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# Emerging Trends in Heart Valve Engineering: Part III. Novel Technologies for Mitral Valve Repair and Replacement

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**Abstract**—In this portion of an extensive review of heart valve engineering, we focus on the current and emerging technologies and techniques to repair or replace the mitral valve. We begin with a discussion of the currently available mechanical and bioprosthetic mitral valves followed by the rationale and limitations of current surgical mitral annuloplasty methods; a discussion of the technique of neo-chordae fabrication and implantation; a review the procedures and clinical results for catheter-based mitral leaflet repair; a highlight of the motivation for and limitations of catheter-based annular reduction therapies; and introduce the early generation devices for catheter-based mitral valve replacement.

**Keywords**—Heart valve engineering, Mitral valve repair, Mitral valve replacement, Transcatheter mitral valve.

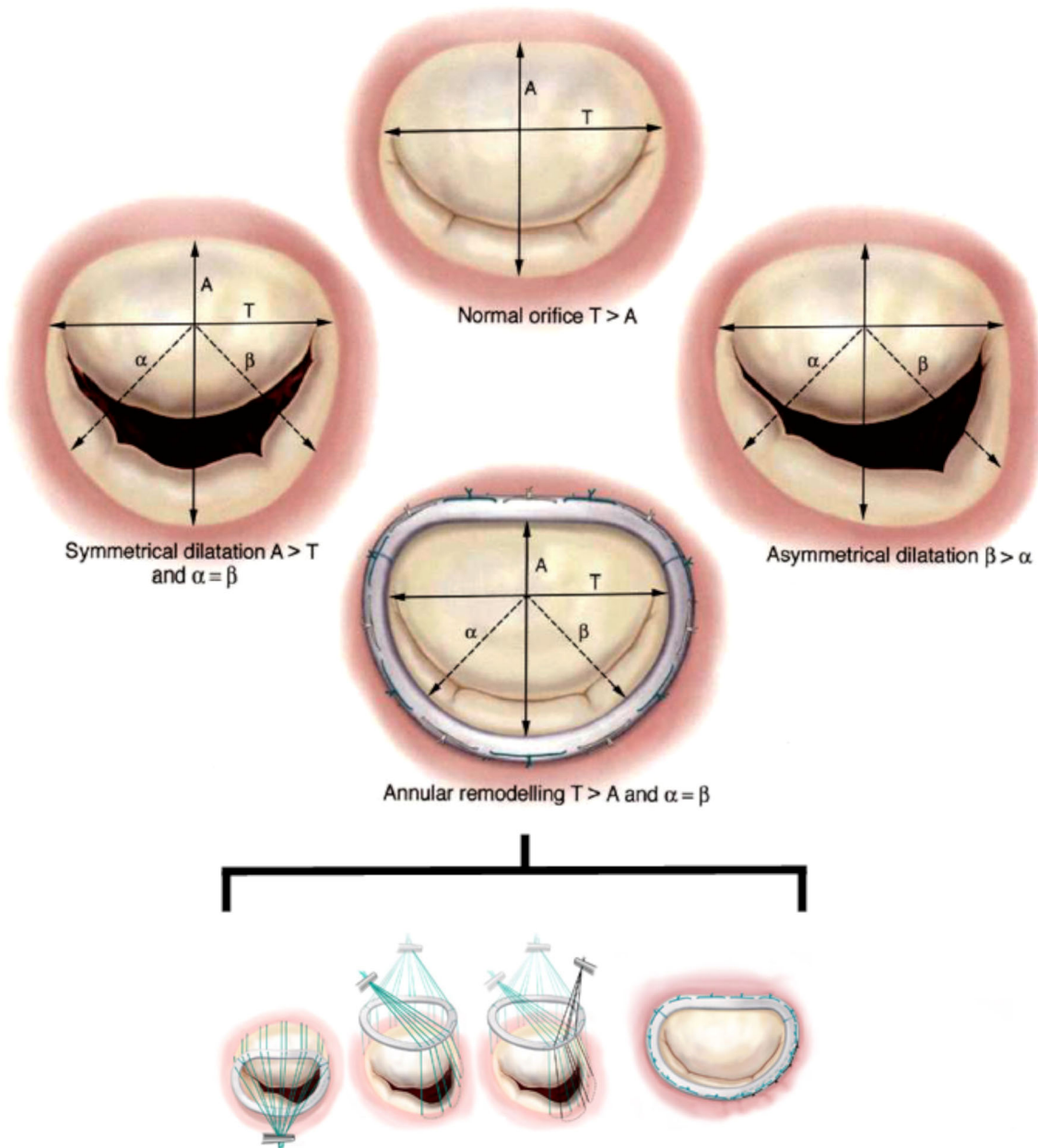
## INTRODUCTION

Mitral valve dysfunction becomes increasingly common with advanced age. Mitral valve regurgitation (MR) can be classified as either primary or secondary (functional) MR. The most common etiologies of primary MR include mitral valve prolapse (Degenerative MR, Myxomatous mitral valve disease), rheumatic valve disease, and valve dysfunction as a result of endocarditis or ischemic heart disease. Mitral valve prolapse (MVP), the most common cause of primary MR, is associated with myxomatous remodeling of the leaflets and chordae, leaflet area increase and chordae elongation and/or rupture.<sup>31,32</sup> Functional MR (FMR) results from annular enlargement and leaflet tethering due to left ventricular (LV) systolic dysfunction and is associated with stiffer tissues and fibrotic remodeling.<sup>33</sup>

By the 6th decade of life, the prevalence of significant mitral valve disease within the U.S. population is estimated to be greater than 6% and rises steadily thereafter.<sup>1,17,51</sup> As such there is intense interest within the clinical and engineering communities to develop optimal technologies to address this increasing disease burden. Several decades of surgical advances, improvements in functional imaging and materials development have revealed several important principals for successful

