Recent Advances in Transcatheater Heart Valve Replacement: A Review on Aortic and Mitral Implantation

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Abstract: Heart valve disease is a serious problem, especially in aging societies. If left untreated, many patients can die from the disease itself or complications associated with it. However, many are denied open-heart replacement surgeries due to advanced age and co-morbidities. Thus, other solutions had to be explored. One successful solution is transcatheter heart valve implantation and is now seen as the only viable treatment. Transcatheter heart valve implantation is a minimally invasive technique of inserting an artificial heart valve by means of a catheter without requiring open heart surgery. However, challenges are always there with every successful technology. Obstacles that need to be overcome include anatomical constraints, appropriate delivery technique, satisfactory performance of the transcatheter heart valve and so on. In this review, these challenges associated with aortic and mitral valve will be analyzed due to the prevalence of the diseases associated with them. On top of that, design considerations, hemodynamic performance and current state-of-the-art and recent patents of aortic and mitral valves are discussed, with particular emphasis on their engineering aspects.

Keywords: Percutaneous, hemodynamic, stenosis, regurgitation, heart valve disease, clinical trial, aortic valve replacement, mitral valve replacement, valve prosthesis, valved stent, mock circulatory system, catheterisation, minimally invasive, valve design, heart valve implantation.

INTRODUCTION

In an increasingly aging population, age-related diseases are on the rise. One of them is heart valve disease [1]. It has been estimated that by 2018, there will be a total of 4 million people aged between 75 and 84 in the United Kingdom [2]. Thus, there is a need to tackle this increase in heart valve disease among the elderly before it becomes overwhelming.

Firstly, the human anatomy and the disease need to be understood before the problem can be solved. The purpose of heart valves is to maintain the uni-directional flow of blood in the heart. There are four heart valves which are responsible for this task. The tricuspid valve is situated in between the right atrium and right ventricle, allowing deoxygenated blood to flow only from the atrium to the ventricle. As its name suggests, it has three leaflets, the anterior, posterior and septal leaflets and an oval-shaped annulus [3]. Mitral valve, on the other hand, is bileaflet even though it serves the same function on the left side of the heart. Mitral valve has an elliptical and asymmetrical annulus and its leaflets are thicker and better defined than the tricuspid leaflets [3]. The other two valves are the semilunar valves which prevent backflow of blood into the ventricles. These semilunar valves have three cusps shaped like half-moons. The semilunar valve on the right side of the heart is called the pulmonary valve while the one on the left side of the heart is called the aortic valve [4]. When diseased, all these four valves can become stenosed or regurgitant. The most common heart valve diseases that occur in adults aged seventy years old and older are aortic stenosis and mitral regurgitation [5, 6].

Valvular stenosis is the narrowing of the valve opening, impeding the forward blood flow through the valve. As a result, the heart has to work harder to push blood through the valve which eventually weakens the heart muscle and leaves one feeling tired and short of breath [7]. The heart muscle initially thickens to make up for the increase in resistance to maintain forward cardiac output but eventually the heart chambers dilate and decompensates, leading to a decrease in cardiac output and heart failure [8]. Other complications arising from valve stenosis include pulmonary hypertension and sudden death which highlights the seriousness of this disease.

Valvular regurgitation, on the other hand, occurs when the leaflets are not able to coapt or close, hence blood flows backwards, nullifying the function of the valve. As a result, less blood flows forward, forcing the heart to work harder to make up for it [9].

This review will discuss the latest treatment option of these life-threatening diseases, focusing on aortic stenosis and mitral regurgitation as they are the most prevalent. The main focus of this paper is to analyse the engineering design aspect of transcatheter valve replacement and the valve performance. The disease state is first analyzed followed by the treatment options available. Then, the fundamental design parameters and the current state-of-the-art devices are
discussed. Finally, essential features pertaining to transcatheter heart valves such as hemodynamics and clinical trials are elaborated. The motivation of this paper is to provide a timely review of transcatheter heart valve implantation in response to the significant progress that has been made in the past few years.

AORTIC VALVE

Aortic valve stenosis is a concern as it affects 3% of the general population and its prevalence increases with age [10]. It represents the most common valvular lesion and is one of the leading causes of death [11, 12].

DISEASE STATE – AORTIC STENOSIS

Causes of aortic valve stenosis include congenital heart defects, calcified aortic valve particularly affecting those older than sixty-five years old, and rheumatic fever which is a complication of streptococcal throat infection. Rheumatic fever can cause fibrotic scar tissue formation on the valves and lead to stenosis or it can produce a rough surface on the valve expediting the deposition of calcium onto the valve [7]. In cases where rheumatic fever is the cause, aortic stenosis can be an adjunct to mitral stenosis or regurgitation or both. Aortic stenosis can also afflict the young whose valve has two cusps instead of three or has an abnormal funnel shape [13]. This becomes an issue when more blood is pumped through the narrowed valve as the person grows older. Over time the valve becomes stiffer as a result of calcium deposition. People with aortic stenosis may experience chest pain during physical exertion even though the pain usually ease with rest [13]. In many cases, patients with this affliction may not be aware that they have the disease which could lead to fainting or sudden deaths during exercise as the blood supply to the heart muscle is inadequate.

TREATMENT OPTIONS

Pharmaceutical & Valvuloplasty

Medications may be prescribed to help the heart deal with the effects of aortic valve stenosis. Examples include diuretics to cope with heart failure, drugs like Digoxin to regulate heart rhythm and also medications to reduce blood pressure or cholesterol [7, 13]. Nitrates must be used with caution as excessive consumption might decrease the blood pressure more than necessary. Patients with severe symptomatic aortic stenosis who refused surgery and were treated medically only had an average survival of about two to five years [14].

Percutaneous balloon valvuloplasty or the use of balloon to push open the stenosed aortic valve may be useful to temporarily control or palliate symptoms. The stenosed valve gradient may fall slightly but the valve area remains in the critical range. The benefit achieved by this treatment lasts for only three to six months [15].

Open-Heart Surgery

Surgical replacement of the aortic valve markedly improves the symptoms of the patient and the patient’s long term survival. In normal patients, these operations carry a perioperative mortality of only about 3% to 4% [12]. However, it has been estimated that about a third of the symptomatic aortic stenotic patients do not receive surgery [15], due to a myriad of reasons like old age, multiple comorbidity such as poor left ventricular function, presence of coronary artery disease, kidney disease, chronic severe lung disease, patient’s preference not to undergo open heart surgery, previous operation and porcelain aorta [10, 17]. In view of these confounding factors, there is a need for a less invasive treatment strategy for this group of patients who would otherwise be relegated to medical treatment with a universally poor prognosis.

Percutaneous Approach

The search for a lower risk therapy led to the idea of percutaneous or transcatheter treatment [18-20]. Transcatheter therapy is done through the lumen of a catheter which is inserted into the patient’s artery or vein. The device is delivered to the desired location by passing through the catheter. The first percutaneous treatment was percutaneous balloon valvuloplasty performed in 1985 to dilate calcified aortic valves [21].

