and commissural annuloplasty are being performed less frequently. Insertion of Gore-Tex neochordae to support and suspend the prolapsing segment has now become a standard surgical approach. The repair is often supplemented with annuloplasty using either an annuloplasty band or ring. In fact, all mitral valve repairs in the prospective MIDA database for degenerative MR were supplemented with annuloplasty rings. There were geographic differences in the type of devices used, with

European centers preferring semi-rigid and rigid rings, and US centers favoring flexible annuloplasty bands (11).

Bands and rings can be either complete, supporting the entire circumference of the annulus, or incomplete, supporting the annulus only partially. The primary difference between the surgical band and ring is flexibility or ability to conform to the given shape of the annulus. Bands are made of flexible material and surgical rings can either be rigid or semi-rigid. Choice of band versus ring depends on surgeon and institutional preferences. Type of annuloplasty device plays a crucial role in deciding candidacy for future valve-in-ring (VIR). As the options for transcatheter therapies continue to broaden, it is important for the implanting surgeon to think about not only getting the best result for the patient at the current time, but to also consider possible future options for the patient if the prosthesis fails. Individual characteristics of currently approved surgical annuloplasty devices are noted in *Table 1*.

Several transcatheter therapies for MR have emerged as alternatives to surgery. Transcatheter edge-to-edge repair (TEER) is effective in reducing symptoms and allowing for left ventricular remodeling with two to three grade reduction in MR, and was demonstrated to be equivalent to surgery in patients who are at high or prohibitive risk in terms of improvement of MR and NYHA class symptoms (13-15). Consequently, TEER has earned a class IIa indication for treating patients with primary MR who are considered to be at elevated risk for surgery per the recent American College of Cardiology and American Heart Association (ACC/AHA) valve guidelines (16). More recently, TEER was shown to improve symptoms, prolong life and reduce hospitalization in appropriately selected patients with severe secondary MR and reduced ejection fraction (17). Transcatheter mitral valve replacement (TMVR) is being evaluated in the global multicenter APOLLO (Intrepid Valve) and SUMMIT (Tendyne Valve) trials, currently testing the safety and efficacy of this therapy.

Surgical bioprosthetic valves

Bioprosthetic valves can be classified as xenografts, homografts or autografts. Xenografts are animal derived, chemically treated tissue valves that can be bovine/porcine or equine. The tissue used is from the animal's cardiac valve, pericardium or jugular venous valve. Transcatheter valves are also grouped into xenografts. Homografts are derived from humans, either a cadaver or a live donor during heart transplantation. Finally, an autograft involves transplantation

of the patient's own valve from one position to another.

There are three main components of a surgical bioprosthetic valve: valve leaflets, the stent frame and the suture ring. The valve leaflets are often sewn in the inner aspect of the stent frame. The exception to this is the Mitroflow (Sorin Group USA Inc, Arvada, CO, USA), Trifecta (St Jude Medical Inc, Saint Paul, MN, USA) and the Dokimos (Labcor, Belo Horizonte, Brazil) valves. In these valves, the tissue leaflets are sutured on the outside of the stent to allow for better valve area and hemodynamics. The characteristics of the surgical heart valves used in the mitral position are described in *Table 2*.

Stentless valves lack a stent frame and are composed of only valvular tissue and the sewing ring. They are not used routinely in the mitral position. Sutureless valves are valves that have a stent frame that anchors in the aortic root (rather than a sewing ring) and thus are not used in the mitral position.

Choosing the optimal valve for each patient requires a thorough work up and a detailed discussion with the patient regarding the risks and benefits associated with each valve type. Mechanical valves are noted to be more durable but require lifelong anticoagulation. Tissue valves on the other hand do not require lifelong anticoagulation but are subject to structural valve deterioration (SVD).

Understanding the dimensions of the prosthesis

Unlike the aortic valve, mitral valve is not a circular structure. Rather, the mitral annulus is a complex asymmetric fibrous structure that has a 3D saddle shape and exhibits geometrical changes throughout the cardiac cycle. The saddle shaped annulus is described as having an anterior and posterior horn which are the two most atrial segments along the annulus. The anterior horn continues as a fibrous ridge towards the aortic valve and constitutes the intervalvular fibrosa, commonly referred to as the "aortomitral continuity". The anterior horn remains stable in shape during systole and diastole. The base of the two horns is formed by medial and lateral trigones. These are fibrous triangular structures at the inflection of the mitral annulus. The distance between the medial and lateral trigones is known as the intertrigonal distance (IT). The valve comprises of a longer anterior leaflet and a shorter posterior leaflet which is noted to have scalloped indentations. The distance between the two ends/commissures is known as the commissure to commissure distance (CC). The distance between the anterior and

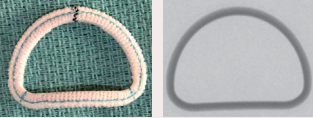

Table 1 Properties of commercially available mitral valve annuloplasty bands and rings							
Name	Type	Flexibility	Fluoroscopic visibility	Available sizes [range]	Image		ViR feasible
Medtronic Simulus Band	Incomplete Band	Flexible	Yes	9 [24 to 40 mm]			May not be suitable due to lack of circumferential support
Cosgrove-Edwards Band	Incomplete Band	Flexible	Yes	7 [26 to 38 mm]			May not be suitable due to lack of circumferential support
St. Jude Tailor Band	Complete Band	Flexible	Yes	6 [25 to 35 mm]			Feasible for sizes 25 to 33 mm
Sorin Sovering	Complete Band	Flexible	Yes	8 [26 to 40 mm]			Feasible for sizes 26 to 30 mm. Due to flexible nature may expand hence use larger size when in doubt
Duran AnCore	Complete Band	Flexible	Yes	7 [23 to 35 mm]			Feasible. Band may expand. Upsize if in between sizes
Sorin AnnuloFlo	Incomplete Ring	Rigid	Yes	6 [26 to 36 mm]			Feasible. Higher incidence of PVL and deformation of implanted Sapien valve
Carpentier-Edwards Classic	Incomplete Ring	Rigid	Yes	8 [26 to 40 mm]			Feasible. Higher incidence of PVL and deformation of implanted Sapien valve
St. Jude Rigid Saddle	Complete Ring	Rigid	Yes	6 [24 to 34mm]			Feasible. Higher incidence of PVL and deformation of implanted Sapien valve
Medtronic Profile 3D	Complete Ring	Rigid	Yes	9 [24 to 40 mm]			Feasible. Higher incidence of PVL and deformation of implanted Sapien valve
Edwards Myxo ETlogix	Complete Ring	Rigid	Yes	6 [30 to 40 mm]			Feasible. Higher incidence of PVL due to rigid triangular ring
Edwards IMR Etlogix	Complete Ring	Rigid	Yes	6 [24 to 34 mm]			Feasible. Higher incidence of PVL and deformation of implanted Sapien valve

Table 1 (continued)

Table 1 (continued)

Name	Type	Flexibility	Fluoroscopic visibility	Available sizes [range]	Image	VIR feasible
Edwards GeoForm	Complete Ring	Rigid	Yes	4 [26 to 32 mm]		Higher incidence of PVL due to the saddle shaped ring
St. Jude Séguin	Complete Ring	Semi-rigid	No	9 [24 to 40 mm]		Feasible. Needs echocardiographic guidance due to inadequate visualization with fluoroscopy
Sorin AnnuloFlex	Complete Ring	Semi-rigid	Yes	6 [26 to 36 mm]		Feasible
Sorin Memo 3D	Complete Ring	Semi-rigid	Yes	8 [24 to 38 mm]		Feasible
Medtronic Simulus	Complete Ring	Semi-rigid	Yes	9 [24 to 40 mm]		Feasible
Medtronic CG Future	Complete Ring	Semi-rigid	Yes	8 [24 to 38 mm]		Feasible
Edwards Physio II	Complete Ring	Semi-rigid	Yes	9 [24 to 40 mm]		Feasible
Edwards Physio I	Complete Ring	Semi-rigid	Yes	9 [24 to 40 mm]		Feasible

Adapted from valve-in-valve application. VIR, valve-in-ring; PVL, paravalvular leak.

posterior edge is known as the septolateral distance (SL) (Figure 1).

