Transcatheter Mitral Valve Replacement and Repair Technology

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A Senior Thesis submitted in partial fulfillment
of the requirements for graduation
in the Honors Program
Liberty University
Spring 2020

Acceptance of Senior Honors Thesis

This Senior Honors Thesis is accepted in partial
fulfillment of the requirements for graduation from the
Honors Program of Liberty University.

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Abstract

The mitral valve is a two-cusp valve that is located between the left atrium and left ventricle of the heart. As blood flows from the lungs and enters the atrium, it must pass through this valve in one direction to enter the ventricle and be pumped out to the systemic circuit.

Mitral valve disease occurs when normal mitral valve function is impaired. Many different repair and replacement options exist. These options are contingent upon age and risk factors for patients. This paper focuses on the four main transcatheter mitral valve replacement devices that have limited human trials. It concludes that while the technology serves a niche purpose in the status quo, much greater progress will need to be made to make it the prevailing technological procedure to treat heart valve disease in the United States and worldwide.

Background

The mitral valve is a two-cusp valve that is located between the left atrium and left ventricle of the heart. As blood flows from the lungs and enters the atrium, it must pass through this valve in one direction to enter the ventricle and be pumped out to the systemic circuit. Mitral valve disease occurs when normal mitral valve function is impaired (Yoon et al., 2017). The natural (human or patient) heart valves are incredibly designed structures, able to open and shut over a few billion times during a normal lifetime while withstanding substantial pressure gradients. Tissue leaflets are comprised of three thin layers of extra-cellular matrix with proteoglycans. This provides the leaflets with both flexibility and strength that allows them to open easily and softly yet still close with enough rigidity to prevent regurgitation. (Kheradvar et al., 2014). The most common types of the disease are stenosis and regurgitation. Each of these conditions causes the heart to pump a lower amount of blood out of the left ventricular chamber, leading to symptoms of fatigue, shortness of breath, coughing, and lightheadedness. A population-based study in 2006 estimated that 2.5% of the total population in the United States has valvular heart disease. Based on the 2000 census, this would put the population prevalence estimate between 4.2 and 5.6 million adults. According to worldwide estimates of valvular heart disease, there are more than 100 million people affected by valvular diseases yearly. Of these valvular diseases, mitral regurgitation is the most common. In the United States, about 40,000 mitral valve replacements occur each year (Yoon et al., 2017). Older age was the biggest risk factor for all valvular disease. Over six percent of patients above the age of sixty-five have mitral regurgitation, for example. For mitral regurgitation and stenosis, biological sex did not play a

significant factor in prevalence (Nkomo et al., 2006). Remedies for mitral regurgitation and stenosis will be focused on primarily for the technology analyzed in this paper.

Mitral Regurgitation and Classifications

Mitral regurgitation is the most common form of valvular heart disease in the United States. About 10% of individuals above the age of 75 years are affected by mitral regurgitation in western countries (Del Val et al., 2019). Regurgitation is typically due to coronary disease and termed ischaemic or is non-ischaemic. The mitral valve has two leaflets (anterior and posterior). The posterior leaflet is shorter but has a greater circumference than the anterior leaflet. Severity of regurgitation is classified by the freedom of movement these leaflets have. Carpentier's classification classifies normal valve movement as type I, type II as excess movement and type III as restrictive movement. Prolapse occurs when type II excessive movement occurs with a billowing mitral leaflet or eversion of the leaflet up into the atrium. Measurements are taken of the effective regurgitant orifice (ERO) regurgitant volume (Enriques-Sarano et al, 2009). Primary mitral regurgitation is degenerative and leads to valve prolapse. Functional regurgitation or secondary mitral regurgitation results in annular expansion and issues with tethering of valve leaflets (Kheradvar et al., 2015). Consequences of regurgitation include high atrial pressure, which leads to potential heart failure and hypertension in the lungs. Some typical physical symptoms of regurgitation include an erratic apical impulse, loud heart murmurs, and cardiomegaly. This is determined primarily through doppler echocardiography, transthoracic echocardiography and transesophageal echocardiography (Enriques-Sarano et al, 2009). Patients with severe mitral regurgitation have a mortality rate 6.3% higher than normal (Nishimura et al., 2016).

Doppler echocardiography allows for determination of mitral heart stroke volume, left-ventricular volume, and flow measurements. After measurement by echocardiography, an ERO of 20-39 mm^2 and a regurgitant volume of 30-59 mL is considered moderate severity. An ERO above 40 mm^2 and regurgitant volume above 60 mL is considered severe (Enriques-Sarano et al., 2009). In the past, transesophageal echocardiography was utilized less as transthoracic echocardiography was preferred. However, the advent of new real-time three-dimensional transesophagael echocardiography technology has greatly improved surgical teams' ability to carry out preliminary checks and analysis for valve implantation procedures (Omar et al., 2019). Physical cardio exercise tests such as supine-biking test peak oxygen consumption under physical strain (Enriques-Sarano et al., 2009). Primary mitral regurgitation occurs when the mitral valve leaflets degenerate and are elongated. These leaflets push back into the atrium and cause regurgitation. Secondary mitral regurgitation affects the left ventricle itself. While the leaflets are unaffected and the same as normal physiology, the myocardial wall thins, the orifice of the valve or annulus is dilated, and this leads to a loss of leaflet coaptation. Medical therapies for secondary mitral regurgitation include angiotensin inhibitors, beta blockers, and aldosterone antagonists.