The first catheter-based stent valve was invented and implanted into the pulmonary valve of a human patient in the year 2000 [22]. This was followed by the first transcatheter aortic valve replacement which was performed in 2002 [23]. Transcatheter aortic valve implantation (TAVI) is performed on heavily symptomatic patients who are not able to undergo open-heart surgery. It is done on a beating heart without the use of cardio-pulmonary bypass. TAVI valve is usually made of a tri-leaflet biological valve of animal origin sutured within a crimpable metallic stent frame [24]. Optionally, these stents may be coated with a layer of expanded Polyfluoroethylene (ePTFE) to minimise paravalvular leakages across the site of implantation [25]. The valve is crimped and placed in a catheter and delivered to the heart where it is deployed. The native heart valve is not removed for both techniques but is pushed to the walls of the heart by the artificial valve. This percutaneous approach was met with much optimism and boosted success rates of 94% and a 30-day survival of 89% [12]. Even though the overall mortality rate was higher than conventional open heart surgery, it was much lower than that predicted by the logistic EuroSCORE for this high surgical risk group of patients [26]. Further improvements and modifications to current designs give hope to achieving similar outcomes to open heart surgery or even better ones. Advantages of this treatment over others are its non-invasiveness, shorter recovery time and reduced surgical risk. On the other hand, mild paravalvular leaks are common and stroke rate is higher than conventional surgery [27]. Other more uncommon disadvantages include migration of artificial valve and damage to blood vessels [26, 28].

TRANSCATHETER AORTIC VALVE REPLACEMENT

Design Considerations

In the course of developing a percutaneous transcatheter valve replacement solution, several physiological characteristics of the native heart valve have to be considered. The heart valves function to ensure unidirectional flow of blood across
the various chambers of the heart. This is done by the substantial and proper coaptation of the valve leaflets [29]. In addition, blood flow across these valves must be obstructed and the valves must not inflict damage to blood elements, cause thromboembolism or generate excessive stresses on the valve leaflets [29]. Thromboembolism is generally influenced by the surface properties of the prosthesis, blood flow at the site of implantation and the hypercoagulability of the patient’s blood. Mechanical heart valves are known to cause significant thromboembolism and bleeding which can be life threatening and thus, highly undesirable [30]. Finally, the ideal prosthetic heart valve should produce minimal valve closure sounds. Patients with mechanical heart valve implants have reportedly been disturbed by the ticking sound produced by the closure of the mechanical valve leaflets [31].

In the following sub-sections, the three major components that make up the transcatheater aortic valve replacement system will be discussed in detail. These three components are material, stent frame design and delivery techniques.

Material – Leaflet & Stent

A tri-leaflet bioprosthesis valve is often employed in transcatheter aortic valve implantation (TAVI) [32]. The leaflets are derived mainly from equine, bovine or porcine pericardium [24]. However, in the course of development, other leaflet sources and materials have been explored. In the Lutter aortic valve prosthesis, a glutaraldehyde fixed bovine jugular vein segment containing a bicuspid valve was sutured directly onto a stent frame [33]. This represents a novel approach to employ tissue engineering techniques in the development of a transcatheter aortic valve replacement device [24]. Other more advanced leaflet materials include nanosynthesized E-nitinol used in the PercValve system developed by ABS [24].

The radially collapsible stent frame of TAVI is the main structural support of the device. In order to provide the necessary structural strength, metallic materials have been used to construct the stent. Early iterations of TAVI devices mainly used 316L stainless steel as the material of choice for the stent frame [23, 24]. This is due to the wide availability and biocompatibility of stainless steel. At present, more advanced stent materials such as cobalt chromium (used in the newer Edwards SAPIEN XT valve) and shape memory nickel-titanium alloy (nitinol) are being employed in the next generation TAVI stents [24]. Many of the newer TAVI designs use nitinol as the material of choice for the stent frame [24]. This is because the superelasticity and shape memory properties of nitinol have allowed for the designing of elaborate stent shapes that could not be done previously with stainless steel or cobalt chromium material [34]. On top of that it is biocompatible, corrosion resistant and has comparable mechanical properties to stainless steel (see Table 1).

Expanded Polytetrafluoroethylene (ePTFE) is commonly coated onto the stent frame to improve sealing of the TAVI device onto the annulus of the aortic valve to minimise paravalvular leakages. ePTFE is used because it is non-porous and has a lower thrombogenicity than other graft materials such as polyester [36].

Paravalvular leakage is a serious issue faced by many of the transcatheter heart valve. It decreases the efficiency of the valve and increases the workload on the left ventricle as compared to surgically implanted bioprosthesis [37]. Thus, recent developments in TAVI have seen various research groups attempting to tackle this issue by attaching a cuff or skirt made of biocompatible material [38-40]. The Symetis aortic stent valve sports a skirt made of Polyethylene terephthalate (PET) at the ventricular end of the stent to provide a seal between the stent frame and the aortic annulus [38]. The Sadra Lotus valve on the other hand, uses a flexible sealing membrane made of polyurethane (PU) [40].

Stent Design Considerations & System

There are a few design considerations that should be noted when designing a transcatheter aortic valve. The design should take into account the anatomical constraints such as the diameter of the aorta, distance between the aortic root and the coronary artery roots, position of the coronary arteries, diameter of the coronaries and the stent-endothelium mechanics [41].

Port angle is one of the parameters that are important in stent design. Port angle is the angle between two joined struts that form a lip. A narrow port angle would obstruct the coronary flow while a wide port angle would compromise the valve’s stability [41]. Strut thickness should also be considered as thicker struts can improve the radial strength and support of the valve but it can also cause injury, restenosis and block the coronary blood flow [42]. Anatomically, the aortic annulus has an elliptical shape hence, if the transcatheter aortic valve is circular in shape, it’s conformation to the oval shape of the annulus may have unintended effects such as the non-coaptation of the leaflets. Although the conformation of the CoreValve ReValving System to the oval shape of the annulus had no short-term adverse effects, the same cannot be said for other transcatheter aortic valve valves [43]. In addition, there can be a problem of incorrect sizing of the prosthetic valve due to the industry guidelines of a circular shape annulus [44].

The stent should have minimal surface area to minimise thrombus formation. On top of that, the stent should be radiopaque to ensure that it can be visualised via imaging systems. An advantage would be a thin wall thickness so that it has a narrow crimped profile which would facilitate catheterisation [45]. Blunt hooks can also be added to the stent to enable it to anchor onto the endothelium of the aorta.

Generally, the stents used in TAVI are cylindrical in nature, such as the Edwards SAPIEN XT and Sadra Lotus valves [39, 40]. There are also designs that have flares at the ends of the stent that serve as anchorage in the aorta, like the one seen in the Medtronic CoreValve ReValving System [46].

In TAVI, the stent is designed to provide a large radial resistive force to prevent valve collapse from external forces after deployment. The large radial force will also ensure the valve is anchored securely with enhanced sealage of the
Table 1. Mechanical Properties of Nitinol, Stainless Steel (316LVM), Titanium (cp-Ti, Grade IV) and Ti-6Al-4V Alloy [35].