Annuloplasty ring/band dimensions

Rings and bands are sized by the surgeon using manufacturer provided ring/band sizers that are inserted into the annulus at the time of the operation. The

strategy for sizing is dependent largely on the underlying pathophysiology of MR (functional versus primary degenerative pathology). The sizing is based on the CC distance for most even numbered annuloplasty device sizes, and for odd numbered devices the sizing is mostly based on IT distance (18). Table 3 demonstrates the conventional placement of complete and incomplete annuloplasty bands and rings during mitral valve repair.

Table 2 Properties of commercially available surgical bioprosthetic heart valves used in the mitral position and depiction of alignment of transcatheter heart valve within a failed mitral bioprosthesis

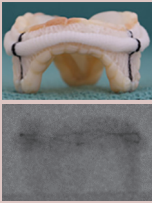
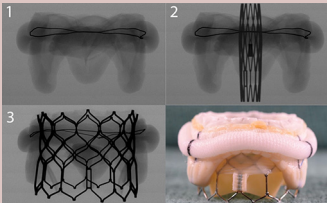
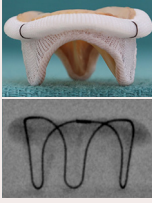
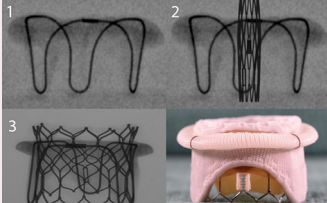
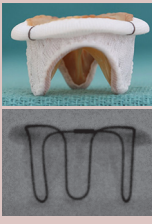
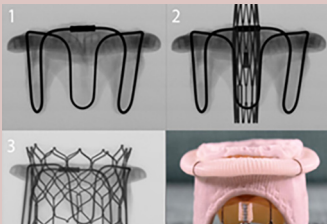
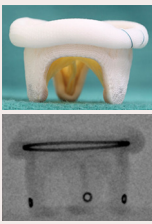
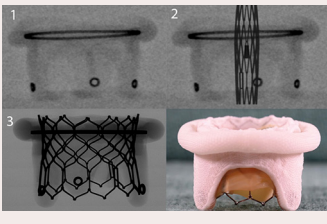
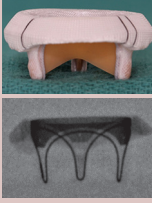
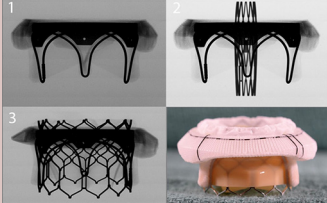
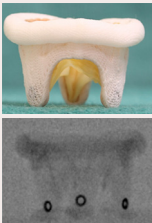
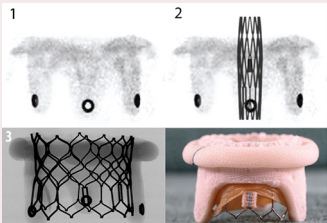
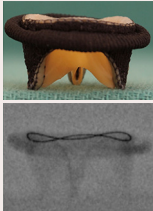
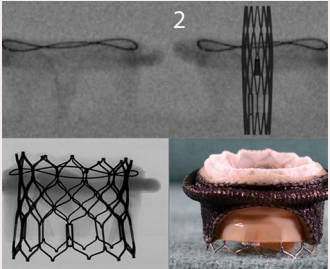
Name	Type	Fluoroscopic marker for valve positioning	Available sizes [range]	Image	Alignment during VIV using Sapien S3	VIV deployment
St. Jude Biocor Epic	Porcine leaflets	Sewing ring serves as a marker. The stent posts are not well visualized on fluoroscopy	5 [25 to 33 mm]		Align the base of the central marker with the sewing ring	
Carpentier-Edwards SAV	Porcine leaflets	Stent post is well visualized	5 [25 to 33 mm]		Align the base of the central marker 3–5 mm below the base of the stent frame	
Carpentier-Edwards Standard	Porcine leaflets	Stent post	6 [25 to 35 mm]		Align the base of the central marker 3–5 mm below the base of the stent frame	
Medtronic Hancock II	Porcine leaflets	Sewing ring and the circular markings on the stent post tip are visualized by fluoroscopy	5 [25 to 33 mm]		Align the outflow of the crimped S3 2 mm below the surgical valve circular markers	
Carpentier-Edwards Perimount Magna	Pericardial leaflets	Distinct stent post. Well visualized on fluoroscopy	5 [25 to 33 mm]		Align the base of the central marker 3–5 mm below the base of the stent frame	
Medtronic Mosaic	Porcine leaflets	Circular markings on the stent post tip are visualized on fluoroscopy	5 [25 to 33 mm]		Align the outflow of the crimped S3 2 mm below the surgical valve circular markers	

Table 2 (continued)

Table 2 (continued)

Name	Type	Fluoroscopic marker for valve positioning	Available sizes [range]	Image	Alignment during VIV using Sapien S3	VIV deployment
Sorin Pericarbon More	Pericardial leaflets	Sewing ring is visualized on fluoroscopy	8 [19 to 33 mm]		Align the base of the central marker with the sewing ring	

Images adapted from VIV application. For optimal valve function the target depth of implantation should not be more than 20% at the atrial aspect. VIV, valve-in-valve.

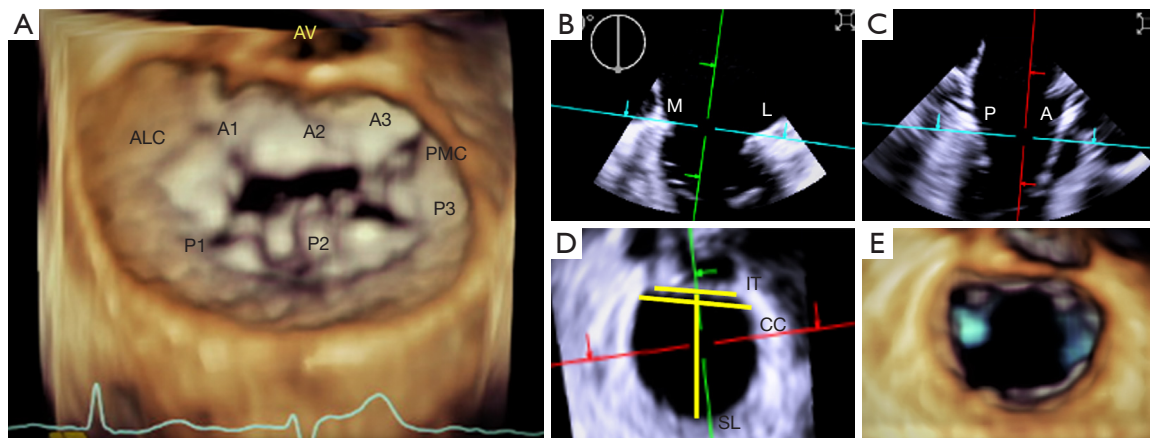


Figure 1 (A) Three-dimensional imaging of the mitral valve displaying the mitral valve en face in surgeon's view. (B-E) Multiplanar reconstruction of the mitral valve at the level of the mitral valve annulus in mid diastole where the commissure to commissure measurement as well as the septolateral or the anterior-posterior measurement is done. AV, aortic valve; CC, commissure to commissure distance; SL, septolateral distance; IT, intertrigonal distance; ALC, anterolateral commissure; PMC, posteromedial commissure.