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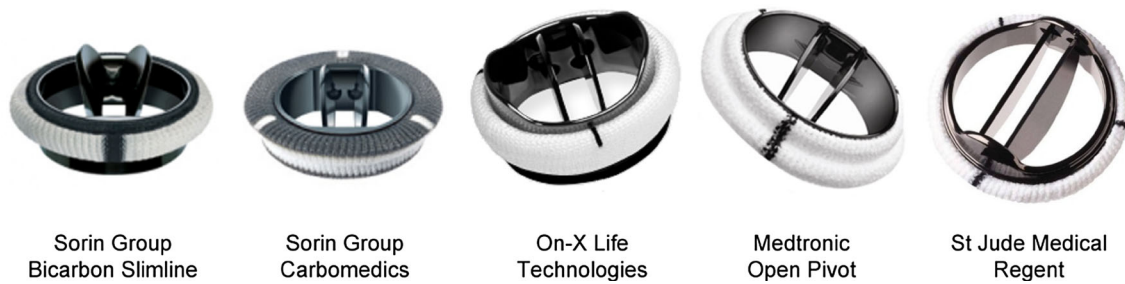


**FIGURE 1.** This figure illustrates the normal mitral apparatus and both symmetrical and asymmetric dilatation of the annulus as defined by the transverse (T) and anterior to posterior (A) dimensions. With surgical annuloplasty (annular remodeling), the goal is both a reduction in total annular area and focal reduction of the anterior-posterior annular dimension as is seen in the figure. Adapted from Carpentier's *Reconstructive Valve Surgery*: Saunders (Elsevier), 2010.

restoration of mitral valve function. In general, all repair methods aim to achieve maximal leaflet coaptation area during systole, and the acute reduction (or elimination) of MR. More recent surgical developments have focused on reduction of the total annular area and focal reduction of the anterior-posterior annular dimension, as seen in Fig. 1. In addition to preservation of the 3D annular geometry, normal cyclic motion and proper leaflet coaptation have been recognized as an important functional goal. As such,

all methods of MV repair aim to achieve maximal leaflet coaptation *via* chordal manipulation, annular reduction, direct leaflet apposition (clipping) or combination of these maneuvers.

Ultimately, the long-term success of any valve repair procedure will depend upon both the rate of primary disease progression (including ongoing myxomatous leaflet or chordal remodeling), and upon the ability of the MV repair technique to achieve a relatively low mechanical stress state to reduce further damage to the



**FIGURE 2.** The composite image of examples of mechanical mitral valves from the major manufactures.

valve avoiding repair failure. It is expected that the most durable MV repair methods will be those that achieve MR reduction while optimizing leaflet strain, reducing annular area, and maintaining functional synchrony between the contracting left ventricle (LV) and the dynamically deflecting annulus.

To create the next generation of heart valves, computational models are being used as a platform to design, test, and optimize valve replacement strategies. Once fully developed and validated, computational models may offer several advantages over physical experiments as they can mimic the flow in complex geometry of the heart while also providing control over a variety of parameters that can be used to improve functionality. Advanced constitutive models can be used to approximate the response of heart valves to a wide range of flow rates and pressures that mimic both healthy and diseased states.

## MECHANICAL MITRAL VALVES

Due to their durability, mechanical mitral valves are a mainstay of surgical treatment for mitral valve disease. Particularly valuable in younger patients, these valves are manufactured by several companies and each valve has common and unique characteristics. The most common valve design today utilizes a bileaflet mechanism with two semicircular disks surrounded by a suturing ring that surgeons use to implant the valve during open-chest procedures. The disks are often composed of pyrolytic carbon, a material similar to graphite, because blood clots have difficulty forming on surface of this material. Here, we have summarized an overview of the currently available mechanical mitral valves organized by the manufacturer, and the emerging trends in mechanical valve design.

Through the acquisition of ATS Medical in 2010, Medtronic offers the Open Pivot™ line of mechanical heart valves (Fig. 2). The Open Pivot™ comes in a standard version and an AP version, both of which

can be used in the mitral position. Overall, by using an open pivot design, as opposed to a cavity pivot, the open design minimize the recesses or cavities present in most mechanical valves that are a nidus for thrombus formation.<sup>21</sup> An additional novel feature of this line of valves is the continuous passive washing through an unimpeded flow of blood, which minimizes hemolysis and is considered a secondary mechanism to diminish thrombus formation.<sup>37</sup> Medtronic touts the excellent hemodynamics of the valves in addition to their durability, and ease of implantation.<sup>20,61</sup> The Open Pivot standard mitral valve is available in sizes from 25 to 33 mm and the Open Pivot AP has sizes from 16 to 26 mm (Fig. 2). Emphasis should continue to be placed on optimizing the open pivot design to minimize thrombus formation, which is one of the most significant complications associated with mechanical heart valves. A recent study by Van Nooten *et al.* reported a 20-year single-center experience with the Medtronic Open Pivot valve from the University Hospital Ghent in Belgium.<sup>60</sup> The study reports a 6.5% early death after mitral replacement potentially due to the fact that this group of patient included the sickest patients.<sup>19</sup> The Van Nooten study also reports a higher incidence of thromboembolism and hemorrhage in the mitral compared with the aortic group, despite administration of a low dose of the anticoagulation medication in the latter group.<sup>60</sup> In conclusion, this 20-year study demonstrated excellent clinical outcomes with no structural valve failure and suggested atrial fibrillation and elderly age, along with instable anticoagulation, led to the worst long-term outcomes.<sup>60</sup>

St. Jude Medical's mechanical mitral valve product line includes the Masters HP Series and the Regent (Fig. 2). The original Masters Series was first implanted in 1977 and offers excellent durability with a reasonable flow profile.<sup>41</sup> With a controlled torque rotation mechanism and markers on the sewing cuff, the valve improves the ease of implantation.<sup>57</sup> For the Masters HP Series, the sewing cuff was redesigned to facilitate supra-annular placement to minimize interference with subvalvular structures. Hemodynamic

performance, effective orifice area, and pressure gradients were also improved.<sup>68</sup> Finally, the supra-annular Regent maintains the durability of the Masters Series with single digit gradients and excellent hemodynamics even in the smallest sizes.<sup>53</sup> Annular sizes range from 19 to 33 mm for the Masters Series and 17 to 27 mm with the Masters HP Series (Fig. 2).