<table>
<thead>
<tr>
<th></th>
<th>Nitinol</th>
<th>Stainless Steel</th>
<th>Titanium</th>
<th>Ti-6Al-4V</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Austenitic</td>
<td>Martensitic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultimate Tensile Strength (MPa)</td>
<td>800 - 1500</td>
<td>103 - 1100</td>
<td>483 - 1850</td>
<td>540 - 740</td>
</tr>
<tr>
<td>Tensile Yield Strength (MPa)</td>
<td>100 - 800</td>
<td>50 - 300</td>
<td>190 - 1213</td>
<td>390</td>
</tr>
<tr>
<td>Modulus of elasticity (GPa)</td>
<td>70 - 110</td>
<td>21 - 69</td>
<td>190 - 200</td>
<td>105 - 110</td>
</tr>
<tr>
<td>Elongation at Failure (%)</td>
<td>1 - 20</td>
<td>Up to 60</td>
<td>12 - 40</td>
<td>16</td>
</tr>
</tbody>
</table>

device onto the aortic annulus and prevents paravalvular leakage [47, 48]. The large radial force gives the TAVI stent a large effective orifice area (EOA), which minimize pressure drop across the stented valve. The frame radial strength is derived from the frame geometry and frame material [49]. Extensive computer analysis is usually done to obtain the optimum geometric shape and material. However, it should be noted that excessive radial strength can also compress the surrounding structures, including the aortic annulus and leaflet bundle branch which could compromise the intraventricular conduction [50]. Also, a low position or a long stent have been shown to cause intraventricular conduction abnormalities [51].

The tri-leaflet valve made from pericardium tissue is affixed onto the stent by two main methods depending on the type of stent used. In a wire woven stent system, the valve is usually first sutured onto a wire frame before the whole assembly is sutured onto the stent [52]. In the case of a stent derived from laser cutting a tubs, the tri-leaflet pericardial valve is sutured directly onto the stent frame itself. This can be seen in both commercially available Edwards SAPIEN and Medtronic CoreValve valves [46, 53].

The move to more advanced materials such as cobalt chromium (Edwards SAPIEN XT valve) and nitinol (CoreValve Revalving System) has allowed for the stent frames to be thinner but yet retain the structural strength needed to keep the TAVI device in its deployed state [39]. This has resulted in the reduction in delivery catheter size, as exemplified by the Edwards SAPIEN TAVI device that has since reduced its delivery catheter size from 24 Fr to 14 Fr [39]. A similar improvement can be seen in the Medtronic CoreValve Revalving System that reduced its catheter size from 22 Fr to 18 Fr [46].

The use of nitinol has also spurred the development of more elaborate stent designs in newer TAVI devices. This is due to the superelastic and shape memory properties of nitinol. The Medtronic Engager TAVI device sports wing-like projections aimed at accurately positioning the device at the aortic root where the wings would first be deployed to engage against the sinuses prior to complete valve deployment. This allows for minor adjustments such as repositioning and rotation to be done to the valve [32]. A more recent TAVI device developed by Symetis exhibits three wings projected into the aorta and multiple bended crowns near the middle of the stent. The wings serve to self-align the device in an anatomical position before complete deployment while the bended crowns serve to anchor the valve onto the aortic annulus [38].

**Delivery Technique**

There are a few approaches in which delivery of the prosthetic valve to the aortic annulus can be carried out. The first approach is the antegrade technique in which the crimped bioprosthetic valve housed with a catheter is passed through the femoral vein, interatrial septum, mitral valve and finally reaching the desired location. The advantage of this approach is that it is easier to traverse the native valve, especially in patients with heavily calcified valves. However, this approach is technically difficult to perform, requiring the expertise of experienced cardiologists. On top of that, the mitral valve can be damaged in the process [54]. Given the many drawbacks of this approach, it is no longer being used.

The next approach is the retrograde technique. This technique involves the catheter going up the femoral artery, passing through the aortic arch to reach the dissected aortic valve. It is a much simpler and faster technique to perform but is not suitable for some elderly patients mainly due to the fact that many of these patients suffer from diseased femoral and iliac arteries or that their arteries are too small to fit an 18 F or 24 F sheath [55, 56]. Moreover, the deployment of the bioprosthetic valve across the calcified aortic valve in this retrograde approach has been proven to be an arduous task [54].

In contrast to the two approaches discussed earlier, the transapical technique requires a small incision to be made in between the ribs to allow access to the apex of the left ventricle. A needle is then used to puncture the apex to make way for the sheath which is used to deliver the prosthetic valve to the diseased valve. This method is advantageous to those suffering from arterial diseases like atheroma or those with small or tortuous arteries as it surpasses the peripheral vascular access sites [47]. It is a faster procedure and technically less demanding as compared to the transvenous antegrade and the transarterial retrograde techniques. Lower incidence of stroke has also been reported with this technique as compared to the retrograde route [57]. However, the relative downsides to this approach are the small opening on the
In search for other routes of entry into the heart, interventionalists and surgeons came up with non-conventional access routes such as the transsubclavian/axillary artery and the direct ascending aorta [62-64]. These alternative routes provide a viable solution for those patients with peripheral vascular access problems. The shorter distance to the aortic annulus decreases the risk of injury to the patient’s vascular system and avoids apical access complications such as severe bleeding and aneurysm formation [60]. Nonetheless, complications can arise in such procedures, for instance a study has reported that obstructive dissection of the subclavian artery and transient left arm paralysis can occur in the subclavian approach [65].

Upon reaching the heart, balloon valvuloplasty is often performed to dilate the native valve leaflet in preparation for the delivery of the TAVI device. Rapid pacing of the heart is then performed via a transvenous pacemaker attached to the right ventricle to reduce cardiac and catheter motion, transvalvular flow, and cardiac output so as to facilitate the placement of the prosthetic valve onto the annulus for balloon expandable valves [66, 67]. Valve positioning and subsequent deployment in the heart is monitored using transesophageal echocardiography (TEE) coupled with fluoroscopic and angiographic monitoring [66, 68]. Valve deployment is usually achieved via catheter balloon expansion [66]. However, other valves with stent material made of superelastic nitinol like that of the Medtronic CoreValve System and the prototype Lutter Mitral Valve Prostheses are deployable via self-expansion without the aid of a balloon catheter [66, 68]. The stent is initially cramped and placed in a sheath before being deployed at the treatment site. This is possible due to nitinol’s shape memory property that allows the stent to be expanded to its predetermined shape by passing warm saline solution through it or allowing blood to come into contact with it. The higher temperature at which it reverts back to its original shape is known as the transformation temperature and it is dependent on the alloy composition and processing history [69].

All in all, the choice of the delivery technique will depend on the patient’s condition such as the vessel size, tortuosity and the presence of lung disease. For example, the transapical approach will be chosen if there is no access through the patient’s diseased femoral or subclavian arteries. A pre-operative contrast-enhanced computed tomography (CT) scan can be done to analyse the feasibility of the associated anatomy such as the aortic arch.