Bioprosthetic valve dimensions

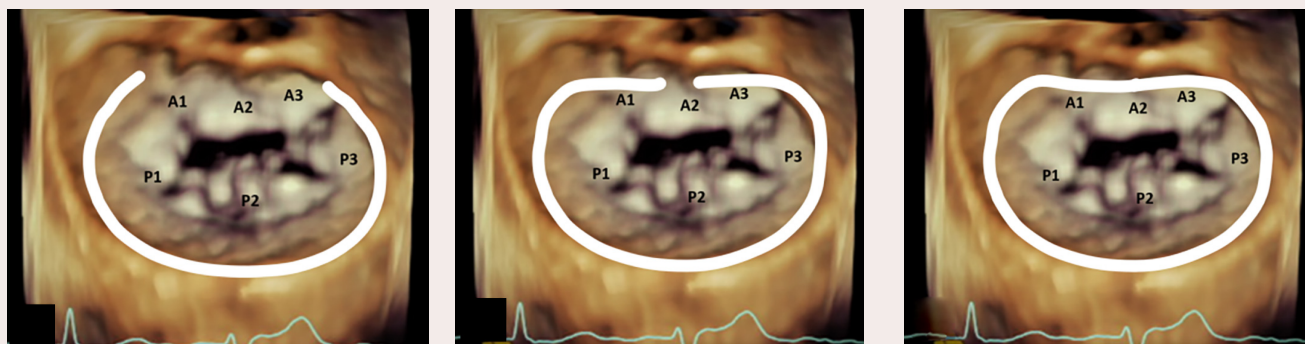
Choosing the right size and type of valve for the right patient is an essential step in optimization of outcomes associated with mitral valve replacement. The goal is to select a prosthesis model that provides the largest possible effective orifice area (EOA) with the best hemodynamic performance. This helps in preventing patient prosthesis mismatch (PPM) as well as early SVD. The hemodynamic performance is superior in valves that provide the best valve area. The newer generation valves are notably better when compared to the older generation. Valves with

leaflets mounted on the outside of the stent frame provide improved hemodynamic performance when compared to those with leaflets mounted in the interior of the stent frame. Thus, stentless valves are superior to stented valves. Surgical valves are also sized at the time of surgery using sizers. The subvalvular chordae are preserved as much as possible to maintain the left ventricular geometry after the surgery.

It is crucial to note that the manufacturer provided size, based on the sizer, is not the true dimension of the valve. There is no standardization of surgical heart valve sizing across

Table 3 Conventional placement of complete and incomplete annuloplasty bands and rings during mitral valve repair

Incomplete Band	Incomplete Ring	Complete Ring
Extends from commissure to commissure	Extends beyond the commissure	Extends throughout the circumference of the annulus
Does not cover the anterior annulus	Covers the anterior fibrous annulus partially	Entirely covers the anterior fibrous annulus
Allows for unrestricted motion of the anterior leaflet which results in better hemodynamics and valve area	Causes circumferential restriction	Causes circumferential restriction



VIV, valve-in-valve.

manufacturers (19), and valve size labeling may correspond to either the internal or external valve diameters (20). Two different surgical bioprostheses may have distinct internal and external sewing ring diameters despite having the same label size. For VIV therapy, the most relevant parameter relates to valve internal dimensions, which are often significantly smaller than the labeled valve size. Therefore, when planning a VIV procedure, it is imperative that the heart team determine the precise diameters of the failing bioprosthetic valve. Valve specifications are available from the manufacturer, through published tables generated by independent researchers (20,21), or by consulting the VIV online applications (22). The two key dimensions to identify are the stent internal dimension (Stent ID) and the true internal dimension (True ID). Stent ID is the internal dimension of a bare stent covered with fabric or pericardium without accounting for the effect of artificial leaflets sutured within the stent (23). This is the dimension that is listed by the manufacturer as the model size. True ID is the internal dimension of the valve after the leaflets are mounted within the stent frame (Figure 2A).

Bovine pericardial versus porcine valves

The incidence in use of pericardial valves has increased in the past few decades. This is mainly attributed to

studies showing that bovine valves tend to provide better hemodynamics and valve area post-procedure. Porcine valves, in contrast, have higher post-operative gradients (particularly true for smaller valves ≤ 21 mm). However, more contemporary stent assembly and leaflet mounting in porcine valves have helped in improving valve performance. The True ID for porcine valve with leaflets mounted within the stent frame is smaller when compared to pericardial valves (Figure 2B,2C).

Pathological processes like calcification or pannus can further generate a discrepancy between the expected and the observed internal stent diameters. In such cases, multidetector computed tomography (MDCT) and transesophageal echocardiogram (TEE) could be performed to determine the precise dimensions of the surgical heart valves. This information should be used in conjunction with the valve True ID to determine the best transcatheter heart valve (THV). In the case of borderline sizing (i.e., 29 vs. 26 mm THV), it is preferable to use the larger THV where the primary pathology is MR, and the smaller size in cases of mitral stenosis.

Structural valve deterioration

Structural dysfunction, due to progressive tissue

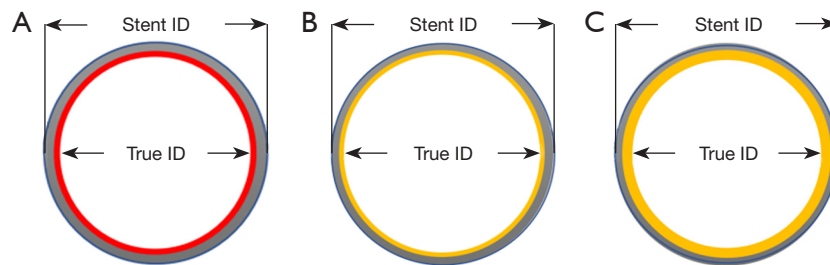


Figure 2 (A) Image depicting the true stent internal dimension and the manufacturer provided stent dimension. (B) Image showing the True ID and Stent ID for a pericardial valve with relatively larger true ID. (C) Image showing the True ID and Stent ID for a porcine prosthesis with the leaflets mounted within the stent frame. ID, internal dimension.

degeneration, is the main cause of bioprosthetic valve failure. The major pathophysiological mechanism underlying this process is leaflet calcification. This process may lead to pure stenosis due to leaflet stiffening or may also result in regurgitation due to resultant secondary micro-tears or malcoaptation (24). Recent studies have suggested that calcification of bioprosthetic valves is an active rather than a passive process that is modulated by numerous mechanisms including immune-mediated responses, lipid-mediated inflammation or dysfunctional calcium and phosphorus metabolism (25). Calcium deposits can be located on leaflet tissue or may also develop in thrombi or endocarditis vegetations (23). Glutaraldehyde valve leaflet pre-treatment is widely used to attenuate calcification and degeneration (26). Glutaraldehyde fixation cross-links and conceals the antigens, thereby making the valves immunologically inactive. However, these valves calcify over time as the glutaraldehyde alters the extracellular matrix and cellular integrity. Manufacturers of bioprosthetic valves are now using stable capping of free aldehydes and glycerolization of the animal derived valve tissue, which has been shown to substantially decrease the incidence of valvular degeneration over time (27). There is ongoing research targeted towards strategies to prevent SVD, such as raising genetically modified animals who lack xenogeneic antigens (28,29).

Design-related tearing, rather than leaflet calcification, generally explains the deterioration of bovine pericardial valves (26). The formation of tissue overgrowth (e.g., pannus), thrombus or paravalvular leaks can usually explain bioprosthesis dysfunction not related to leaflet failure. Usually, valve stenosis is the consequence of calcification, pannus or thrombus formation, whereas leaflet destruction or paravalvular leak will lead to regurgitation. The outcome of degenerative tissue valves can also be a combination of stenosis and regurgitation. In mitral

prosthesis, regurgitation is the predominant mechanism of valve dysfunction (49%), followed by stenosis (21%) and combined mechanisms (30).