Sorin group produces a wide range of mechanical mitral valves, which are termed the Carbomedics line (Fig. 2). The three models are Carbomedics Standard mitral valve, standard pediatric mitral valve, and Carbomedics Optiform mitral valve. In the standard mitral valves, a low profile pivot system combined with a flexible sewing cuff reduces the potential for thrombus formation and allows for the preservation of mitral leaflets and subvalvular anatomy.<sup>12</sup> With the Carbomedics Optiform, the cuff was designed to allow for supra-annular, intra-annular or sub-annular placement for patient specific implantation. The Optiform is marketed as being particularly useful in patients requiring redo surgical procedures.<sup>11</sup> Carbomedics valves have shown a low rate of thromboembolism in retrospective analysis of patients when compared to the other brands of mechanical valves.<sup>11</sup> Standard and Optiform mitral valve annular sizes are from 21 to 33 mm. A study by Bottio *et al.*<sup>9</sup> that compared different mechanical prostheses at mitral position in children showed that the Sorin Overline valve led the highest closure volumes ( $p < 0.05$ ) and the highest total regurgitant volume ( $p < 0.05$ ). However, at the end that study suggested the Sorin Overline valve showed the best diastolic performance among the other tested valves.<sup>9</sup>

On-X Life Technologies offers two models of mechanical mitral valves that differ primarily based on their sewing ring (Fig. 2). The valves are referred to as the On-X mitral valve with standard, and with conform-x sewing ring, respectively. Improved annular support and leaflet guarding were used to address tissue interference and pannus overgrowth. Reduced turbulence from improved hemodynamics and smooth backflow patterns through the stasis-free hinges act to reduce hemolysis.<sup>48</sup> All of these features combine to address the reduction of thrombotic complications. Conform-X sewing ring is intended to create a valve that can conform to a wide range of annular sizes. With a standard sewing ring, the valve comes in annular sizes from 23 to 33 mm, and with the conform-x sewing ring there is only one size valve that fits tissue annular diameters from 25 to 33 mm. A study by Wippermann *et al.*<sup>64</sup> reports 3-year experience with on-x conform-X bileaflet prosthesis for ‘atrialized’ mitral valve replacement. In this article, the authors state that the cylindrical housing of the On-X valve shelters virtually the entire motion of the native leaflets, allowing

an uninterrupted function and improved transvalvular flow pattern. The valve’s asymmetrical sewing ring also facilitates anchoring of the ring in an ‘atrialized’ fashion, while the cuff’s flexibility adapts to the native annulus diameters larger than 25 mm.<sup>64</sup>

Regardless of the type of mechanical valve, lifelong anti-coagulation therapy (i.e., warfarin) is still nearly universally prescribed for patients, which increases the risk of major bleeding complications such as hemorrhagic stroke.<sup>30</sup> This increased risk of bleeding limits a patient’s ability to participate in activities that have an increased risk of traumatic injury. Indications for the use of mechanical valves include younger patients in whom a durable valve that can last decades is desirable. The durability of mechanical valves is the primary advantage over bioprosthetic valves where leaflet deterioration is a much greater issue. Another less frequent complaint with the mechanical valves is that very few patients hear a clicking noise as the mechanical leaflets close; that can sometimes lead to sleep disturbances and social embarrassment.<sup>49,52</sup> Louder noises were more common in older designs, such as tilting disk valves, where only one leaflet was present. The current bileaflet design has significantly reduced the amount of noise.

Recent engineering efforts have used advanced computational and experimental techniques to further optimize mechanical heart valve design and reduce complications. Decreasing thrombus formation that often localizes in the valve hinges due to complex and unsteady flows and limiting regurgitation are active areas of research. Computational fluid dynamics (CFD) is being used to study flow through physiologic 3D geometries before and after virtual valve implantation.<sup>3,15,67</sup> CFD can also be used to help estimate the thrombogenicity of devices with several geometries by studying, in combination with experimental approaches, the effect of distinct flow phases on platelet activation.<sup>65</sup> Others have recently used particle image velocimetry to measure steady diastolic leakage flow of regurgitation jets,<sup>22,28</sup> orifices,<sup>23</sup> and at the hinges<sup>36</sup> of mechanical valves. Valve optimization is difficult as areas of high velocity and viscous shearing may lead to platelet activation and hemolysis, while areas with low velocity can promote thrombus formation due to increased residence time. Once built, ex vivo biocompatible flow chambers can also be used to test the performance of prosthetic heart valves.<sup>66</sup>

Until more durable valves are introduced, the mechanical heart valves will remain the first choice for younger patients. In the next few years, the mechanical heart valve field should continue evolving from efforts to optimize hemodynamics, testing devices, and surface coatings. Advancements in CFD, particle image velocimetry,<sup>22</sup> and echocardiography<sup>38</sup> can provide



further input to improve mechanical heart valve geometry and dynamics. In particular, complicated hinge points are regions where continued advancements in technology will provide improvements. Finally, surface coatings on valves need to be further improved to reduce platelet activation, thrombus formation, and protein aggregation. One relatively new technique utilizes a polymerization process that uses horseradish peroxidase (HRP) as a catalyst to make hydrophilic polymers needed for a non-adhesive outer coating.<sup>6</sup> While mechanical heart valve design will minimally improve over the next decade, their overall usage is likely to continue to further decline as bioprosthetic valve durability improves.

### BIOPROSTHETIC MITRAL VALVES

Bioprosthetic valves are primarily composed of Glutaraldehyde-fixed tissues such as porcine valve leaflets and/or bovine pericardium. The biocompatible surface and improved blood flow dynamics minimize red blood cell damage, reducing thrombus formation and thus mitigate the need for anticoagulation. However, durability is a concern as they last only 15–20 years, and tend to deteriorate more rapidly in younger patients. Bioprosthetic valves require replacement within 10 years in 30% of patients and within 15 years in 50% of patients.<sup>18</sup> As the techniques in stent design and fixative methods improve, bioprosthetic valves are becoming more durable. The goal of creating a bioprosthetic valve with the durability of a mechanical valve is unlikely to be achieved in the near future; however, progress is being made and will likely be driven on by the advent of transcatheter valve technology. Here, we provide an overview of the currently available bioprosthetic mitral and aortic valves.