There are multiple factors that influence a decision for therapy when mitral regurgitation is discovered. A study that examined the characteristics of patients with mitral regurgitation to determine whether they should receive surgery or not examined 396 symptomatic patients in Europe with isolated mitral regurgitation. The average age of patients analyzed was 66 years. In the study, 51% of patients were operated on. Of those 135 that had surgery, 79 of them (59%)

had a valve replacement and 56 of them (41%) had a valve repair. As Mirabel et al. (2007) analyzed their findings, they determined that:

> Surgery was denied more frequently in older patients, in those with congestive heart failure, diabetes, and comorbidity as attested by a higher comorbidity Charlson index, Patients with ischaemic MR were more often considered candidates for surgery than those with non-ischaemic, in particular degenerative, MR. Patients were more frequently denied surgery when LVEF was <60% and MR was graded 3/4 vs. 4/4 (p.1361).

For the age factor, patients in the age range between 60-70 at the highest amount of operations. For the Charlson comorbidity index, the percentage for operating dropped by approximately 20%, 15%, and 5% for each additional comorbidity. This index predicts mortality within the year of a patient with pre-existing conditions. Under a multivariable analysis, lower left ventricular ejection fraction, non-ischaemic causes, increased age, higher severity of regurgitation (grade 3), and a higher Charlson comorbidity index were the five factors that led to a failure to operate (Mirabel et al., 2007). A classification for patients that is important to define is the New York Heart Association classifications. Class I is for patients that experience a lack of issues with their normal physical activity. Class II is for patients with cardiac disease that experience slight limitations to normal physical activity. These symptoms could include fatigue, dyspnea, angina, or palpations. Class III is for patients with cardiac disease who have class II symptoms such as fatigue, dyspnea, angina, or palpations after little physical activity. Class IV is for patients with cardiac disease that cannot participate in any physical activity (Resnik and Resnik, 2018). Most patients with severe mitral regurgitation fall under the NYHA class III and IV categories.

Mechanical Valves

While porcine valves were primarily utilized in the past, the majority of valves today utilize bioprosthetic bovine valves. One reason is that bovine valves have proven to have less left ventricular output obstruction (Ben-Shoshan et al., 2019). Mechanical, non-biologic prosthetic valves also typically require patients to be on anticoagulant medicines for the rest of their lives and this increases risk for both hemorrhages and thromboembolisms. Due to the fact that biological prosthetic valves degenerate faster, they are usually recommended for an older age range than the longer-lasting mechanical valves. A study sponsored by Stanford University in California analyzed mortalities of patients who received biological prosthetic mitral valves and mechanical mitral valves. Till 30 days, the mortality of patients 40-49 years of age was higher with biological prosthetic valve implantation. The other age range comparisons did not have a significant difference. When longer-term mortality was analyzed (After 15 years), patients between 40-49 years of age and 50-69 years of age had a higher mortality rate of 44.1% instead of 27.1% for the 40-49 age range and 50.0% instead of 45.3% for the 50-69 age range. Among the 70-79 age range the mortality rates did not differ significantly between the type of valves (less than 1% difference) (Goldstone et al., 2017). The study by Goldstone et al (2017) concluded that:

> Mechanical mitral valves were associated with lower mortality than biologic valves among patients up to 70 years of age, whereas the benefit of a mechanical aortic valve disappeared by 55 years of age. In both cases, the implantation of a mechanical prosthesis was associated with a significantly lower risk of reoperation than was the implantation of a biologic prosthesis; however, mechanical valves were associated with a higher risk of bleeding and, in some age groups, stroke (p. 1857).

This study challenges an over-reliance on bioprosthetic valves, especially when determining potential therapies for younger patients.

Mechanical mitral valves are durable and more applicable in cases of younger patients. The majority of mechanical valves designed are comprised of a ring that encircles two semicircular disks with two leaflets (Figure 1). The largest issue with mechanical valves is coagulation and thromboembolism. Specific materials such as pyrolytic carbon and composite graphite are chosen to prevent blood clot formation. This is important as the largest risk factor

Figure 1: Examples of mechanical mitral valves from the major manufacturers (Kheradvar et al., 2015).

for mechanical valves is coagulation and thromboembolism. Additionally, many of these designs are extremely old. For example, the original St. Jude Medical mechanical valve was first utilized in 1977. This valve features a torque rotation mechanism and a sewing cuff that allows for easy installation. The Medtronic Open Pivot mechanical valve has the distinctive feature of passive washing by allowing a small amount of blood to flow at all times to diminish thrombus accumulation. (Kheradvar et al., 2015). The Sorin group valves boasts a lower rate of thromboembolism in studies when compared to other mechanical valves. The On-X Life