The incidence of mitral bioprosthesis SVD requiring reintervention is 20% to 30% at ten years and over 50% at fifteen years. A younger age at implantation, renal failure, hyperparathyroidism, higher post-operative gradients, PPM and mitral valve position are associated with a higher risk of tissue valve deterioration (25,31-33). One of the most likely hypothesis for the greater frequency of mitral bioprosthetic failure relative to aortic bioprosthetic failure may be partially related to the higher close-off pressure in the mitral position (usually >10 versus <100 mmHg in the aortic position). Also, the closure time is expected to be greater with a mitral prosthesis compared with an aortic prosthesis, possibly contributing to a higher degeneration rate (28).

Currently available transcatheter devices for failed mitral bioprostheses

The first in-human cases of VIV and VIR procedures for mitral valve or ring dysfunction were reported in 2009 and 2011, respectively (34,35). Most cases of mitral VIV and VIR have been performed with the balloon-expandable Edwards system using the Sapien S3 valve, via transapical or antegrade transfemoral (TF) approaches. The balloon-expandable Melody valve (Medtronic, Minneapolis, Minnesota) has been used in a minority of cases (36,37). More recently, the use of self-expandable transcatheter valve systems for treating mitral valve dysfunction has also been reported (38).

A THV is selected based on user preference and access route. In general, only transcatheter valves with short profiles can be used in the mitral position given risk of left ventricular outflow tract (LVOT) obstruction. Currently in

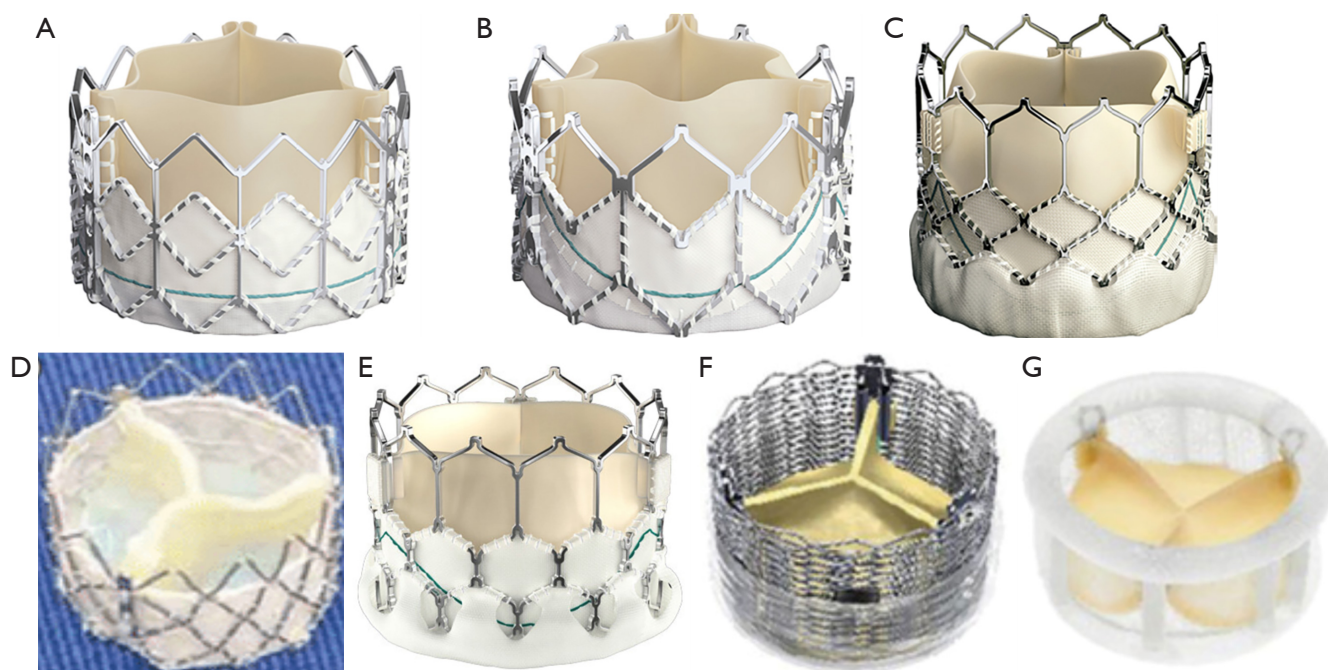


Figure 3 (A) Edwards Sapien Valve; (B) Edwards Sapien XT; (C) Edwards Sapien S3; (D) Inovare Valve; (E) Myval Valve; (F) Lotus Valve; (G) Direct Flow Valve.

the market, the most experience has been with the Edwards Lifesciences (Irvine, CA, USA) Sapien balloon expandable valves (Sapien, Sapien XT, Sapien 3). Of late, the only valve that is predominantly being used in the United States for mitral VIV and VIR is the Edwards Sapien S3 Ultra valve. Other THV devices used are Inovare, Myval, Lotus and Direct Flow (36) (*Figure 3*). To optimize anchoring and to limit paravalvular leakage in a mitral VIV intervention, a minimum of 2 mm oversizing of the transcatheter valve compared with the true internal diameter (ID) of the surgical device is preferred due to higher closing pressures and risk of embolization (37). It is not appropriate to perform extreme oversizing, as a significantly under-expanded transcatheter valve may lead to incorrect leaflet coaptation, elevated transvalvular gradient and limited durability. Under-expansion increases the risk of leaflet pin wheeling, possible thrombosis and decreases durability (39).

Pre-procedural assessment

Akin to transcatheter aortic valve replacement (TAVR) and VIV options in the aortic prosthesis realm, use of transcatheter devices in treating degenerated mitral bioprosthesis and failed mitral valve repairs with annuloplasty

rings has opened a potential alternative to surgery for these patients. Experience in mitral VIV and VIR, although still limited, is on the rise. Although similar in many ways to the aortic VIV procedures, it is different with respect to patient selection, planning and procedural steps.

A thorough history detailing knowledge about native valve pathology, type of surgery and implant including the size and model and date of implantation in conjunction with information regarding additional cardiac interventions is crucial. Like aortic VIV procedures, an accurate knowledge of the surgical mitral prosthesis or ring is essential for planning a mitral VIV or VIR procedure. The first step is to identify the type and size of bioprosthesis. In the mitral position, unlike the aortic position, only stented bioprostheses are used (38). Details of the bioprosthesis can be obtained from the operative note, valve card given to the patient or from the manufacturer. In cases where information regarding the mitral valve prosthesis is not available, given that the fluoroscopic appearance of each bioprosthesis is unique, fluoroscopy guided identification of the prosthesis is very useful. Once the type of bioprosthesis is identified, the next step is to determine the true ID. As noted above, true ID is the most important dimension and determines the size of the THV to be implanted within a

given failed bioprosthesis.

All patients should also undergo a multidisciplinary team evaluation including the interventional cardiologist, cardiologist proficient in structural imaging, cardiothoracic surgeons, cardiac anesthesiologists, nurses and possibly geriatricians and psychiatrists when appropriate.

Transthoracic echocardiography (TTE) is the first step in diagnosis of prosthetic valve dysfunction. After valve surgery, a postprocedural TTE helps in establishing the baseline prosthetic valve function. The ACC/AHA 2020 valvular heart disease guidelines recommend repeat imaging at five to ten years and then annually for follow-up of bioprosthetic heart valves, and after one year following mitral valve repair. Earlier imaging is reasonable if there are change in signs or symptoms or if early degeneration is suspected (e.g., renal failure, younger patients, diabetes, etc.). TTE provides information on change in transmitral gradients, overall cardiac function and may help in diagnosis of prosthetic valve regurgitation or stenosis. However, there are certain limitations to imaging prosthetic valves in the mitral position with TTE: (I) acoustic shadowing of the left atrium by the prosthetic stent frame may lead to an underestimation of the degree of valvular or paravalvular regurgitation, (II) poor spatial resolution may impair ability to diagnose the type of SVD.