Edwards Lifesciences offers a large and frequently used line of pericardial heart valves for the mitral position. Currently available mitral valves include the Carpentier-Edwards PERIMOUNT™ Magna Mitral Valve, PERIMOUNT™ Magna Mitral Ease Valve, PERIMOUNT™ Plus Mitral Valve, PERI-

MOUNT™ Theon Mitral Replacement System, Duraflex Low Pressure Porcine Mitral Bioprosthesis and the Carpentier-Edwards Mitral Porcine Bioprosthesis. Edwards second generation bovine pericardial valves, the Carpentier-Edwards PERIMOUNT™ line show excellent durability compared to the first generation pericardial valves (Figs. 3, 4).<sup>45</sup> In elderly patients, there is an extremely low rate of reoperation due to structural valve deterioration.<sup>45</sup> The Duraflex™ and standard mitral porcine valves are xenograft porcine valves treated with Edwards' patented XenoLogiX treatment and mounted on a flexible stent.<sup>14</sup> These valves exhibit excellent hemodynamics and low rates of calcification.<sup>14</sup> All PERIMOUNT™ valves have sizes from 25 to 33 mm, Duraflex models have sizes from 27 to 35 mm and the Carpentier-Edwards Mitral Porcine Bioprosthesis has sizes ranging from 25 to 35 mm.

Medtronic offers two bioprosthetic valve lines that are implanted used in mitral position. The Hancock II® is a porcine bioprosthesis that demonstrates very low rates of structural deterioration and overall low amount of valve related complications (Fig. 3).<sup>7,59</sup> Similar to the other bioprosthetic valves, the hemodynamics are vastly improved over those of mechanical valves.<sup>7</sup> Mosaic® and Mosaic Ultra® are the second line of bioprosthesis available from Medtronic. Using porcine valve tissue combined with a flexible stent to reduce tissue stress, they have shown excellent durability with excellent hemodynamics.<sup>54,55</sup> Through the use of the proprietary Cinch™ Implant System, the Mosaic line is especially suited for minimally invasive procedures.

St. Jude Medical offers the Biocor® Stented Valve system and the Epic™ Stented Valve with Linx™ AC Technology for implantation in the mitral position (Fig. 3). These valves use porcine leaflets and have excellent durability, even in young patients.<sup>10</sup> A touted feature of the Biocor® valves is the high effective orifice areas provided compared to other manufacturers valves, particularly at small valve sizes. Identical in design to the Biocor® valves, the Epic™ Stented Valves have the addition of Linx™ AC Technology, which is an anti-calcification treatment. Animal work

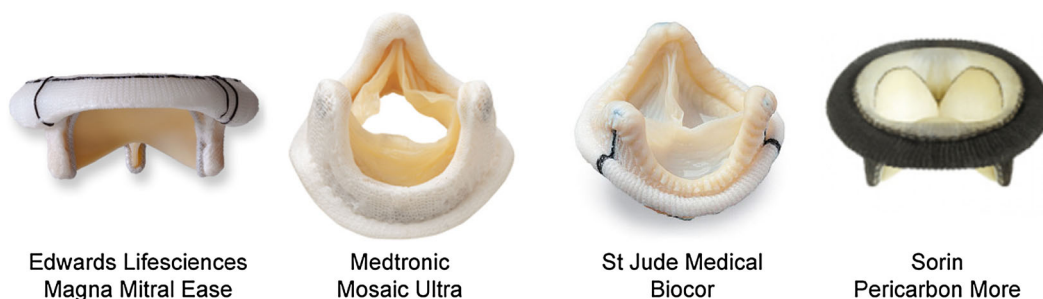
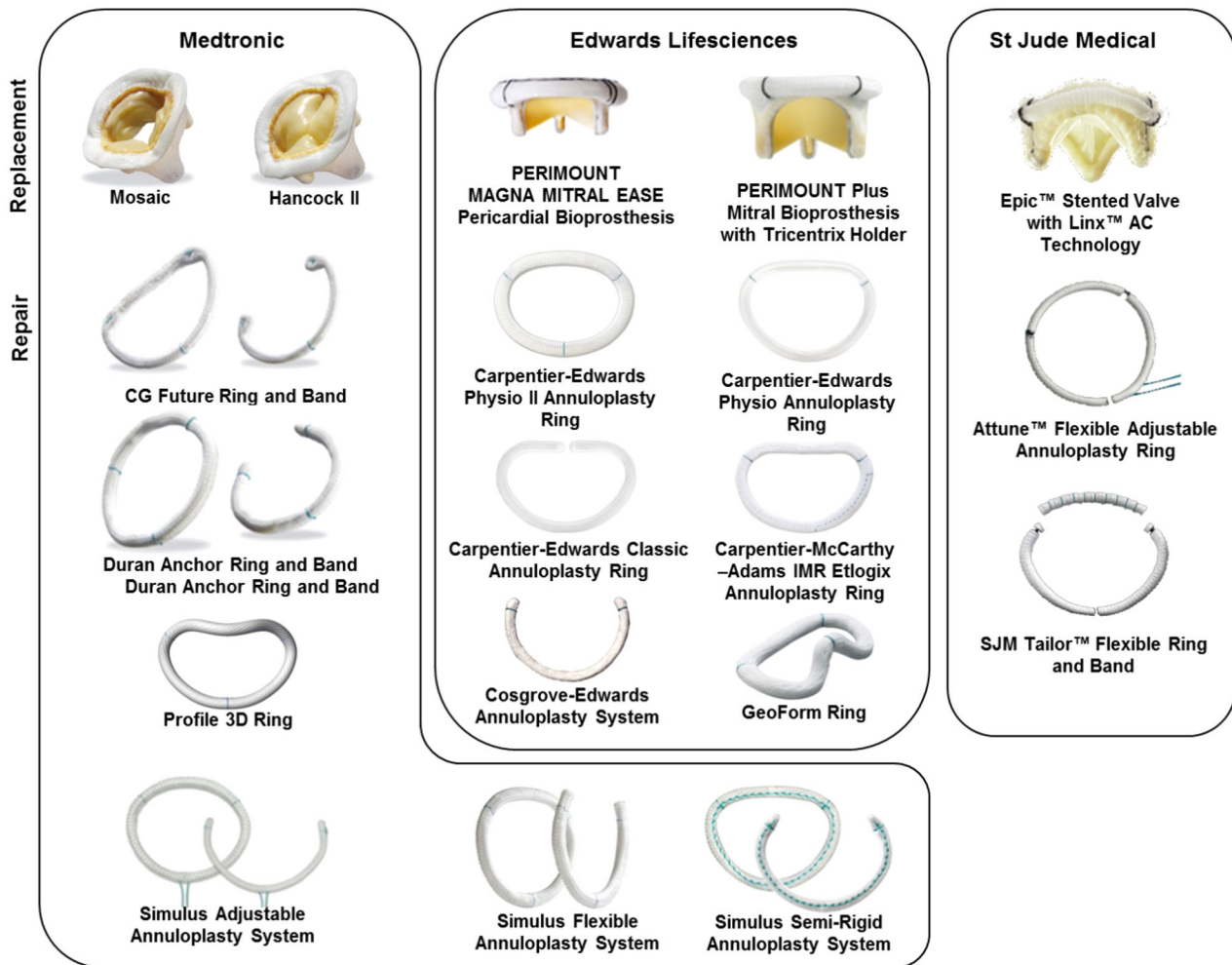