Technologies valve boasts flexibility of sizes and the valve's sewing ring allows it to be easily anchored to the radius of an annulus that may be a larger size. Unfortunately, patients are required to take blood-thinners and anti-coagulants such as warfarin for the rest of their lives after having mechanical valve implantations. Mechanical designs also are louder and have caused disturbances and a lack of comfort to patients, although manufacturers have worked to reduce sound levels eventually through more effective sound dampening in the newer iterations of their technologies. Newer technologies such as computational fluid dynamics and new 3D geometry programs have allowed engineers to test potential mechanical valve hemodynamic performance. With this analysis, engineers are targeting improvements to hinge points in the valve that cause flow friction as well as testing new polymers to coat valves with to reduce thromboembolism. However, while these improvements will be made, these valves will still be utilized less than bioprosthetic mitral valves, especially as technology advances. Ultimately, the need for open heart surgery to implant these valves still rules out a significant portion of patients who are at high risk for surgery (Kheradvar et al., 2015).

Bioprosthetic Valves

In contrast to the mechanical valves, bioprosthetic porcine or bovine pericardium valves have preferable hemodynamics and reduce thromboembolism significantly so that patients are not required to take anticoagulants for the rest of their lives. However, durability is lacking and within 10 years 30% of patients require replacement procedures. Within 15 years, 50% of patients require replacement procedures. Edwards Lifesciences valves are porcine valves that have low reoperation rates for older patients (Figure 2). Medtronic's Mosaic Ultra is a similar porcine valve with the distinguishing feature of having a unique cinch implantation system that

allows the procedure to be less invasive. St. Jude Medical's valve systems have preferable durability for younger patients and have treatments that limit calcification. Sorin's Pericarbon More valve has its own propriety coating that effectively reduces mitral disease (Kheradvar et al., 2015). While these valves are preferable to the mechanical valves for higher age ranges due to the decreased risk of thromboembolism, the need for open surgery still inhibits their use and transcatheter mitral valve replacement must be investigated further (Kheradvar et al., 2015).

Figure 2: Examples of bioprosthetic mitral valves from each major manufacturer.

Transcatheter Mitral Valve Repair

While roughly half of the patients are operated on, what can be done for the other half of patients who have too many traditional risk factors with severe mitral regurgitation? Many transcatheter mitral valve repair and replacement technologies have been developed in recent years to serve as a less invasive, less risky alternative to traditional surgery. The only repair system that has been approved by the United States FDA (Food and Drug Administration) is the MitraClip by Abbott Labs. This device clips the anterior and posterior leaflet together in the middle, forming two openings instead of one. It is approved for patients with severe, primary mitral regurgitation who are at high risk for surgery. Surgical repairs such as annuloplasty

correct ventricular dilation. This has not been shown to be very effective, as most patients require surgery within the next year and mortality rates remain high. When the MitraClip is used for secondary mitral regurgitation, there are better results than typical surgery for regurgitation after 1 year. However, it has not been proven that any procedures to correct secondary mitral regurgitation improve long-term outcomes (Nishimura et al., 2016).

Transcatheter Mitral Valve Replacement

While the MitraClip is effective at repairs for primary mitral regurgitation, there is a need for full replacement in many cases. In a review carried about by Del Val et al (2019), 11 transcatheter mitral valve replacement systems were analyzed in 308 patients. The 11 valve replacement technologies tested were: AltaValve by 4C medical, Caisson TMVR by LivaNova, CardiAQ Valve by Edwards Lifesciences, CardioValve by CardioValve, Fortis by Edwards Lifesciences, HighLife Mitral Valve by HighLife SAS, Intrepid TMVR by Medtronic, MValve System by MValve Technologies, Tiara by Neovasc, Sapien M3 by Edwards Lifesciences, and Tendyne by Abbott (Figure 3).

There are a few distinguishing factors between these devices in design and features offered. The majority utilize a self-expanding nitinol frame and bovine leaflets instead of porcine. The anchoring mechanisms vary between external anchors, annular frames, ventricular anchors, and a few other custom systems. The delivery and access points for the majority of the valves utilize a transapical approach, with a few being transfemoral. Sizes of valves range from 29-50 mm. In the study of these valves conducted by Del Val et al. (2019) the baseline characteristics of patients were as follows:

The mean age of the patients was 75 years (range: 69–81 years), and 65.9% of patients were men. Most patients (81.5%) were in New York Heart Association (NYHA) class III or IV, and almost half (47.2%) exhibited at least 1 episode of heart failure hospitalization within the year before the TMVR procedure. The mean Society for Thoracic Surgery Predicted Risk of Mortality (STS-PROM) score was 7.7±0.8%, ranging from 6.14% to 8.6%. Severe comorbidities were frequent, including coronary artery disease (70.3%), prior coronary artery bypass grafting (44.2%), chronic renal insufficiency (60.3%), and atrial fibrillation (55.2%). Mean left ventricular (LV) ejection fraction was 42±4% (range: 30–46%). The indication for TMVR was predominantly secondary (functional) or mixed severe MR (87.1%), and 36 patients (12.9%) were diagnosed with primary MR (Del Val et al., 2019).