Transesophageal echocardiography (TEE) provides excellent anatomical and hemodynamic evaluation of the bioprosthetic mitral valve. Superior spatial resolution can aid diagnosis of the etiology of SVD. The posterior position of the TEE probe allows for clear visualization of the valvular and paravalvular structures. Three-dimensional imaging is critical in evaluating prosthetic valve failure and is a crucial part of valvular assessment. Thrombi, pannus, vegetations or leaflet tears are often well visualized. Quantitative assessment of degree of MR can be done using 3D multiplanar reconstruction (MPR) and measurement of the 3D vena contracta area. 3D MPR also helps in measurement of the true ID. This is especially important for valves with pannus ingrowth or calcification where true ID is much smaller than what is estimated. Selection of the VIV implant size thus changes and a smaller valve may be needed. This is demonstrated in the example in *Figure 4* where a 26 mm Sapien S3 was implanted in a 29 mm Carpentier-Edwards (CE) Supra-Annular Valve (SAV) due to the presence of pannus ingrowth resulting in internal dimensions of around 22–24 mm (expected true ID was 25 mm).

Computed tomography (CT) is also very useful in providing information regarding valve dimensions and

other geometric considerations. LVOT obstruction is one of the potential complications of mitral transcatheter valve procedures, and the proximity between the surgical valve and LVOT, as well as LVOT dimensions should also be assessed (*Figures 5,6*). Preprocedural CT also helps in planning of key procedural aspects such as optimal site of transeptal (*Figure 7*) and angle of approach for attaining coaxiality. It can be helpful to measure the angle from the long axis of the left ventricle (LV) (from the center of the mitral valve to LV apex) to a perpendicular line drawn from the valve (or ring) plane. An angle of $>15^\circ$ for Sapien S3 ($>20^\circ$ for Sapien S3 Ultra) should raise the concern for post-implant paravalvular leak (PVL) (40). Although CT scans are emerging to be an important imaging modality in these patients, characterization of different bioprosthesis based on CT scans is not standardized and thus, they can only be used as an adjunct to the sizing information in the mitral VIV application (39).

The majority of mitral VIV cases are performed within a dedicated hybrid theater or in an operating room under general anesthesia with TEE guidance and continuous hemodynamic monitoring using invasive blood pressure monitoring and pulmonary artery swan-ganz catheters (24). The team is multidisciplinary consisting of interventional cardiology, cardiothoracic surgeons, cardiac anesthesiologists, interventional echo-cardiologist with perfusionist team on standby. Given multiple team members, pre-procedure discussion with the entire team regarding the key procedural steps, monitoring and potential bailout strategies is essential to ensure best outcomes with minimal risks.

Unlike mitral VIV, mitral VIR is much more complex due to varying types of rings. Regarding the mitral rings, the D-shape of the annuloplasty ring may result in the occurrence of paravalvular leaks following transcatheter valve implantation. Because ring circularization is important to ensure efficient sealing, a transcatheter VIR procedure should be limited to deformable complete and rigid semilunar annuloplasty devices. All the known surgical mitral rings amenable to a VIR procedure include complete rings and bands (*Table 1*).

Procedural steps

The majority of mitral VIV or VIR procedures are performed via the TF, transeptal approach. However, there are certain circumstances in which a transapical approach may be preferred. It is also possible to implant

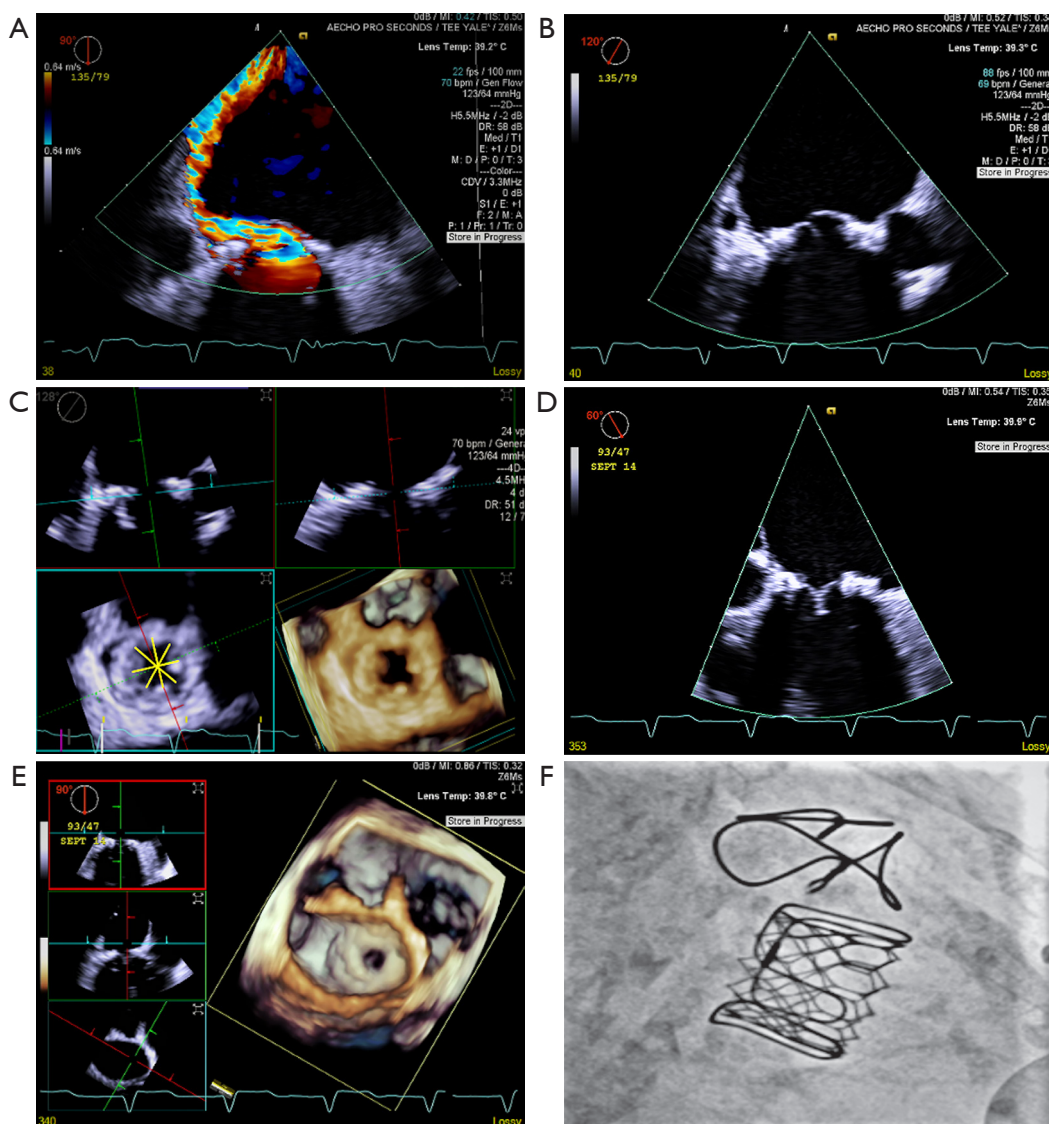


Figure 4 Example of a mitral VIV for a failed 29 mm CE SAV. (A) Mid-esophageal TEE view of the mitral valve in 2-chamber demonstrating severe eccentric intravalvular regurgitation. (B) Two-dimensional image demonstrating flail posteromedial leaflet (arrow). (C) 3D MPR with measurement of the internal dimension at the time of the procedure which demonstrated pannus ingrowth and dimensions ranging from 22–24 mm. (D,E) Three-dimensional en face view of the mitral valve after deployment of a 26 mm Sapien S3 Ultra valve. (F) Fluoroscopic image of the valve after deployment. The valve was deployed after aligning the ventricular portion of S3 and CE. VIV, valve-in-valve; TEE, transesophageal echocardiogram; CE, Carpentier-Edwards; SAV, Supra-Annular Valve; MPR, multiplanar reconstruction.

the valve under direct visualization via transatrial approach either by sternotomy or right thoracotomy. Transatrial implants, though more invasive, may be necessary if there is concern for outflow tract obstruction. The benefit of an open procedure is that the leaflets of the prosthetic valve can be excised, thus allowing blood to flow through the THV frame in systole. Without excision, the old leaflets

are stretched around the outside of the THV frame, in essence creating a tube graft that can obstruct LVOT flow. This is also a risk in VIR. A percutaneous approach to lacerate a potentially obstructive leaflet has been pioneered (LAMPOON), but experience is limited (41).