CURRENT STATE-OF-THE-ART & THEIR LIMITATIONS

One of the earliest designs of transcatheter aortic valve came from Edwards Lifesciences. The Cribier-Edwards valve is made of three equine pericardium leaflets sewn onto a balloon expandable 14mm long stainless steel stent (see Table 2). It is the first valve replacement done via the antegrade approach in which the catheter moves up the femoral vein, crosses the interatrial septum and the mitral valve and reaches the diseased valve [54]. This technique is no longer in use as other more efficient approaches have taken its place. The main characteristics of this valve are its high radial stiffness and low flexibility [70]. It was also found that the larger valve (26 mm) was better as it had a lower rate of migration, paravalvular leak and embolization, especially for patients with a bigger valve annulus [54]. However, occurrence of paravalvular insufficiency is common [56]. This version was improved and modified to give birth to Edwards SAPIEN THV (see Table 2), which is also a trileaflet valve held by a balloon expandable stainless steel stent. The difference is its bovine pericardium leaflets, longer sealing cuff and the omission of antegrade delivery approach [39]. Results showed low occurrence of valve embolisation and coronary impendence. However, shear stress and strain were high during peak flow phase which can damage the aortic wall [71]. Other than that, there is high vascular complication associated with this valve due to the large diameter of the delivery sheath [39]. Further modifications to this version of the Edwards valve led to the next generation of Edwards valve, the Edwards SAPIEN XT (see Table 2). Improvements were made to the stent material to achieve thinner struts and lower profile without comprising the structural integrity. It also allows for a more open design that gives a more compact cramped state and thus, improves the delivery profile and increases the pool of patients who can undergo this procedure. Moreover, the scalloped geometry of the bovine pericardium showed enhanced durability [39]. Performance of this valve has been shown to be similar to the SAPIEN THV but involve lesser vascular complications and thus expands its clinical applications [72]. Both SAPIEN THV and XT valves have attained CE mark for their European commercial sales (see Fig. 1). Currently, two new Edwards valves are being developed to tackle the problem of large catheter system that has a risk of injury to the patient. One of them is the Edwards SAPIEN 3 valve. It is designed to achieve a very low delivery profile of 14 F for a transapical approach and exhibits low paravalvular leakage. It is balloon expandable and utilises bovine pericardial tissue. The other new valve is the Edwards CENTERA valve. It also employs a 14 F delivery system. Its unique motorised delivery system ensures stable deployment. Moreover, it is repositionable and self-expanding. These two devices are not commercialised yet.

Another revolutionary invention is the CoreValve ReValving System by Medtronic (see Table 2). This 50 mm long, self-expanding nitinol stent sutured with a trileaflet animal pericardial tissue has three distinct segments. It has a somewhat hour-glass shape in which the top section is flared so as to allow the valve to sit on the top portion of the aortic annulus (see Fig. 2). The porcine pericardium is found in the tapered middle section of the valve, and it is fashioned in such a way that it does not block the coronary flow [70]. The lower section of the stent has a high radial strength to push the native valves and be held in position [10]. The first generation CoreValve is made up of bovine pericardium and required a 24 F delivery catheter. A smaller delivery profile of 21 F, a change to porcine pericardium and a better anatomical fit of the CoreValve gave rise to a second generation. Finally, the third generation CoreValve system
Table 2. Transcatheter Aortic Valve Technologies

<table>
<thead>
<tr>
<th>Valve</th>
<th>Manufacturer</th>
<th>Valve Material</th>
<th>Stent Material</th>
<th>Mechanism</th>
<th>Delivery Approach</th>
<th>Size (mm)</th>
<th>Year of First-in-Human Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cribier-Edwards</td>
<td>Edwards Lifesciences</td>
<td>Equine pericardium</td>
<td>Stainless steel</td>
<td>Balloon expandable</td>
<td>AG/RG/TA</td>
<td>23, 26</td>
<td>2002</td>
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<tr>
<td>Edwards SAPIEN XT</td>
<td>Edwards Lifesciences</td>
<td>Bovine pericardium</td>
<td>Cobalt chromium</td>
<td>Balloon expandable</td>
<td>RG/TA</td>
<td>20, 23, 26, 29</td>
<td>2011</td>
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<td>Edwards Lifesciences</td>
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<td>Balloon expandable</td>
<td>TA</td>
<td>-</td>
<td>-</td>
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<td>Edwards CENTERA</td>
<td>Edwards Lifesciences</td>
<td>Bovine pericardium</td>
<td>Nitinol</td>
<td>Self-expandable</td>
<td>TF/SC</td>
<td>-</td>
<td>-</td>
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<tr>
<td>CoreValve ReValving System</td>
<td>Medtronic</td>
<td>Porcine pericardium</td>
<td>Nitinol</td>
<td>Self-expandable</td>
<td>RG/SC</td>
<td>26, 29, 31</td>
<td>2004</td>
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<td>Paniagua</td>
<td>Endoluminal Technology Research</td>
<td>Porcine pericardium</td>
<td>Cheatham-Platinum (CP) 8228</td>
<td>Balloon expandable &amp; Self-expandable</td>
<td>RG</td>
<td>20</td>
<td>2005</td>
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<td>Advanced Bioprothetic Surfaces</td>
<td>Nano-synthesised e-nitinol</td>
<td>Nano-synthesised e-nitinol</td>
<td>Self-expandable</td>
<td>AG</td>
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<td>Nitinol</td>
<td>Self-expandable</td>
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<td>TA</td>
<td>23, 25, 27</td>
<td>2009</td>
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<td>Direct Flow</td>
<td>Direct Flow Medical</td>
<td>Bovine pericardium</td>
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<td>Inflation of ring balloons by a polymer</td>
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<td>22</td>
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<td>Heart Leaflet Technologies</td>
<td>Heart Leaflet Technologies</td>
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<td>Nitinol</td>
<td>Self-expandable</td>
<td>TF</td>
<td>21, 23</td>
<td>2009</td>
</tr>
</tbody>
</table>

incorporated improvements that were made to the sealing cuff to ensure uniform thickness and a better profile. The problem with this valve is the need for permanent pacemaker post procedure. This problem was attributed to its long stent that enter the left ventricular outflow tract and the compression of the surrounding apparatus including the left ventricular atrioventricular node and its left bundle branch which damaged the atrioventricular conduction system [50, 51]. Thus, the pacemaker is required in such instances to restore the electrical conduction in order to establish the correct heart rate. Even so, CoreValve brings about great clinical benefit and has attained CE mark for the direct aortic and subclavian implantation.

Another avant-garde is the Paniagua (see Table 2). It was the first valve implanted via the retrograde approach. Even though the patient died after five days possibly of pulmonary embolism, the valve function was acceptable. Moreover, TEE showed satisfactory hemodynamic performance verified by the increase in aortic pressure and decrease in transvalvular pressure post-procedure [73]. Furthermore, when the valve was tested in an in vitro model, it demonstrated excellent hemodynamic performance and had no deterioration [74]. Another advantage is that this valve can be implanted using an 11 Fr or 16 Fr sheath which is not the case for many other prosthetic valves.
An innovative transcatheter aortic valve made by a German group is the JenaValve (see Table 2). The valve’s simple, yet novel design consists of three components, the nitinol self-expandable stent, a root valve fitted with an outer porcine pericardial patch and the JenaClip. The three feelers on the stent assist the surgeon in positioning the valve while the clip secures the valve in place by attaching onto the native leaflets once the lower section of the valve is released (see Fig. 2) [75]. The valve’s design strength lies in its ability to be completely repositionable, retrievable and its secure fixation that prevents it from retrograde dislodgement [24, 76]. However, paravalvular leak is an issue which is a problem shared by many other percutaneous heart valves [76]. JenaValve has been commercially available since September 2011 and has also received CE mark for its second generation transapical transcatheter aortic valve.