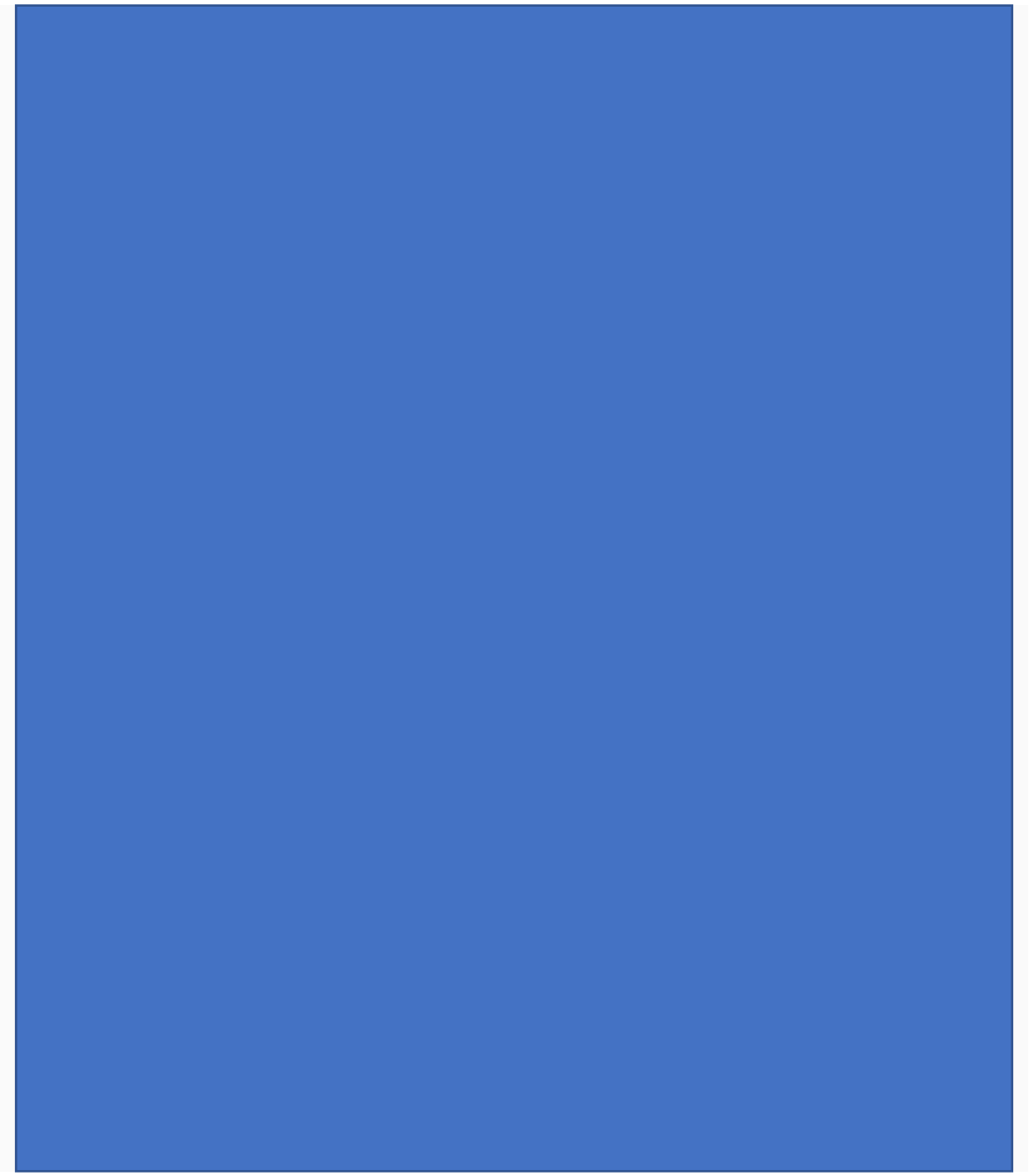

Figure 3: Transcatheter mitral valve replacement (TMVR) devices. **A**, AltaValve, 4C Medical with **B**, it's fluoroscopic image. **C**, Caisson TMVR, LivaNovaand **D**, fluoroscopic image. **E**, CardiAQ Valve, Edwards Lifesciences and **F**, Fluoroscopy image. **G,** CardioValve, Dr. Maisano,

Heart Center University Hospital, Zurich, Switzerland, and **H**, fluoroscopic image. **I**, Fortis, Edwards Lifesciences, and **J**, fluoroscopic image. **K**, HighLife Medical valve, HighLife SASand **L**, fluoroscopic image. **M,** Intrepid TMVR, Medtronic, and **N**, fluoroscopy image. **O**, MValve System and **P**, fluoroscopic image. **Q**, Tiara, Neovasc Medical Inc. and **R,** fluoroscopic image. **S**, Sapien M3 System, Sapien and **T**, fluoroscopic image. **U**, Tendyne, Abbott Labs, and **W**, fluoroscopic image. (Del Val et al., 2019).

A transapical approach was utilized for 81.5% of patients for the valve replacements with a technical success rate of 91.7%. Malposition or migration of the valve was present for 4.2% of total patients. Thrombosis and acute valve dysfunction occurred in 1.7% and 0.8% of patients respectively. Open heart surgery was then necessary for 11 or 4.0% of patients. The mortality rate was 4.6% (Table 1).