TF transeptal approach is the preferred technique for VIV and VIR implants. The only commercially approved

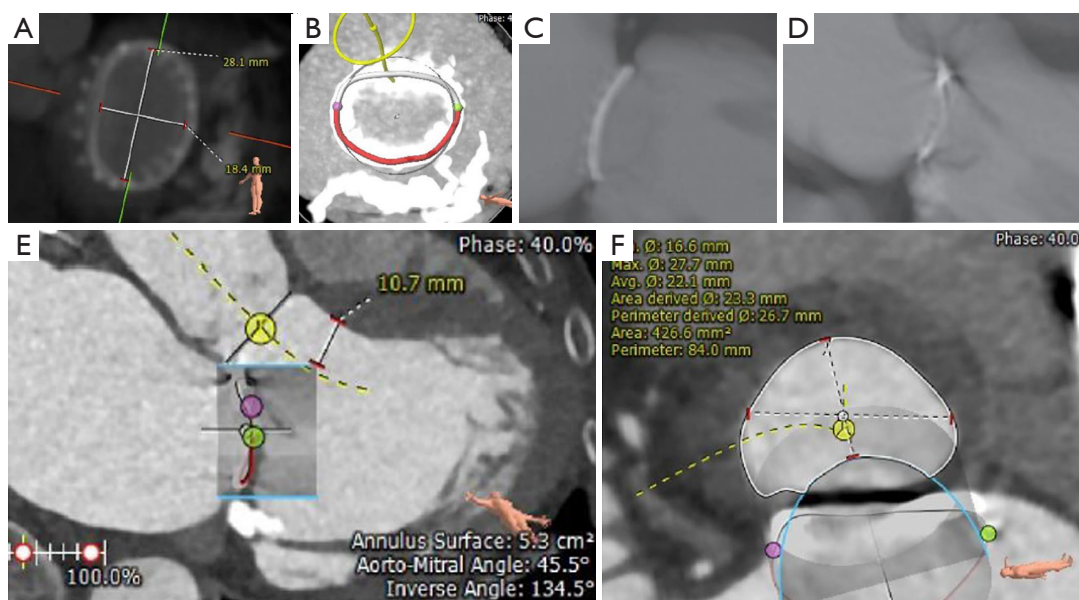


Figure 5 Evaluation for VIR using 3Mensio (Pie Medical Imaging, The Netherlands) CT scan analysis for a failed 30 mm Edwards Physio II complete ring (A,B). Note the pronounced saddle shape of the ring (C,D). Image (E) demonstrates the ideal position of the proposed THV, a 29 mm Sapien S3. The inflow of the THV would be 10.7 mm away from the LVOT, suggesting the neo-LVOT should be sufficiently large. Image (F) shows the neo-LVOT in cross section at its smallest area, measuring 426 mm², well above the cutoff of 120 mm². Thus, the risk of outflow tract obstruction is low. VIR, valve-in-ring; THV, transcatheter heart valve; LVOT, left ventricular outflow tract.

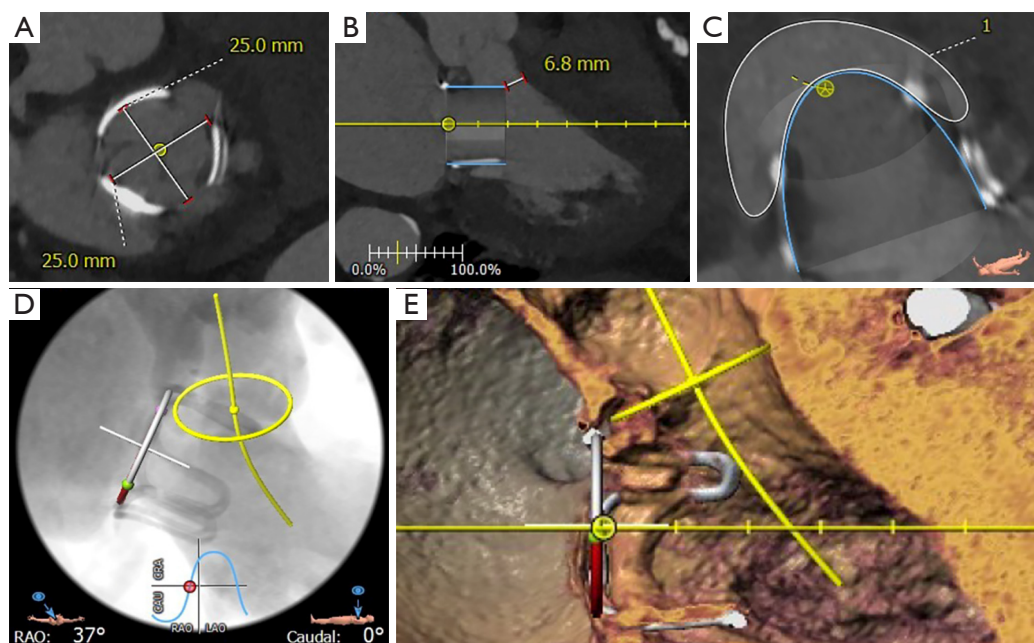


Figure 6 Preprocedural assessment cardiac CT in a patient with a failed 29 mm CE SAV. The internal diameter of the valve is 25 mm at the level of the annulus (A). A 26 mm Sapien S3 virtual valve was placed using 3Mensio (Pie Medical Imaging) which demonstrates 6.8 mm of clearance from the interventricular septum (B) and a neo-LVOT area of 312 mm² (C). A deployment angle (RAO 37°, Caudal 0°) is determined by aligning the inflow of the SAV (D), as well as the aorto-mitral angle (114°) (E). CE, Carpentier-Edwards; SAV, Supra-Annular Valve; LVOT, left ventricular outflow tract.

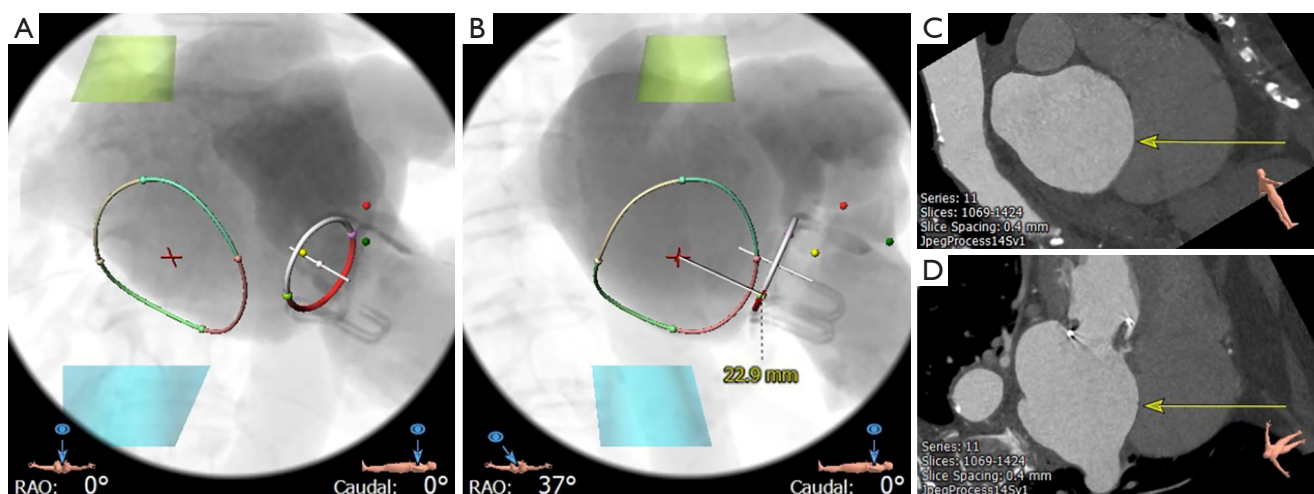


Figure 7 Transeptal planning using 3Mensio analysis of CT scan. A virtual puncture site can be identified that is central on the fossa. In the AP projection (A), the site should line up with the lowest portion of the SAV inflow, and ideally no more superior than the mid portion of the SAV. The coplanar angle can be used to determine the height of the puncture site above the valve annulus (B). A height of 2.5–3.5 cm is desirable, and more height can be gained by puncturing more posteriorly. Two-dimensional imaging can also be used to visualize the puncture site (C,D). There was a large degree of valve pannus formation in this valve (D). SAV, Supra-Annular Valve.