FIGURE 3. A composite of bioprosthetic mitral valves from each of the four major manufacturers.



**FIGURE 4.** Commercially available bioprosthetic mitral valves and annular rings.

has shown a dramatic decrease in valve calcification due to the treatment with Linx™ AC Technology.<sup>63</sup> Both valves come in sizes from 25 to 33 mm.

In the mitral valve space, Sorin Group has the Pericarbon More mitral valve. This is a stented pericardial valve with Sorin Group's exclusive Carbofilm™ coating for enhanced hemocompatibility. The valve has excellent 10 year safety data and proven reduction in mitral valve disease over the long-term.<sup>27</sup> Sizes range from 19 to 33 mm.

Regardless of the manufacturer, the available bioprosthetic mitral valves do not capitalize on the natural saddle shape of the mitral annulus. Unique among heart valves, the mitral valve actively participates in the systolic and diastolic function of the left ventricle.<sup>47</sup> Currently, mechanical valves and stented bioprosthetic valves obliterate the natural function of the mitral annulus and thus impair filling and LV contraction.<sup>35</sup> Work is currently underway to create replacement valves for the mitral position that aim to maintain the

native annular function by mimicking the saddle shape and its dynamic motion.<sup>40</sup> Additional work to utilize a bileaflet design, as with nature designed, is underway.<sup>39,40</sup> There are several promising prosthetic mitral valves in clinical and preclinical development.<sup>24,40</sup>

### *Surgical Annuloplasty*

The saddle-shaped geometry of the mitral annulus has been recognized for many years (Fig. 1).<sup>42</sup> This basic saddle-shape is accentuated during systole as the annulus undergoes a sphincter motion, narrowing down the orifice to facilitate coaptation of the two leaflets and widening during diastole to allow for easy diastolic filling of the left ventricle. In addition, the entire annulus descends towards the LV apex during systole, although the extent of this apically directed displacement is heavily influenced by the LV systolic function. In recent years, it has been recognized that in

myxomatous disease the native mitral annulus is significantly dilated with relatively preserved annular motion and apical descent. In functional MR, however, due to either global or regional LV systolic dysfunction the annulus remains relatively flat with reduced apical decent.<sup>43,62</sup> This pattern of annular dysfunction mirrors the basic categorization of MR as either primary, also known as organic MR (leaflet dysfunction, and annular enlargement with preserved dynamic function) or functional MR (grossly normal leaflets, and annular enlargement with loss of dynamic function).

The goal of mitral valve annuloplasty is to restore mitral valve competence by reestablishing the physiological form and function of the normal mitral valve apparatus. Mitral valve repair carries a class I (level of evidence B) recommendation as the preferred therapy to mitral valve replacement for severe MR when both procedures are feasible.<sup>50</sup> Today, all manner of annular ring devices are available including flexible, semi-rigid, rigid, incomplete or complete, planar or saddle-shaped, adjustable and non-adjustable with various degrees of 3D folding incorporated into each ring design (Fig. 4). While they all aim to create a uniform “under sizing” of the native mitral annulus they vary widely in the advantages claimed by each model. The principal aim of the surgical implantation of an annular ring is to decrease the distance between the most anterior and posterior elements of the mitral annulus in an effort to improve leaflet coaptation, and once the repair is completed, the ring serves to stabilize the repair to prevent further annular dilatation. In general, flexible rings (either partial or full circumference) are preferred for the repair of myxomatous MR where dynamic annular function is still present and can be preserved by use of a flexible band. On the other hand, full circumference rigid rings are generally preferred for the repair of functional MR where annular motion is already severely impaired. While the general goal of all devices is the same, flexible bands are intended to maintain the three-dimensional contour of the native annulus and some of its natural dynamics. Rigid rings are intended to provide stable support of the mitral valve components under the most dilated and high-pressure conditions. Ultimately the choice of which annular ring to use is based on the underlying etiology of MR, as well as the preference of the implanting surgeon.