One of the most unique valves to date is the PercValve (see Table 2). The entire device is made of nano-synthesised nitinol, making it a transcatheter mechanical valve (see Fig. 2). Its distinct surface has been shown to promote endothelisation within two weeks which would give it a non-thrombogenic coating in a short amount of time (Advanced Bioprosthetic Surfaces, TX, USA) [77]. However, more studies have to be done to demonstrate its hemodynamics performance and durability.

Another valve that has the same delivery approach as the PercValve is the Lotus valve (see Table 2) [78]. Its strength is the ability to assess its in vivo performance, its repositionability before final deployment, its anchoring mechanism and the polyurethane seal that prevents paravalvular leak. Upon deployment, it shortens longitudinally, locks into place and exerts a high radial force for anchoring (see Fig. 2) [79, 80]. Even though its implantation in human has displayed promising results, it has a large delivery profile and required the use of a permanent pacemaker [40].

Basically, the Lotus valve, Engager and Acurate share similar valve constituents – biological leaflets which are supported by a self-expandable nitinol stent. Their differences and uniqueness can be found in their designs. The Engager is similar to the JenaValve as it has three support arms that
align it perfectly in the aortic sinuses and provide axial fixation (see Fig. 2). Its fluid dynamic and anatomical shape minimises pressure loss across the valve as well as give it a good fit and does not obstruct the coronary ostia [32]. Paravalvular leak was present but within the acceptable range and 10% of the patients required permanent pacemakers due to the blockage of atrioventricular node. Thus, modifications were also done to the valve so as to allow for accommodation onto bulkier calcified leaflets and to provide a better fit to the aortic annulus [32].

On the other hand, Acurate has stabilisation arches that extend to the aortic root to facilitate positioning (see Fig. 2). It is also equipped with a polyethylene terephthalate (PET) skirt that reduces paravalvular leak [81]. Acurate is one of the few percutaneous valves that utilises a regular porcine tissue valve instead of the thinner pericardium tissue. Kempfert et al. argued that its bioprosthetic valve does not require a tight cramped profile as it is delivered via the transapical route. This valve also has the ability to be rotated to an anatomically correct position. Results showed a success rate of 95%, minimal paravalvular leak and a 30 day mortality rate of 12.5% [82]. However, biological tissue valve has been shown to have inferior intrinsic biological properties such as collagen content [83]. Thus, its use in this prosthesis is questionable.

Other newer transcatheter aortic valves include the Direct Flow valve, Portico valve and Heart Leaflet Technologies (see Table 2) [84]. The Direct Flow valve is unique in the sense that it is completely non-metallic and stentless. This valve allows the physician to study its hemodynamic performance before final deployment. It is also repositionable. The Portico valve by St. Jude Medical, on the other hand, looks very similar to CoreValve. However, it is a next-generation heart valve such that the valve can be repositioned or retrieved, unlike previous innovations. It also allows for greater control and positioning accuracy. The first-in-human study showed that the number of patients requiring pacemaker is low which is an improvement from the CoreValve. This can be attributed to the absence of a flared inflow and ease of repositioning [85].

Mitral Valve

Mitral valve regurgitation is the most common type of valvular heart diseases. In a US population-based study, 163 out of 1745 adults older than 75 years suffer from this condition [86]. Globally, it affects 1.75% of the population and this figure soars to 10% for those older than 75 years old [87]. In our aging society, this problem will be more pressing as time goes by.

Disease State – Mitral Regurgitation

Causes of chronic mitral valve regurgitation include mitral valve prolapse in which there is weakening of the cords supporting the valve, degenerative mitral valve changes, rheumatic fever, endocarditis which is infection and inflammation of the endocardium, prior heart attack, untreated high blood pressure and congenital heart defects [88]. While the causes are plentiful, the effect of backflow is the same. Patients with this affliction have increased blood volume and pressure in the left atrium. The rise in the left atrium blood pressure then intensifies the pressure in the pulmonary vein which leads to the enlargement of the left atrium. An enlarged atrium is unable to beat in a regular fashion (atrial fibrillation), causing blood clots to form in the atrium which can lead to stroke if the clot breaks loose and is pumped out of the heart. The important effect that results from severe long term mitral regurgitation is that the heart has to pump harder to adequately produce a forward cardiac output to cope with the back flow into the left atrium. The heart initially enlarges to cope with this extra volume workload but eventually it weakens and develops congestive heart failure. This leads to fluid accumulation in the lungs due to increased pressure in the left atrium and deprivation of blood because of the diminished forward flow [89].

TREATMENT OPTIONS

Pharmaceutical

Unlike in aortic stenosis, most drugs used in the treatment of heart failure can be used in controlling symptoms due to mitral regurgitation. Mild conditions of mitral valve insufficiency do not require much attention other than the use of antibiotics before dental and medical procedures in some cases as damaged valves are susceptible to bacterial infection [89]. For the more serious cases, medications such as diuretics are often prescribed to reduce fluid accumulation. Blood pressure regulators such as nitrates and ACE inhibitors are also given to those with high blood pressure as high blood pressure aggravates the regurgitation [88, 90]. Digoxin and beta blockers can also be used to control ventricular rate [91]. However, medical treatment in severe mitral valve regurgitation achieves only symptom control and gives universally poor long term prognosis.

Open-Heart Surgery

Surgery can correct the intrinsic valve malfunction by repairing or replacing the valve with a mechanical, bioprosthetic or polymeric heart valve. Both these procedures involve open heart surgeries in which a cut, the length of the sternum, is made and a heart-lung machine is used to circulate the blood [88]. The surgeon can repair the native valve by correcting the valve itself or the ring around the valve, rejoin the valve back together or by removing excess tissue from the valve so that the valve can coapt [88]. This is usually the preferred treatment because a repaired native valve usually performs better than a mechanical or bioprosthetic valve and the patient does not have to be on lifelong anticoagulant therapy [89]. In valve replacement, the surgeon removes the diseased valve and an artificial valve will take its place. The patient may then have to take anticoagulant medication for a lifetime to prevent blood clots especially if a mechanical valve was used.

Percutaneous Approach

The percutaneous or transcatheter approach was recently developed for those patients who are not suitable for invasive treatments. Mitral valve repair can be performed in such an approach. This can be done by delivering a clip to the heart using a catheter via the femoral vein and deploy it
once it is in position across the mitral valve. Thus far, this technique has been successfully developed using the MitraClip [92]. It is based on the principle of the surgical Alfieri stitch repair for degenerative or functional mitral valve regurgitation [93]. However, this technique is only suitable for a very highly selected group of patients with suitable mitral valve anatomy and regurgitation mechanism.

Transcatheter mitral valve replacement is another viable solution for mitral valve disease, especially for those with a low chance of having a successful repair or are denied open-heart surgery. Hence, many are developing and testing out novel ways of implementing this technique [94, 95].

On top of that, it is possible to perform a valve-in-valve implantation into a failing mitral valve bioprosthesis of patients who had surgically implanted biological mitral valve replacement. This is done via a transapical technique using the same device and prosthesis as the TAVI procedure [96].

TRANSCATHETER MITRAL VALVE REPLACEMENT Design Considerations

Although there exist differences between the design considerations of transcatheter aortic and mitral valves, both share certain basic design aspects such as allowing only unidirectional, unobstructed blood flow, does not cause thromboembolism or produce noise upon closing and the type of material used [29, 31]. The noise produced by prosthetic valves can cause unnecessary distress to the patients [31].