TF system in the United States is the Edwards Sapien device, and the following discussion will focus on this approach. After perclose of the right femoral vein (Perclose ProGlide, Abbott), serial dilators are used to upsize to the Edwards e-sheath (14 or 16 Fr) or a 24 Fr sheath. Our preference is the GORE DrySeal (24 Fr, 33 cm long) given its excellent hemostatic valve. Using this larger sheath allows for the Edwards Sapien valve to be mounted directly on the balloon, which reduces the amount of catheter that needs to extend beyond the sheath tip during final preparation of the valve and delivery system. If the valve is mounted in the traditional location (used for aortic procedures), the nosecone of the delivery system may protrude well across the intra-atrial septum to advance the balloon from the sheath. Special note needs to be made of the valve that is mounted “upside down” when compared to a TF TAVR case.

After placement of the large bore sheath, a transeptal puncture is performed. Our preference is to use an SL1 sheath with a Baylis needle. The Baylis needle uses radiofrequency energy to puncture the septum. It is important to note whether the interatrial septum was intervened upon during the initial mitral valve surgery. It may be challenging to introduce devices across the septal puncture site if the area has been patched or over sewn. Performing balloon dilation of the site (described below) will facilitate the

delivery of equipment (*Figure 8*). The preferred location for the transeptal puncture is guided both by fluoroscopy and TEE. With the image intensive intensifier in the AP view, the height of the transeptal puncture site should be at the most caudal portion of the sewing ring. Puncturing slightly higher than this may be beneficial in patients who have a relatively flat aorto-mitral angle, allowing for a more coaxial alignment of the new valve.

Following transeptal a puncture, the pigtail Baylis needle is placed in the left atrium (LA). At this point our preference is to exchange the transeptal sheath and dilator for an 8.5 Fr (medium curve) steerable Agilis NxT sheath (Abbott). This allows for more control and support when attempting to cross the surgical valve as well as delivering the stiff wire. We then use a balloon wedge catheter (balloon inflated in the LA with CO₂) or a pigtail catheter to cross the mitral valve. If a balloon wedge catheter is used, it needs to be exchanged for a pigtail using a long 035J wire. Over the pigtail, a stiff guidewire can be introduced. Our preference is a Confida guidewire (260 cm, Medtronic) in most cases. A stiffer wire (e.g., Lunderquist Wire, Cook Medical) may put too much pressure on the lateral wall of the LV. The delivery system may prolapse towards the outer wall of the LA if a more flexible wire is used (e.g., Amplatz Wire, Boston Scientific). When placing the stiff guide wire in the LV, it is important to check that the wire is free from

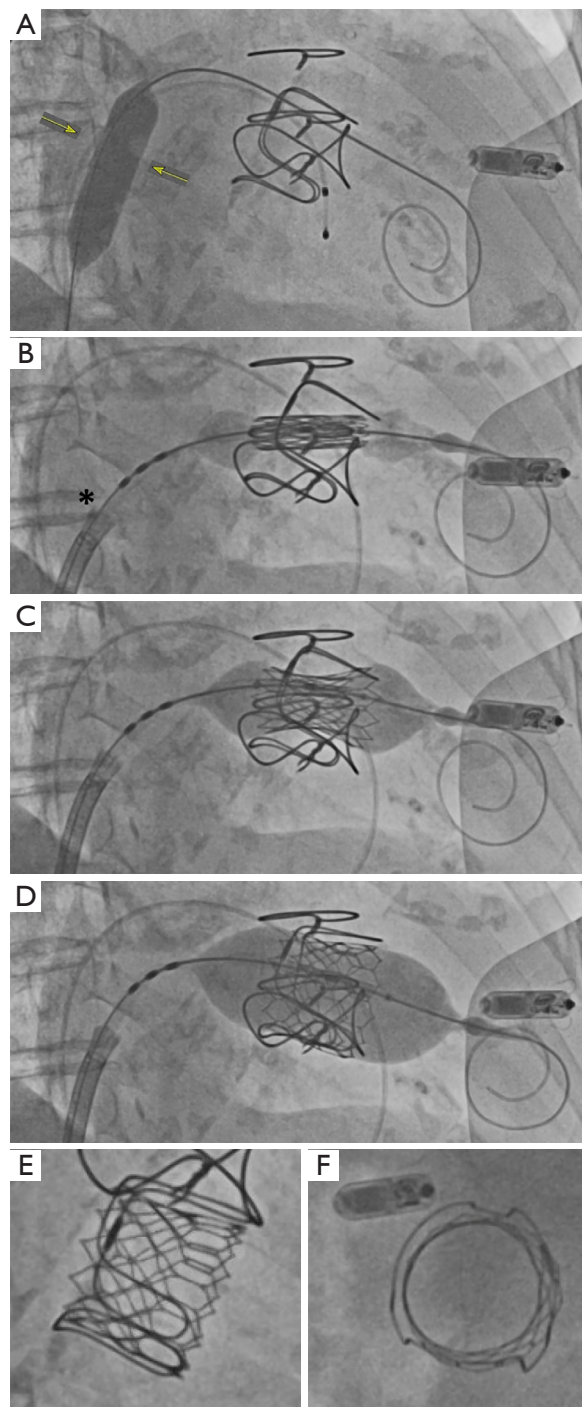


Figure 8 Deployment sequence of a 26 mm Sapien S3 in a 29 mm CE SAV. The mechanism of failure of the SAV was prolapse of two cusps due to leaflet degeneration resulting in severe MR. After delivery of the Confida guidewire, the septal puncture site (yellow arrows) was dilated with a 14×40 mm balloon (A). The valve is delivered into position (B) and the pusher is withdrawn more proximally than typical [*] to increase flexibility of the system during deployment. As the THV balloon is inflated, the valve self-centers as it anchors on the SAV facilitated by the operator in position one applying forward pressure on the system (C,D). Coplanar and en face images of the VIV are shown in images (E,F). (Note: patient also has a Micra leadless pacemaker in the apex of the right ventricle). CE, Carpentier-Edwards; SAV, Supra-Annular Valve; VIV, valve-in-valve; THV, transcatheter heart valve.

the subvalvular apparatus using TEE.

Over the stiff guidewire, a 14×40 mm balloon (100 cm shaft, 0.035 inch) is introduced. In cases of prosthetic mitral stenosis, we advanced the balloon to first predilate the valve. The same balloon is then retracted and used to dilate the intra-atrial septum. The balloon is exchanged and the Edwards Commander Delivery System is introduced with the Edwards logo facing down (180 degrees from usual). If the valve is mounted as described on the balloon, the balloon catheter does not need to be pulled back as the first step. Rather, the fine adjustment wheel can be used to direct the valve into position between the two Valve Alignment Markers on the Flex Catheter. The system is then advanced with progressive addition of flex on the catheter (usually reaching roughly two-thirds of full flex when crossing the septum). When the valve has crossed the mitral annulus, the valve “pusher” can be retracted. It is often helpful to retract the pusher further back than usual as that causes the shaft to be more flexible and facilitates a coaxial implant during balloon inflation.