When analyzing the overall results, the technical success was high (92%), and regurgitation was less in severity after the majority of procedures. However, the mortality rate of 13.6% after the replacement procedure was high. This was attributed by the study to comorbidities, the presence of secondary mitral regurgitation, and human error from these procedures being new (Del Val et al., 2019). Based on which valve was used, the Tendyne system by Abbot Labs was utilized the most with a hundred case sample test size. The Tiara and Intrepid systems had 58 and 50 procedures, respectively. The Tendyne system had the lowest procedural mortality at 0%, high technical success rate at 97%, low post-procedure severe mitral regurgitation at 1%, 8% acute kidney injury, and higher bleeding rates at 20%, and no other significant issues. The Tiara system by Neovaschad 95% technical success, 0 mortalities, 5% of cases converted to open heart surgery, 1 case with post-procedural severe mitral regurgitation,

and 32.4% of cases with acute kidney injury, and no other significant issues (Meredith et al., 2016). The Intrepid system had 98% technical success, 6% mortality rate, 18% of cases with bleeding, no cases that required a conversion to open heart surgery, 10% of cases with acute kidney injury, and no other significant issues (Table 1). The system has a bovine cross-linked leaflets inside a metal frame (Kheradvar et al., 2015). For delivery, the left ventricular apex is cut into with a needle puncture. A wire is traced through to follow and the system is inserted and positioned with the mitral annulus, and then the anchors are released (Reguiero et al., 2017). Few human tests have been carried out for the valve, and further studies have to be done to determine overall effectiveness of the valve (Kheradvar et al., 2015).

The Intrepid system by Medtronic has been studied in multiple reports of studies. It has a nitinol valve, is delivered transapically, and has an atrial brim to place the device, along with an outer and inner stent frame. The outer frame fixates to the annulus and the bovine valve is in the inner frame. The symmetric valve pushes against the annulus with its cork-like shape and fills the D-shaped mitral annulus. This is the distinguishing feature of this specific valve design (McCarthy et al., 2019).

Delivery through a 35-F catheter is performed while the patient is under general anesthesia and is guided by transesophageal echocardiography and computed tomography. After the catheter is

Table 1: Procedural and 30-Day Clinical Outcomes

	AltaValve	Caisson	CardiAQ	CardioValve	Fortisa	HighLife	Intrepid	MValve System	Tiara	Sapien M3	Tendyne	Global Cohortb
All-cause 30-d mortality	0/1 (0.0)	2/11 (18.2)	7/26 (26.9)	3/5 (60.0)	5/13 (38.5)	3/15 (20.0)	7/50 (14.0)	1/1 (100)	6/58 (10.3)	0/15 (0.0)	6/100 (6.0)	40/295 (13.6)
Procedure-related mortality	0/1 (0.0)	NA	3/26 (11.5)	1/5 (20.0)	4/13 (30.8)	2/11 (18.2)	3/50 (6.0)	NA	0/59 (0.0)	0/15 (0.0)	0/100 (0.0)	13/280 (4.6)
Technical success	1/1 (100)	18/23 (78.3)	22/26 (84.6)	5/5 (100)	10/13 (76.9)	8/11 (72.7)	48/49 (97.9)	1/1 (100)	56/59 (94.9)	13/15 (86.7)	97/100 (97.0)	278/303 (91.7)
Procedure time, min	NA	177 ±65	NA	43.6±13.1	123±27	NA	100 (80–124)	NA	82 (60–155)	189 ±100	136.1±36.3	121.4 (43.6–189)
Approach												
Transfemoral		23/23 (100)	14/26 (53.8)	5/5 (100)						15/15 (100)		57/308 (18.5)
Transapical	1/1 (100)		12/26 (46.2)		13/13 (100)	15/15 (100)	50/50 (100)	1/1 (100)	59/59 (100)		100/100 (100)	251/308 (81.5)
Conversion to open heart surgery	0/1 (0.0)	4/23 (17.4)	NA	NA	2/13 (15.4)	2/11 (18.2)	0/50 (0.0)	NA	3/59 (5.1)	0/15 (0.0)	0/100 (0.0)	11/272 (4.0)
LVOT obstruction	0/1 (0.0)	0/17 (0.0)	NA	0/5 (0.0)	0/13 (0.0)	1/15 (6.6)	0/50 (0.0)	NA	0/58 (0.0)	0/15 (0.0)	0/100 (0.0)	1/274 (0.4)
Device embolization or migration	0/1 (0.0)	0/17 (0.0)	NA	NA	0/13 (0.0)	NA	0/50 (0.0)	NA	2/58 (3.4)	0/15 (0.0)	0/100 (0.0)	2/254 (0.8)
Malposition	0/1 (0.0)	NA	1/13 (7.7)	NA	1/13 (7.7)	NA	1/50 (2.0)	NA	3/59 (5.1)	NA	2/100 (2.0)	8/236 (3.4)
Moderate or severe MR	0/1 (0.0)	1/11 (9.1)	0/26 (0.0)	0/5 (0.0)	0/13 (0.0)	0/15 (0.0)	0/50 (0.0)	NA	1/37 (2.7)	1/15 (6.6)	1/100 (1.0)	4/273 (1.5)
Valve dysfunction	0/1 (0.0)	NA	NA	NA	0/13 (0.0)	0/11 (0.0)	0/50 (0.0)	NA	NA	1/15 (6.6)	0/100 (0.0)	1/190 (0.5)
Device thrombosis	0/1 (0.0)	NA	NA	NA	1/13 (7.7)	1/15 (6.6)	0/50 (0.0)	NA	NA	NA	1/100 (1.0)	3/179 (1.7)
Stroke	0/1 (0.0)	0/11 (0.0)	NA	NA	0/13 (0.0)	0/15 (0.0)	2/50 (4.0)	NA	2/37 (5.4)	1/15 (6.6)	2/100 (2.0)	7/242 (2.9)
Bleeding	0/1 (0.0)	0/11 (0.0)	1/13 (7.7)	1/5 (20.0)	0/13 (0.0)	NA	9/50 (18.0)	NA	NA	0/15 (0.0)	20/100 (20.0)	31/208 (14.9)
Access site complication	0/1 (0.0)	0/11 (0.0)	NA	1/5 (20.0)	NA	NA	0/50 (0.0)	NA	4/58 (6.9)	0/15 (0.0)	1/100 (1.0)	6/240 (2.5)
Acute kidney injury	0/1 (0.0)	NA	NA	NA	2/13 (15.4)	NA	5/50 (10.0)	NA	12/37 (32.4)	1/15 (6.6)	8/100 (8.0)	28/216 (13.0)
Mean transmitral gradient, mm Hg	NA	3.1	NA	4.4	3±1	NA	4.1±1.3	NA	NA	5.53±2.2	3.0±1.1	3.5 (3.0–5.53)
Length of stay, d	9	NA	NA	NA	10±6	NA	NA	NA	NA	6.3 ±3.2	11.1±8.7	10.4 (6.3–11.1)