#### *Surgical Neo-Chordae Tendinae*

Expanded polytetrafluoroethylene sutures (ePTFE) have been used for replacement of chordae tendinae (so called neo-chordae) since 1985.<sup>16</sup> Although the details of the surgical technique may vary, in general to

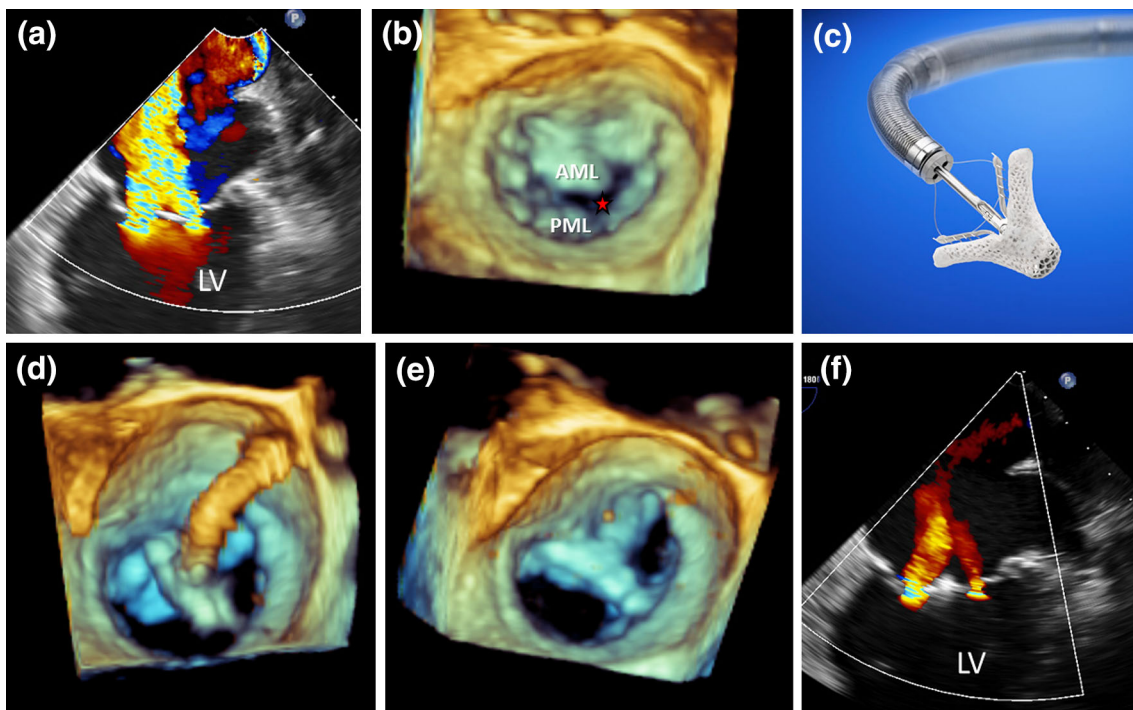
create artificial chordae a single suture is passed successively through the fibrous portions of the papillary muscle and the free margin of the prolapsing segment of mitral leaflet, followed by tying the ends together on the papillary muscle head. The creation of such neo-chordae can be tailored for varied surgical approaches such as the standard open sternotomy, a minimal-access sternal sparing approach (right thoracotomy), or even for robotically assisted endoscopic mitral valve repair surgery. Since the length and number of artificial chordae required for each patient is unique, this tailored approach to the creation of neo-chordae permits the repair of several different mitral pathologies including prolapse of multiple myxomatous leaflet scallops (so called Barlow’s condition<sup>2</sup>), repair of a single flail scallop due to native chordae rupture, or improving coaptation in mixed degenerative disease leaflet phenotypes. In addition, neo-chordae have also been used for correction of prolapsed tricuspid valve leaflets as well as for resuspension of the papillary muscles during mitral valve replacement to preserve the mitral annulus and papillary muscle continuity. PTFE chordae have repeatedly demonstrated excellent long term durability.<sup>34</sup> In an initial study by David *et al.* the freedom from moderate mitral regurgitation was 88% and the freedom from reoperation was 92% at 10 years.<sup>16</sup> In general, outcomes with respect to mortality, morbidity, rates of reoperation, long-term function, and complications of artificial chordae implantation are excellent in both children and adults.<sup>8</sup>

PTFE sutures are an excellent material to replace chordae tendinae, appear to be free of adverse effects, and have become a valuable adjunct to the surgical armamentarium to treat mitral and tricuspid valve disease. The remaining technical challenges of neo-chordae implantation are the determination of ideal neo-chordae length, the development minimally invasive off-pump delivery systems and the requirement for direct or video-assisted visualization by the surgeon while implanting the neo-chordae. As such, opportunities exist to standardize and simplify the challenges of fabricating neo-chordae of an ideal length for a specific valve condition, and to establish catheter-based implantation strategies that would avoid the morbidity of an open surgical procedure.

#### *Catheter-Based Leaflet Intervention*

Open-heart surgery is current standard treatment method for patients with severe mitral valve regurgitation; however, it is invasive and is not offered to patients with prohibitive surgical risk on the basis of other comorbidities including liver disease, previous chest surgeries, and advanced age. Newer repair devices based on a catheter delivery model have been





**FIGURE 5.** Catheter-based mitral valve repair procedure. Color Doppler demonstrates severe mitral valve regurgitation (a). 3D transesophageal echocardiography (3D TEE) demonstrates a large coaptation defect (star) between the anterior (AML) and posterior mitral valve leaflets (PML), as viewed from the left atrium (b). MitraClip™ device mounted on its delivery catheter (c). 3D TEE depicts the MitraClip being positioned across the leaflet coaptation defect (d) and immediately after release from the delivery catheter (e). Color Doppler confirms only mild mitral valve regurgitation after MitraClip implantation (f).

developed for approaches to leaflet repair, and for indirect and direct annuloplasty in patients who otherwise do not have a surgical option. The MitraClip™ (Abbott Laboratories, Abbott Park, IL) is the only alternative to mitral valve regurgitation surgery that has been approved by the FDA. MitraClip™ implantation is a catheter-based procedure that mimics the surgical method of edge-to-edge valve repair.<sup>25</sup> The procedure is performed in a cardiac catheterization laboratory in the beating heart, with use of both fluoroscopic and TEE guidance. The implant system consists of two parts: (1) the clip delivery system and (2) the steerable guide catheter. The MitraClip™ device comes in one size with two arms each 8 mm long. A femoral vein approach is preferred, and the device is then advanced from the femoral vein through to the left atrium *via* a trans-septal puncture. The MitraClip™ grasps and coapts the mitral valve leaflets resulting in fixed approximation of the mitral leaflets throughout the cardiac cycle (Fig. 5). The clip itself is made of cobalt-chromium alloy and is covered in polyester to promote the tissue growth around the clip. The arms of the clip device can be adjusted to any position from fully opened, fully inverted, and fully closed. These positions are designed to allow the MitraClip™ to grasp and approximate the leaflets of

the mitral valve using controls on the delivery catheter handle.