The anatomy of the mitral valve is more complex than that of the aortic valve. This is due to the tricky position of the mitral valve (see Fig. 3). Thus, when designing a transcatheter mitral valve, one has to appreciate the anatomical features that are in close proximity to the mitral valve and their relationships. These anatomical structures include the circumflex artery, coronary sinus, atrioventricular node, and the aortic valve (see Fig. 3) [37]. Other than the surrounding anatomical constraints, the mitral valve has a characteristic saddle-shaped annulus. Its annulus undergoes a series of change to its circumference and valve area in order to facilitate the opening and closing of the valve [97]. Accordingly, the valve design should take into account these anatomical considerations.

In the following sub-sections, we would be discussing in detail the three major components that make up the transcatheter mitral valve replacement system. The three components are material, stent frame design and delivery techniques.

Material – Leaflet & Stent

A tri-leaflet bioprosthetic valve derived from the pericardium of bovine or porcine origin is often employed in transcatheter mitral valve implantation (TMVI) [98]. Pericardial valve has been shown to have better hemodynamic performance than porcine valves due to its lower forward flow pressure gradient. This may be the reason behind its frequent use in THV even though it exhibits higher regurgitation than porcine valve [99].

The stent frame used in TMVI devices are made mostly of 316L stainless steel or nitinol, with the latter being the material of choice for more recent designs [25]. This is due to the unique superelastic and shape memory properties of nitinol [14].

Expanded polytetrafluoroethylene (ePTFE) is commonly coated onto the stent frame to improve sealing of the TMVI device onto the annulus of the mitral valve to minimise paravalvular leakages. An example can be seen in the ePTFE

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Fig. (3). Relationships of the mitral valve as seen from the top of the left atrium [87]. Retrieved from Anatomy of the Mitral Valvular Complex and Its Implications for Transcatheter Interventions for Mitral Regurgitation by Van Mieghem et al.
coated TMVI prototype designed by Leonzschi and colleagues [25]. ePTFE is used because it is non-porous and has a lower thrombogenicity as compared to other graft materials such as polyester [36].

Stent Design & System

In contrast to TAVI devices where radial resistive force from the stent is used to anchor and provide a tight seal for the device onto the aortic annulus, the radial force employed by the stents in TMVI is mainly used for stent expansion to its final deployed conformation only [25, 48]. Although the use of radial force has been largely successful in TAVI, it is not so in the mitral position. The myocardial muscle that makes up most of the mitral annulus is elastic, drastically minimising the effectiveness of stent radial force in securing the valve in place [100]. Also, the use of radial force at the mitral position may compress the left ventricular outflow tract (LVOT) due to its close proximity to the aorta and consequently may affect optimal cardiac output [68, 87].

In view of that, radial force is inadequate for securing the transcatheter mitral valve. As a result, many designers have turned to alternative means of anchoring the device onto the mitral annulus tissue and native mitral valve leaflet tissues. This can be seen in the edovalve-Hermann prostheses as well as the CardiAQ prostheses where specially designed hook-like projections have been employed to anchor the prosthesis to the mitral annulus tissues and native valve leaflets [94]. The Lutter prosthesis on the other hand, uses a backward bending nitinol stent frame that results in a deployed form resembling a star-shaped umbrella [68].

Just like in TAVI devices, the tri-leaflet pericardial valve in most TMVI is sutured directly onto the metallic stent frame [25, 68].

The other critical challenge facing TMVI designer at present is the issue of paravalvular leakages via the interface between the TMVI stent and the mitral annulus. This is in part due to D-shaped elastic nature of the mitral annulus [87]. Thus, ePTFE coating on TMVI stent frames are commonly employed in an attempt to achieve a tight seal on the mitral annulus to minimise paravalvular leakages [25, 68].

Delivery Technique

The delivery technique of the bioprosthetic mitral valve is not as well developed as the bioprosthetic aortic valve due to the challenging anatomical constraints of the mitral valve. Nonetheless, a few techniques have been adopted from transcatheter aortic valve implantation.

Most companies and research institutes have published results for the transapical delivery of their transcatheter mitral valve. In this approach, a small 5-7cm anterolateral thoracotomy incision is performed in close proximity to the left ventricular apex of the heart [48]. Thereafter, the left ventricular apex of the heart is punctured and the delivery catheter containing the valve prosthesis is advanced to the target delivery site at the valve annulus [66]. This is the preferred delivery technique for many surgeons as the distance to the mitral valve is short and is a relatively simple procedure [101]. However, the surgeon has to be skilled enough to manoeuvre around the tendinous cords such that they do not hamper the positioning, expansion and anchoring of the bioprosthetic valve [68].

The antegrade transfemoral delivery route was recently established for TMVI in a porcine model [102]. In this approach, the delivery catheter containing the cramped prosthesis is threaded from the femoral vein via a guide wire to the heart. Once at the heart, the interatrial septum is punctured to gain access to the mitral valve [66, 103]. This method offers an alternative solution to those denied of open heart surgery and transapical mitral valve replacement. Results of this approach reflect success but more studies have to done to show the safety and efficacy as well as its long term effects.

CURRENT STATE-OF-THE-ART & THEIR LIMITATIONS

Due to the anatomical constraints of the mitral valve and the limitations of transcatheter valve technologies, open-heart surgical treatment of mitral regurgitation remains the gold standard [87, 104]. Nonetheless, transcatheter mitral valve replacement offers palliative treatment for the elderly who are denied surgery, especially for those with multiple co-morbidities. Thus, many have attempted to overcome the limitations of this treatment by coming up with novel designs and implementation strategies (see Table 3) [25, 105].

Segesser and colleagues were the first to implant prosthetic mitral valve transannular in a porcine model (see Table 3). The double-crowned valve stent was deployed via a left thoracotomy and a left atrium incision. The team designed a fixation system and a valve system to overcome the complex anatomy of the mitral valve. The fixation system comprises of two nitinol Z-stents that form two crowns for fixation onto the ventricular side of the mitral annulus. The valve system is made of glutaraldehyde-treated porcine aortic or pulmonary valve sutured onto a Dacron conduit. The system showed no significant hemodynamic changes after valve deployment but three out of eight animals had mild paravalvular regurgitation [106].

Using a similar approach, Leonzschi and coworkers' designed their version of the transcatheter mitral valve to include three components. The valve design has an atrial fixation system made of metal springs covered with ultrahigh density polyester, a valve system which is comprised of porcine or bovine valve sutured onto a nitinol stent and a ventricular fixation system. Having two fixation systems and being delivered transapically is the key feature that sets this design apart from the double-crowned valve stent. Results showed low transvalvular gradient but ventriculogram displayed paravalvular regurgitation in two out of the ten pigs tested [25]. Further modifications were made to the group’s original valve’s design by substituting the valve material with a tricuspid bovine pericardial valve (see Table 3). They reduced the external wall of the valve so as to reduce the diameter of the stent and thereby allowing a smaller delivery system to be used. A flat star-like disk was incorporated as the atrial fixation system and an enhanced ventricular fixation system that has four tethering cords aids
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the anchorage of the valve onto the ventricular wall [107]. On top of that, ultra-thin polytetrafluoroethylene was coated onto the stent to prevent paravalvular leakage. Even so, mild paravalvular regurgitation was found in one out of the six animals [68]. Thereafter, further improvements were made to this valve to give rise to the flat ring valved stent (see Table 3). As its name suggests, it has an atrial ring covered with a waterproof membrane to prevent paravalvular leakage. This also acts as the atrial fixation system. It is connected at an angle of 45° to a tube that houses the bovine pericardial valve and its ventricular fixation comprises of neo-chordae. While the ring structure alleviated the paravalvular leak, its circular shape contributed to the fracture of the atrial side of the valve. This is possibly due to the non-conformity of the valve to the saddle shape of the mitral annulus. Even though hemodynamics performance was stable and valve migration
was not observed, transvalvular pressure doubled after 4 weeks which Dr Lutter attributed to the undersizing of the valve. Other than that, the atrial element of the valve was covered with 70% of tissue growth in 2 months. This might aid the sealing of the gap between the prosthetic valve and the annulus, hence giving rise to a smaller, non-dilated annulus [108].