Values are mean±SD or n/N (%) except as noted. LVOT indicates left ventricular outflow tract; MR, mitral regurgitation; NA, not available.
[a] In late 2015, Edwards Lifesciences stopped the Fortis program. The valve is not currently available.
[b] Values are weighted mean (range) or n/N (%).

guided into the left atrium, a hydraulic mechanism expands the outer brim of the device to lock it into place and the valve is deployed. Baseline characteristics for the study by Bapat et al. (2018) for 49 patients were as follows:

> 43 patients (86.0%) having NYHA functional class III or IV symptoms, and hospitalization for heart failure having occurred within the prior year in 29 patients (58%). Severe comorbidities were frequent; overall, the Society for Thoracic Surgery Predicted Risk of Mortality was 6.4 ± 5.5% … MR, as assessed by the echocardiographic core laboratory, was severe in 47 patients (95.9%), with the predominant mechanism classified as either secondary (n = 42; 84%) or primary (n = 8; 16%) MR. Two patients were treated initially for severe MR, and were subsequently determined to have moderate severity during further formal review. Overall, the mean left ventricular ejection fraction at baseline was 43 ± 12% (range: 20% to 70%); only 15 of 49 patients (30.6%) had a left ventricular ejection fraction >50% (p. 16).

After the procedures, a total of 7 mortalities were reported. Mitral regurgitation was significantly reduced in severity of classification and symptoms for all patients. Successful implantation of the valve occurred in 98% of the patients. Chest wall bleeding post-procedure was present in 18% of patients. This was linked to an overuse of anticoagulant medication. The design of the valve was effective as the anchor self-centered and the inner stent with the bovine valve was flexible and adaptable to differing heart conditions. Due to its smaller size, the Intrepid valve may be preferable for patients that have small ventricular size such as women (Bapat et al., 2018). The adaptability of the inner stent containing the bovine valve in the Intrepid valve allowed the valve to work for a greater majority of patients. In the APOLLO trial for the Intrepid valve that targeted 1380 patients, one significant issue was with bleeding due to retrieval issues from the transapical approach. A transfemoral vein approach and delivery was suggested to improve outcomes with the Intrepid valve (McCarthy et al., 2019). The CardiAQ valve system can be

used with both transfemoral and transapical delivery. The frame anchors to the annulus without radial force and protects the leaflets in a nitinol frame. Out of all the valves, the CardiAQ valve system, the Tiara valve system, the Intrepid valve, and the Tendyne valve are the only valves that have human implantation trials. The FORTIS valve by Edwards Lifesciences was also implanted, but that valve has been discontinued. Because these valves are the only valves with human implantation trials, their study results will be explored further by this paper.

Tendyne Valve by Abbot Labs

The Tendyne valve by Abbott Labs had exceptional success and mortality rates in the Del Val et al (2019) study that compared multiple valves. Unlike the Intrepid valve by Medtronic, the Tendyne valve utilizes a trileaflet porcine valve (Figure 1). The Tendyne valve has a unique tether component that is anchored to an epicardial hemostatic pad. A transapical approach is utilized for deployment with computed tomography and transesophagael echocardiography. A 36F catheter delivery sheath is guided to the atrium. In an analysis of clinical outcomes for 30 patients studied in the Tendyne Global Feasibility Study 29 (93.3%) of patients had technical success. Mitral regurgitation was eliminated for 25 patients and was reduced to mild severity in one. At 30 days, the rate of success was 86.6%. Mitral annular calcification is a severe condition wherein the support of the mitral valve degenerates and brings many difficulties for mitral valve replacement. It is common in those over 70 years old and can cause embolism and strokes as well as regurgitation, prolapse, atrial fibrillation, and other cardiac risk factors (Atar et al., 2003).