The EVEREST (Endovascular Valve Edge-to-Edge Repair Study) II trial randomized 279 patients with moderately severe or severe MR in a 2:1 ratio to percutaneous treatment with the MitraClip™ system (Abbott Vascular; Santa Clara, CA;  $n = 184$ ) or surgical repair/replacement ( $n = 95$ ). At 4 years, patients with mitral valve regurgitation who had repair with the MitraClip™ system experienced mortality rates and mitral regurgitation levels comparable to those of the surgically treated group. Although surgery demonstrated an early advantage in MR reduction and the need for surgical re-intervention, few differences between treatment groups were apparent beyond 1 year.<sup>46</sup>

After 4 years of study follow up, freedom from death occurred in 83% of patients in the MitraClip™ group and 82% in the surgery group ( $p = 0.91$ ) and rates of significant recurrent MR ( $\geq 3+$ ) were not significantly different between the two different treatment groups.<sup>46</sup> Despite this data of similar mortality benefit, the study design has been criticized<sup>13</sup> and concerns have been raised that implantation of a MitraClip™ creates a diffusely fibrotic valve condition that makes any subsequent surgical repair much more difficult.<sup>4,29</sup>

However, recognizing that clinical outcomes with MitraClip™ were superior to medical therapy alone, in October, 2013 the U.S. Food and Drug Association (FDA) approved MitraClip™ use for a subgroup of patients “for the percutaneous reduction of significant symptomatic MR ( $\geq 3+$ ) due to primary abnormality of the mitral apparatus (degenerative MR) in patients who have been determined to be at prohibitive risk for mitral valve surgery by a heart team, which includes a cardiac surgeon experienced in mitral valve surgery and a cardiologist experienced in mitral valve disease”.<sup>26</sup>

#### *Catheter-Based Annular Intervention*

Although surgical plication of the mitral annulus is the standard approach for repair of functional MR, several novel catheter-based therapies have been developed for use in patients with prohibitive surgical risks. Similar to the MitraClip™, these devices for annular repair are also implanted into a beating heart within a closed chest. The approach to annular plication varies by device. The Carillon Mitral Contour System (Cardiac Dimension Inc., Kirkland, WA) takes advantage of the proximity of the coronary sinus to the posterior and lateral mitral annulus. A device is placed in the coronary sinus to create tension that is then transmitted to the annulus with the intended effect of reducing the anterior-posterior annular dimension. The device has a proximal and distal anchor connected by a ribbon that creates tension as the delivery system is adjusted. First and second generations of the Carillon device were studied in the Amadeus and Titan clinical trials respectively.<sup>56,58</sup> Patients who received the device had significant benefits with reductions in quantitative measures of functional MR severity, sustained LV remodeling and improved quality of life. However, this technology does have several important limitations including: (1) Concern for the anatomic distance between the coronary sinus and the mitral annulus in some patients with dilated hearts. This simple anatomic separation means that the device affects a cinch of the left atrial wall and not the mitral annulus thus failing to reduce MR severity; (2) The implication of the close relationship between the coronary sinus and the circumflex coronary artery that can be inadvertently compressed if the artery courses between the coronary sinus and the annulus; and (3) The finding that several patients had fractures of the Nitinol wire ribbon in both clinical trials.<sup>56,58</sup>

While indirect annuloplasty exploits the coronary sinus position, direct annuloplasty devices have also been developed to more closely replicate the surgical approach to annular area reduction. The Mitralign™ system (Mitralign Inc., Tewksbury, MA) takes a retrograde transventricular approach to deliver a suture

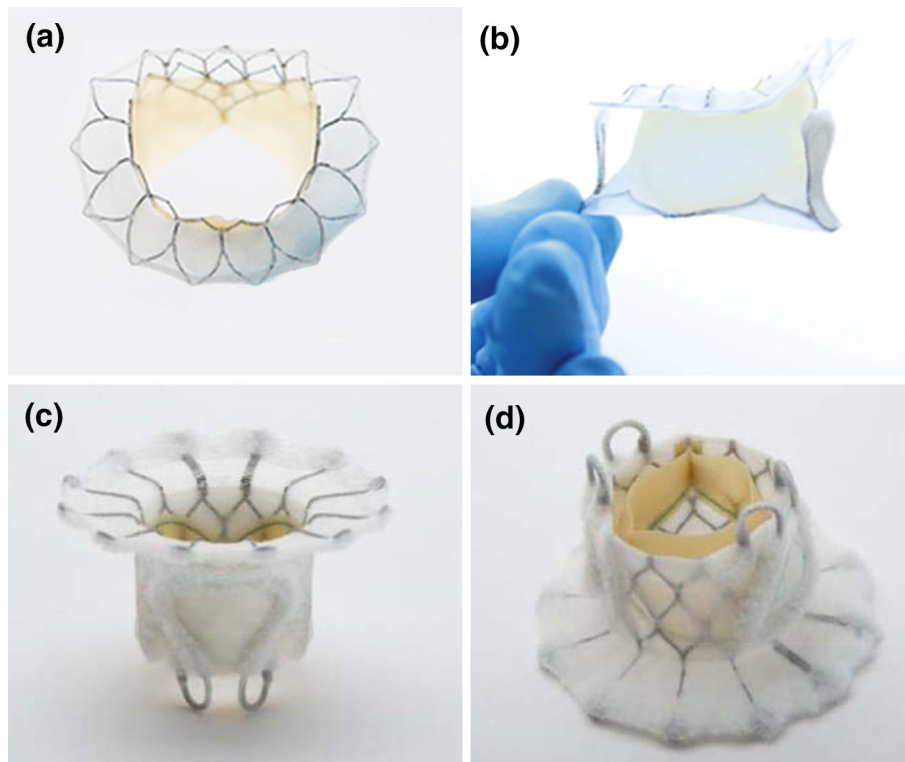
annuloplasty. From the catheter, radiofrequency energy is used to effect guidewire penetration of the mitral annulus from the LV to the left atrium. Then pairs of pledgets are implanted along the medial and lateral aspects of the annulus. When cinched together by a suture the annular area is reduced and the mitral leaflet coaptation area increased. This technology has already been approved in Europe and early clinical experience is encouraging.<sup>44</sup>