Another interesting design involves the customisation of the prosthetic valve to the patient’s pulmonary veins and atrium [109]. The prosthesis covers part of the bifurcated pulmonary veins down to the left atrium. The tubular hollow body is made of polyvinylidene fluoride (PVDF) and supported by a nitinol skeleton. A biological valve is sutured onto the atrial side of the stent (see Table 3). The delivery technique of this valve is similar to the double-crowned valve stent. The transcatheter method was not performed in both these cases as it was not necessary for the proof of concept study. The unique feature of this valve is its anchoring mechanism which makes use of the pulmonary ostia instead of radial force to secure the valve into place. Results showed that blood circulation was not compromised and there were no signs of thrombus formation even though PVDF covered a significant portion of the heart wall. However, visualisation of the prosthesis was poor so thorough evaluation of its performance could not be carried out [109].

VALVE PERFORMANCE

Hemodynamics & Hydrodynamics

Transcatheter heart valve replacement is rapidly gaining popularity and replacing the conventional surgical valve replacement as the gold standard especially for patients with high surgical risk [110]. Thus, it is important to evaluate the hemodynamics of transcatheter heart valves to ensure that they match that of surgically implanted valves. Moreover, a prosthetic heart valve with flawed hemodynamics can cause damage to red blood cell, thromboembolism, injury to the endothelial lining of the wall of the ascending aorta and tissue overgrowth [111]. Criteria of assessment include fluid-induced shear stress, turbulent intensity, Reynolds shear stress (RSS) levels, blood flow velocity, pressure gradient, effective orifice area (EOA) and patient-prosthesis mismatch [112].

Elevated levels of shear stress and turbulent intensity can lead to the hemolysis of blood cells and activation of thrombus formation, thus, measurement of these parameters can be used to estimate the extent of the blood damage induced by the bioprosthesis. The duration at which the shear stress acts is also a determinant of prosthesis-induced hemolysis. RSS threshold for hemolysis to occur was found to be 800 N/m² with an exposure time of 1 ms whereas turbulent flows have been shown to increase the incidence of hemolysis (see Fig. 4) [113, 114]. Hence, it is important to ensure that these values fall in the acceptable range for the THV that has been designed.

Transvalvular flow (Q) is the flow across the heart valve and is dependent on cardiac output which in turn is associated with the patient’s body surface area (BSA) when the patient is at rest [115]. Transvalvular flow is an important factor in the hemodynamics equation as it affects the transvalvular pressure gradient (TPG). TPG, as its name suggests, is the pressure gradient across the heart valve. Achieving a low TPG value is a highly desirable feature of a prosthetic heart valve. An increase in TPG across the prosthetic aortic valve can impede the regression of the left ventricular dilatation whereas a high TPG across the mitral valve can exacerbate pulmonary hypertension [116]. Another key factor in hemodynamic assessment is the EOA which is the area of the prosthesis subjected to blood flow [117]. Indexed EOA is a more accurate term as it corrects the EOA (cm²) measurement for body size or BSA (cm²/m²) [118]. A low indexed EOA value would result in a prosthesis-patient mismatch in which the prosthesis orifice is too small as compared to the patient’s body size. In this case, there would

![Graph](image-url)

**Fig. (4).** Increase in plasma free hemoglobin (hemolysis) vs. wall shear stress obtained for the laminar and turbulent flow experiments [114]. Retrieved from Turbulent Stresses upon Mechanical Hemolysis: Experimental and Computational Analysis by Kameneva et al.
be high TFG. This relationship is best demonstrated in the hydraulic equation, \( \frac{TPG}{k \times EOA} \), where \( k \) is a constant [115]. Therefore, in order to achieve a low TPG, the EOA has to be proportional to the blood flow across the prosthetic valve or as big an area as the native human valve. However, this is often not the case. This is due to tissue ingrowth and endothelization [118]. Nonetheless, transcatheter aortic valves have been shown to offer better TPG values as compared to their surgically implanted counterparts. This is because transcatheter prosthetic aortic valves are oversized by 2mm to 3mm in order to generate a radial force that would secure the valves into place. Consequently, they attain a higher EOA and so their TPG is lower than the conventional prosthetic valves [110]. On the other hand, the same principle cannot be applied for the mitral valve since radial force is not employed in the deployment of the transcatheter mitral valve as has been mentioned previously.

The regression of the heart to the normal state after valve replacement may differ between individuals. Some may be in a worse state than before. For instance, patients with mild to moderate pulmonary artery pressure before transcatheter mitral valve replacement can acquire severe pulmonary artery hypertension after the procedure due to prosthesis-patient mismatch. As follows, it is vital to identify the factors that can possibly contribute to the failure of this technique and the bioprosthetic valve. Mock circulatory systems (MCS) can be used to analyse the performance of the valve in a flow loop that simulates the cardiovascular system of the human heart. A dual-chamber pulsatile tester with transparent anatomical models of the atrium and ventricle, complete with pulsatile pumps, resistance and compliance chambers can be set up to study parameters like TPG, EOA, leakage rate, regurgitant volumes, and velocity flow fields in an in vitro manner [119, 120]. The chamber allows the physiological contraction and relaxation of the heart chambers with its two distinct pulsatile systems. Flow characteristics are then measured using the particle image velocimetry (PIV). Orifice shape, rigidity, cross-sectional area and valve oversizing should be taken into account when assessing valve hydrodynamic performance in the MCS [119].

**Durability & Fatigue Testing**

Prosthetic heart valves need to be tested for durability before it can be implanted in humans to ensure its long-term performance in the body. It has to be able to withstand the physiological loading of a beating heart and the stress and strain of the blood flowing through it. Testing of transcatheter heart valves involves two parts; the valve and the stent. The valve is tested for leaflets opening and closing, leaflet sutures and strut resistance in the axial direction for 200 million cycles [119]. The stent, on the other hand, is subjected to 400 million cycles which is simulated to be an accelerated time of 10 years [121]. This is to ascertain no structural failure will occur to the stent. Computational simulation exercises such as finite element analysis is usually performed prior to the testing to analyse the stress and strain on the valved stent before and after implantation [122].