Figure 4: Tendyne Valve. Figure of the valve itself, the fluoroscopy picture, and the transesophagael ecocardiography looking into the ventricle.

The Tendyne valve is uniquely suited for patients with mitral annular calcification. As Niikura et al (2019) studied:

> The Tendyne valve has unique advantages for the treatment of patients with severe MAC, with its D-shaped anatomic configuration, ability to retrieve and be repositioned (reducing the risk of LVOT obstruction), robust anchoring system consisting of a tether connected to an epicardial pad (reducing the risk of embolization), and sealing skirts (reducing paravalvular regurgitation). In 2017, the authors reported the first experience of successful TMVR for severe MAC with the compassionate use of the Tendyne valve and demonstrated the feasibility of safe and effective therapy for these high-risk patients (p. 298).

These preliminary studies show promise for the valve. Another study of the Tendyne valve that analyzed left ventricular (LV) output of 36 patients who had the Tendyne implanted concluded that the ventricle had successful re-shaping after implantation. According to the study of Fukui et al., (2020):

> A total of 36 patients (median age 74 years; interquartile range [IQR]: 69 to 78 years; 78% men; 86% with secondary mitral regurgitation) were included in this study. There were significant decreases in LV end-diastolic volume (281 ml [IQR: 210 to 317 ml] vs. 239 ml [IQR: 195 to 291 ml]; $p < 0.001$), LV ejection fraction (37% [IQR: 31% to 48%] vs. 30% [IQR: 23% to 40%]; $p < 0.001$), LV mass (126 g [IQR: 96 to 155 g] vs. 116 g [IQR: 92 to 140 g]; $p < 0.001$), left atrial volume (171 ml [IQR: 133 to 216 ml] vs. 159 ml [IQR: 125 to 201 ml]; $p = 0.027$), and global longitudinal strain (−11% [IQR: −17% to −8%] vs. −9% [IQR: −12% to −6%]; $p < 0.001$) from baseline to 1-month follow-up. Favorable LV end-diastolic volume reverse remodeling occurred in the majority (30 of 36 patients [83%]). Closer proximity of the Tendyne apical pad to the true apex (24 mm [IQR: 21 to 29 mm] vs. 35 mm [IQR: 26 to 40 mm]) was predictive of favorable remodeling ($p = 0.037$) (p. 2046).

The Tendyne implantation is a transapical approach with a mini thoracotomy to the left ventricle. A 0.035-inch guidewire is delivered with a balloon-tipped catheter to the left atrium and the 36-F catheter over that. The valve expands into annulus and is carefully positioned to allow the D-shaped outer shell to be aligned with the annulus. After the valve is in place, the apical tether is connected to the epicardium (Reguiero et al., 2017). Further studies have to be carried out with

larger sample sizes in order to know if the Tendyne valve can be the best solution for a larger majority of patients with primary and secondary mitral regurgitation.

	CardiAQ-Edwards	Neovasc Tiara	Tendyne	Intrepid TMVR
Valve shape	Circular	D-shaped	D-shaped (outer stent) Circular (inner frame)	Circular
Frame	Nitinol, self-expandable	Nitinol, self-expandable	Nitinol, double frame; Self-expandable	Nitinol, double stent; Self-expandable
Anchoring mechanism	Mitral annulus capture with native leaflet engagement	Fibrous trigone capture with native leaflet engagement	Apical tether	Radial force and subannular cleats
Leaflets	Trileaflet Bovine pericardium	Trileaflet Bovine pericardium	Trileaflet Porcine pericardium	Trileaflet Bovine pericardium
Valve position	Supra-annular	Intra-annular	Intra-annular	Intra-annular
Access	Transapical Transseptal	Transapical	Transapical	Transapical
Delivery system size	33-F	32-F	36-F	35-F
Recapture	No	No	Fully recapturable system after complete deployment	No
Valve size(s)	30 mm	35 mm and 40 mm	Outer frame ranges from 30–43 mm in the SL dimension and 34–50 mm in the IC dimension	27 mm with 3 outer stent sizes (43, 46, and 50 mm)
Additional features	Supra-annular position Intra-annular sealing skirt Tapered outflow	2 anterior and 1 posterior anchoring structures	Single inner valve size; Multiple outer frame sizes	Dual stent design; Outer frame provides fixation and isolates the inner stent