#### **TRANSCATHETER MITRAL VALVE REPLACEMENT (TMVR)**

Although percutaneous edge-to-edge mitral valve repair technology has been shown to be non-inferior to open repair in randomized clinical trials, this therapy remains restricted to patients with significant MR and specific mitral valve morphology that are at prohibitive risk for open surgical repair. As such, transcatheter mitral valve replacement (TMVR) is an attractive alternative, which may provide a non-surgical treatment solution to a broad range of mitral valve pathologies, including MV stenosis. Several transcatheter mitral valve implantation technologies, either transapical or transseptal, are in various stages of pre-clinical evaluation.

The FORTIS™ transcatheter mitral valve (Edwards Lifesciences Corp, Irvine, CA) features a cloth-covered self-expanding frame with valve leaflets made from treated bovine pericardial tissue (Fig. 6). The system has been designed to minimize paravalvular leak, and employs a unique anatomical anchoring system. In March 2014, Edwards Lifesciences announced the successful completion of the first three human implants of its FORTIS™ mitral transcatheter heart valve by the Heart Team at St. Thomas’ Hospital in London, UK. This series of implants was performed *via* a transapical approach to allow direct surgical access to the mitral valve complex. The long-term outcome from these interventions has yet to be reported and the FORTIS™ valve is not yet commercially available. Medtronic has also disclosed that it has completed animal studies and is continuing chronic studies using a competing product. Their system is made up of a self-expanding Nitinol frame and a cylindrical, tri-leaflet pericardial heart valve that reportedly has minimum extension into the left ventricle and also preserves the native sub-valvular MV apparatus.

Another valve undergoing evaluation is the Tiara™ mitral valve device (Neovasc, Vancouver, Canada). This device is a self-expanding bioprosthesis with cross-linked bovine pericardial tissue leaflets mounted inside a metal alloy frame (Fig. 6). It is designed to be



**FIGURE 6.** (a) and (b) Tiara™ catheter-based mitral valve replacement system; *adapted with permission from Banai et al. JACC Intv 2014.* (c) and (d) FORTIS transapical mitral valve by Edwards Lifesciences.

implanted using the transapical approach. The pre-clinical experience with this catheter-deployed MV was recently published.<sup>5</sup> Their 3-part preclinical study included: (1) an acute animal model of healthy swine ( $n = 36$ ) which underwent Tiara™ valve implant and followed for at least 90 min; (2) a chronic animal model of sheep ( $n = 7$ ) which were implanted and followed for an average of 150 days; and (3) a human cadaver model where the device was implanted in freshly defrosted human hearts ( $n = 24$ ) from patients with either normal cardiac anatomy or a patient group with a history of valve regurgitation and LV dilatation. The Tiara™ valve was successfully implanted in 29 of the swine (81%). The study authors reported that none of the valves migrated or embolized during or after implantation. Of the animals with successful implantation, all remained hemodynamically stable throughout the procedure. Substantial paravalvular leak was seen only in animals with a mismatch between the mitral valve annulus size and the prosthesis diameters. For the chronic study in sheep, all animals remained clinically stable throughout follow-up. Echocardiographic assessment showed proper valve positioning and alignment. The authors reported mild valvular mitral regurgitation ( $n = 2$ ) and mild or moderate paravalvular leak ( $n = 6$ ), without hemodynamic significance. For implantation in cadaveric human hearts,

the authors reported appropriate geometrical positioning with full circumferential coverage of the atrial aspect of the mitral annulus with good apposition and function of the ventricular anchoring system.

In May 2014, the first results from early clinical experience with the Tiara™ mitral valve system were presented at the annual meeting of the European Association for Percutaneous Cardiovascular Interventions (EuroPCR). Dr. Anson Cheung presented detailed case summaries for 2 patients who had undergone the first human implants of the Tiara mitral valve system in Vancouver, Canada. Both patients were at high surgical risk for open surgical repair of significant MR and received the catheter-based valve replacement under a compassionate use clinical program. Dr. Cheung noted that both Tiara™ implantations resulted in well-functioning prosthetic mitral valves with low ( $< 3$  mmHg) trans-valvular gradients and without paravalvular regurgitation, left ventricular outflow tract obstruction, compression of the circumflex artery, or conduction abnormalities.<sup>5</sup> Both procedures were described as straightforward and relatively short in duration.

Although these early experiences are encouraging, the technical and delivery challenges of catheter-based MV therapies are not trivial. The anatomic challenges include: the variable size and incomplete (or non-



existent) calcification of the mitral annulus, the potential for any mitral prosthesis to obstruct the LV outflow tract, and the need to displace native MV leaflet tissue which may be excessive (i.e., myxomatous) or calcified and degenerative. The functional challenges include: the need to maintain stability while ensuring cyclical native annulus movement, and the requirement for valve competency under many varied hemodynamic flow rates and pressures. While the development of catheter-based MV therapies are well underway, the inherent complexity of MV disease will likely mandate a slower evolution of devices and delivery systems than was experienced during the development of transcatheter aortic valve replacement (TAVR) technologies.

## CONCLUSIONS

Presented here is a review of the currently available technologies for mitral valve repair and replacement. There are multiple mechanisms of mitral valve disease, and the valve itself is a complex organ whose function significantly relies on interdependence with the LV, making repair and replacement challenging. A large volume of work will continue into optimizing the management of mitral valve disease.

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