The appropriate valve position depends on the type of surgical valve that is in place. Broadly speaking, the valve should be deployed with 10% in the left atrium and 90% in the LV (*Figure 8*). For VIR, note that that many rings are “saddle shaped” and thus will not have a flat annular plane. The most atrial portions of the saddle should be used as a visual reference for the implant (with the goal of 10% of the THV being on the atrial side of this reference point). There are references available to identify fluoroscopic landmarks for different types of surgical valves and rings to ensure proper deployment depth (VIV Mitral application, version 2.2, UBQO Limited).

Given the angle of approach from the septal puncture site to the valve annulus, the new valve will not be coaxial to the surgical valve or ring on initial positioning. Maneuvers that can improve alignment usually involve manipulation of both the wire and the balloon catheter. Advancing the wire into the LV while advancing the delivery system forward will tilt inflow of the valve laterally as the system moves forward. Caution should be used to prevent excessive pressure of the guidewire on the lateral wall of the LV, particularly if the patient has increased risk factors for myocardial perforation (e.g., cardiomyopathy, chronic steroid use, advanced age). Some implanters have inserted a 6 Fr sheath percutaneously near the LV apex to externalize the guidewire and improve coaxial implantation.

The deployment of the valve does not necessarily require

rapid ventricular pacing. However, in our experience, this provides some additional confidence that there will be minimal motion during deployment. The inflation of the deployment balloon should be exceptionally slow to allow for the valve to be self-centered and become more coaxial on final deployment. As the balloon is inflated and the THV begins to anchor on the surgical valve, forward pressure on the delivery system will promote the inflow of the valve to translate laterally without advancing further into the LV. We deploy these valves at relatively high pressures (8–10 atm) given the risk of annular rupture is low and a higher pressure deployment will help to flare the LV side of the valve and minimize the risk of valve embolization into the LA during LV systole. Once the delivery balloon is fully deflated, the system should be carefully withdrawn into the left atrium with special care to prevent the nosecone from interacting with the outflow of the THV.

Immediate post-deployment evaluation of the THV using TEE should be performed, evaluating leaflet function, valvular regurgitation (paravalvular or central) and LVOT velocities. The guide wire will likely be impinging on the function of one of the leaflets given how it tracks tangentially cross the valve. When it has been determined that post-dilation or deployment of the second valve is not necessary, the delivery system can be removed from the body and the guidewire can be exchanged for a pigtail. The pigtail can be removed using a long J-wire after a full TEE assessment is made.

The use of a transapical approach is more invasive but can be considered if transeptal approach is not possible. The distinct advantage of this approach is that the delivery catheter is coaxial to the mitral annular plane once inserted. Furthermore, there is greater control of valve position during deployment given the short delivery system and straight trajectory of the system.

Complications

Access complications for the femoral approach are less frequent when compared with TAVR given venous access. Failed Percloses can be managed by placement of an additional Perclose, though given the large sheath size this may not be possible. A sheath can be replaced and pulled manually when the activated clotting time normalizes post procedure. A figure of eight stitch can also be placed over the site when needed. A Femostop (Abbott) can be utilized at low pressure (20–30 mmHg) if there is persistent

bleeding from the site.

Transseptal complications are rare, but depending on the site of injury, may require open surgical repair. We typically only give half of the full heparin dose prior to transseptal puncture, and only administer the remaining heparin after the transseptal is performed and TEE demonstrates no pericardial effusion. We also transduce the pressure waveform from the transseptal needle to help verify crossing from the right atrium (RA) to LA. If at any point there is concern that the transseptal system is not in the LA or RA, the exact position should be verified before moving the device as the system may be providing hemostasis at the errant puncture site.

Mechanical injury to the LV myocardium is a known risk of this procedure due to interaction with the guidewire. An excessive amount of force can inadvertently be placed on the guidewire in an attempt to align the valve. Throughout the cardiac cycle there is repetitive linear injury to the endomyocardial border of the left ventricle that can result in a linear laceration. Ultimately, a hematoma forms and hydraulic forces can cause the hematoma to expand within the muscle, creating a non-uniform intramyocardial injury that ultimately extends into the pericardial space. This often results in a rapidly accumulating pericardial effusion (seen on TEE) and hemodynamic collapse. Angiogram of the LV will show contrast extravasation into the pericardial space. Pericardiocentesis is required in addition to reversal of heparin (blood can be auto-transfused until protamine is given). Blood transfusion should be initiated and preparations for conversion to open surgical repair should be made. Surgical repair of this myocardial injury is very challenging and rarely successful given nature of the injury.

As mentioned above, LVOT obstruction can occur when the surgical valve leaflets (or native leaflet, in the case of VIR) drape over the outer frame of the THV. If high LVOT gradients are noted, treatment includes volume loading, beta blockade and increasing afterload (without increasing chronotropy or inotropy). An alcohol septal ablation can be considered for LVOT obstruction in selected patients who do not respond to the more conservative measures.

Valve embolization can occur during deployment. VIR procedures have a higher risk of embolization into the LV given a narrower landing zone. If the valve embolizes into the LA or LV, the wire should be left in place to keep the valve relatively stationary while preparations can be made for conversion to open surgery. If there is significant PVL due to a valve that is implanted at the improper depth (too

shallow or deep) or too canted, the best course of action is to promptly insert a second valve of the same size but at the proper depth.

Conclusions

Percutaneous transcatheter options have been increasingly employed in patients with failed mitral prostheses deemed high risk for redo surgery. Although there have been few case studies demonstrating the safety and efficacy of TEER in patients with mitral valve repair failure (42), the success of TMVR in high risk patients with prior surgeries has been well documented. The multicenter TMVR and Transcatheter Valve Therapy (TVT) registries have recorded over a combined 2,000 cases of patients undergoing VIV or VIR with TMVR (43-45). These cases represent a high risk patient cohort with a mean Society of Thoracic Surgeons (STS) score of approximately 9–10%. Majority of these cases were performed via a transapical approach with the Sapien platform being a heavy favorite accounting for over 90% of the cases. The TMVR and TVT registries demonstrate an excellent rate of success for mitral VIV, with technical success rates over 90% and procedural success rates close to 75%. All-cause mortality at 30 days was 5.4% to 8.1%, increasing to 14.0% to 16.7% at one year. Notably, transapical access was associated with higher all-cause mortality at one year compared with transseptal access (21.7% versus 15.8%) in the TVT registry (45). The high rates of technical and procedural success in the TVT registry were reflected in significant clinical improvements at one year, with only 9.7% of the patients reporting class III/IV heart failure symptoms, down from 87.1% pre-procedure.

Mitral VIR procedures do not achieve the same rates of success as VIV, with reported technical success rates of 80.9% to 82.9% and procedural success rates of only 57.4%. Patients undergoing a VIR procedure also have higher rates of all-cause mortality both at 30 days (~10%) and at one year (~30%) (43). Overall, patients undergoing TMVR with failed annuloplasty rings and severe mitral annular calcification are nearly twice as likely to die compared to patients undergoing VIV procedures. There is no statistically significant difference in rates of stroke, bleeding, acute kidney injury and major vascular complications. Despite the lower success and higher complication rates for VIR, TMVR may be the more attractive option in these patients rather than redo surgery with TMVR patients

showing equivalent rates of mortality compared to surgical MVR patients, despite having higher STS scores (46).

Future directions

Mitral VIV and VIR therapies, up until this point, have been adapted from TAVR systems. There is no commercially approved device in the United States that is exclusively designed for the mitral position. Future versions of a VIV/VIR device will most likely be based on TF TMVR platforms being developed for native mitral valve replacement. There are ongoing trials for transapical TMVR devices (e.g., APOLLO, Tendyne), some of which are being adapted to a TF system. Though native TMVR valves are quite large (accommodating native annuli from 42 to 48 mm in diameter), a small implant for VIV or VIR could be envisioned that can be delivered using the same delivery system. TF TMVR systems under development prioritize the ability to articulate the delivery catheter in such a way that optimizes coaxial alignment and depth control, two features that will address two primary shortcomings of the current platform.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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