TABLE 2 Continued

	Caisson	HighLife TMVR	MValve system	NCSI NaviGate Mitral
Valve shape	D-shape	Circular	-	Circular
Frame	2 components (anchor and valve); Nitinol, self-expandable.	2 components (ring and valve); Nitinol, self-expandable	Dock system to be used with commercially available valves	Nitinol, self-expandable; Xenogeneic pericardium
Anchoring mechanism	External anchor; Mitral annulus capture with engagement at subannular fibrous groove	External anchor; Valve in subannular mitral ring	External anchor; Mitral annulus capture	Annular winglets
Leaflets	Trileaflet Porcine pericardium	Trileaflet Bovine pericardium	-	Trileaflet
Valve position	Supra-annular		-	
Access	Transseptal	Transapical (Transfemoral artery for loop placement)	Transapical	Transapical, transatrial or transfemoral
Delivery system size	31-F	NA	32-F	30-F
Recapture	Fully recapturable and retrievable	No	Fully retrievable	NA
Valve size(s)	35–40 mm	31 mm	NA	Inflow/outflow: 30 mm/36 mm; 30 mm/40 mm; 33 mm/44 mm
Additional features	SAM Management feature 1 delivery catheter for each system (anchor and valve)	NA	Universal dock system	NA

IC = intercommissural; NA = not available; SAM = systolic anterior motion of the mitral valve; SL = septal-lateral; TMVR = transcatheter mitral valve replacement.

Figure 5: Current TMVR Summary of Features. (Reguiro et al., 2017)

While final valve comparisons are difficult to find due to a small sample size for trials for each valve, there are some distinguishing factors that set apart a few technologies (Figure 5). From the studied analyzed in this paper, the D-shape valves provided better left ventricular output and seemed preferable. While many different valves had differing anchoring mechanisms, the apical tether utilized by the Tendyne valve made noticeable improvements to valve stability. While the Tendyne valve was the only valve of the four human-tested valves (CardiAQ, Tiara, Tendyne, and Intrepid) in the study to use a porcine pericardium trileaflet instead of bovine pericardium, it had comparable regurgitation levels. Another significant difference between the valves discussed in this paper is that the Tendyne valve is the only device capable of being fully recaptured. This ease of use allows for surgical adjustments and corrections to be carried out. In the status quo, the durability of bioprosthetic transcatheter mitral valves are still not enough to justify use for younger age groups. Due to this lack of durability, repeated procedures occur frequently. The ability to recapture the system provides for this concern. Finally, the adjustable outer valve sizes offered by the Tendyne valve and Intrepid TMVR valves allow for more flexibility for patients that have differing annulus shapes and sizes.

Future Consideration

In an ideal world, a mitral valve replacement should have no left ventricular obstruction, no transvalvular gradient, low rates of infection, no embolization, durability, good hemodynamics, and the ability to expand and grow if needed for children. Due to the fact that in the status quo this has yet to be realized, valve replacement therefore merely replaces native

primary or secondary mitral valve regurgitation with a prosthetic valve. This situation currently requires much flexibility for surgical teams. As Maisano et al (2015) stated:

> Due to the wide anatomical variability of MR, physicians dedicated to transcatheter mitral interventions will likely need to develop expertise with more than one device. Most TMVRep approaches will require advanced imaging and specific skills,[36,37] which may limit their uptake, when compared with TVMI. Learning curve is longer in repair, similar to surgery,[38,39] and outcomes can be less predictable in the early operator/centre experience (p. 1655).

In the last 15 years, this technology has grown slowly to what it is now, so it is likely that similar rates of growth will take place and it will take much more time for the technology to be optimized. Regarding the future focus of transcatheter mitral intervention, Maisano et al (2015) stated:

> Transcatheter mitral interventions are the natural evolution of modern mitral valve surgery; in the future, the indications may continue to move from a palliative target (improving symptoms, treating advanced and end-stage disease), towards the aim of improving prognosis. Early repair can restore life expectancy in DMR patients and lead to reverse remodelling in FMR patients.[21,43,51] Outcomes tend to be poor if mitral valve surgery is excessively delayed, and it is likely that transcatheter mitral procedures may similarly be unable to impact the prognosis if unduly postponed (p. 1656).

While many important studies and discussion can be done to invent the most ideal transcatheter repair or replacement technology, it is of utmost important to continue to focus on preemptive solutions and solving the problem before the worst-case possible scenario occurs. This is done

through palliative care that must begin with lifestyle changes. Education on a variety of topics such as diet, exercise, or substance abuse, can promote heart healthiness that lessens strain on the heart in a variety of ways. For the future, Maisano et al. (2015) suggest:

> In the future, careful patient selection will play a fundamental role in identifying specific patients most likely to benefit from TMVI vs. TMVRep vs. mitral valve surgery. Pre-procedural imaging will play a leading role to guide the complex process of patient selection. Some procedures may become complementary (i.e. surgical mitral annuloplasty and subsequent TMVI, or a combination of different TMVRep approaches in the same patients with staged procedures). As an example, the addition of transcatheter annuloplasty to MitraClip therapy may improve acute efficacy and long-term durability. However, timing, indications and sequence of procedures is speculative at the moment. Conversely, certain procedures may preclude others (i.e. following TMVI there are no options for further repair, and a transcatheter edge-to-edge repair may preclude future TMVI). The role of LV remodeling approaches has yet to be defined (p. 1658)

As a promising new technology, the potential of less invasive transcatheter mitral valve replacements is untapped and yet to be discovered. From current pathways of innovation, it seems inevitable that the valves will significantly improve over the next 15 years as further research is carried out.

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