**Device Testing**

To further simulate in vivo conditions, 3D compliant anatomical vasculature models can also be used. This simulator can be equipped with specific cardiac cavities to facilitate transcatheter valve deployment and functionality. Parameters such as valve positioning, deployment accuracy, delivery system trackability, torqueability, flexibility and heart valve-in-vehicle deployment can be explored [123]. The valve deployment can be monitored using a built-in video synchronisation system while the proximal and distal forces can be determined [119].

**CURRENT CLINICAL OUTCOMES**

Clinical outcomes of medical devices are initially judged based on the clinical trials that are conducted. However, with the surge of new transcatheter heart valves, the clinical trials are done with no consensus, making it difficult to make sense of the results [124]. Thus, groups from USA and Europe set up the Valve Academic Research Consortium (VARC) to agree upon the appropriate clinical endpoints reflecting device, procedure and patient-related effectiveness and safety, and standardizing definitions for single and composite clinical endpoints [124]. This is to establish a homogeneous transcatheter aortic valve clinical research. Proposed safety and efficacy endpoints are one year mortality (all-cause mortality as primary endpoint and cardiovascular mortality as secondary endpoint), myocardial infarction, stroke, acute kidney injury, bleeding and vascular complications. According to VARC, transcatheter aortic valve performance in patients is analyzed based on two criteria which are its hemodynamics and clinical findings that demonstrate any cardiovascular or valve failure. Hemodynamics is measured using echocardiography while transthoracic echocardiography (TTE) is used to detect impairment of prosthetic valve function. Transoesophageal echocardiography (TEE) may be used in complex cases. The endpoints of valve performance include valve regurgitation, stenosis, endocarditis and thrombosis. The various unique designs of the prosthetic aortic valve can lead to unexpected complications due to the surrounding anatomical features [124]. In view of that, the consortium came up with a separate endpoint category for associated complications. These endpoints consist of conduction disturbances and cardiac arrhythmias, coronary obstruction and other adverse events. There are also clinical benefit endpoints and therapy-specific endpoints. Examples of the former include exercise performance, quality of life and frailty questionnaire. Therapy-specific endpoints, on the other hand, are dynamic such that it can be applied to anything that is pertinent to clinical outcomes or device performance such as the switch to open heart surgery during TAVI [124]. The final group of endpoints is the composite of more than one endpoint. VARC recommends three composite endpoints that is device success, a combined safety endpoint (at 30 days) and a combined efficacy endpoint (at 1 year or longer). For instance, device success is a mix of device performance, successful delivery of the device and correct positioning whereas combined safety is the combination of safety endpoints such as major stroke and vascular complications [124]. Since TAVI is still in the infancy stage,
further refinements can be done to produce a comprehensive guidance document for prosthetic heart devices. Similarly, the same can be done for TMVI to cater for future influx of new TMVI.

Technical Difficulties

For every new technology, there exist technical challenges that need to be overcome in order to attain desirable results. Some of these may be easy to solve but not for others. Transcatheter heart valve implantation is not exempted from these challenges.

Optimal positioning is crucial in transcatheter heart valve implantation as any malpositioning can cause detrimental results such as the impediment of coronary flow. The imaging modalities available to assist the cardiologist such as fluoroscopy, ultrasound, angiography and supplemental imaging with transthoracic and transesophageal imageries may be suitable for balloon valvuloplasty but are inadequate in providing precise three-dimensional imaging which is required of THV [125]. Fluoroscopy offers limited visualisation of the anatomy due to its poor soft-tissue contrast whereas ultrasound is unable to distinguish the THV from the catheter that is guiding it [126]. In view of this, companies have come up with various modes of imaging tools such as 3D TEE. Better imaging systems should be created so that the surgeons can easily guide the THV to its desired location by providing a clear delineation of the surrounding anatomical structures and also to allow post-surgical evaluation since positioning is vital in THV.

On the other hand, malpositioning of the THV can also be a result of the surgeon’s unfamiliarity to this new procedure. Transcatheter heart valve implantation is known to have a steep learning curve. The transcatheter implantation of the Cribier-Edwards balloon-expandable stent valve via the retrograde approach resulted in improved rates of procedural success, malposition, intraprocedural and perioperative mortality in the second batch of patients as compared to the first [56]. Since this is a new technology, many surgeons will need to learn the skill of controlling and manipulating the THV in the shortest time possible so as to reduce the number of failures.

Other than that, this procedure is usually done in a hybrid operating theatre to allow the switch between THV procedures to open heart surgery if the need arises [127]. Thus, in order to prepare for the worst, surgeons need to have prior experience with THV which includes extensive knowledge of the various access routes and also be fully equipped with the skills needed for open heart surgery which can be demanding. Hospitals should also be furnished with hybrid operating theatres that would allow this technology to be implemented.

CURRENT AND FUTURE DEVELOPMENT

Transcatheter heart valve implantation represents a promising, new technology that aims to replace the high-risk surgical heart valve replacement. Expectedly, it has many hurdles to cross before it can reach its optimum goal. One of the major drawbacks is the issue of paravalvular leakage which is possibly due to the valve not being sutured into place. Paravalvular leakage greatly reduces the efficiency of the valve regardless of the intrinsic design of the THV. Innovators should look into ways of curbing this problem. Another issue that should be looked at is the incidence of stroke. Stroke is a major concern in THV as its incidence is higher in patients receiving THV than those surgically or medically treated. Stroke is brought about by embolic events from the insertion of the cannula, valve implantation and debris from the prosthesis [128]. Hence, the delivery system of the THV should be re-designed such that patients are not subjected to a higher stroke risk as compared to other treatments. Additionally, migration is an issue in THV, especially in TMVI due to the omission of radial force to secure the prosthesis into place. Besides hooks, other locking mechanisms should be explored to prevent migration. On top of that, the locking design should allow simple deployment and should not be compromised during crimping.

This new area also lacks hemodynamic studies. More studies should be done to compare the hemodynamic performance of various THV. In that way, the strengths and weaknesses of the THV will be apparent which can shorten the valve design process. The hemodynamic performance of the valve is crucial in valve design as it will determine whether the valve is in working order or otherwise, thus, more attention should be given to it.

TMVI is an exciting new area because of the complex anatomy of the mitral valve which makes the design of the prosthesis a challenging task. In order to make the process less arduous, design considerations for TMVI should be studied extensively. More computational and experimental research work on the design aspects of the prosthesis and delivery technique should be carried out.

Finally, construction of patient customised prosthetic heart valves should be considered as it would solve many issues, particularly patient-prosthesis mismatch as every individual’s valvular anatomy differs.

CONFLICT OF INTEREST STATEMENT

The authors declares that there is no conflict of interest.

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ABBREVIATIONS

TAVI = Transcatheter Aortic Valve Implantation
ePTFE = Expanded PolyTetraFluoroEthylene
PET = PolyEthylene Terephthalate (PET)
PU = PolyUrethane
EOA = Effective Orifice Area
TMVI = Transcatheter Mitral Valve Implantation
TEE = TransEsophageal Echocardiography
CT = Computed Tomography
THV = Transcatheter Heart Valve
AG = AnteGrade
RG = RetroGrade
TA = TransApical
SC = SubClavian
LVOT = Left Ventricular Outflow Tract
PVDF = PolyVinylIден Fluoride
BSA = Body Surface Area
TPG = Transvalvular Pressure Gradient
MCS = Mock Circulatory System
PIV = Particle Image Velocimetry
VARC = Valve Academic Research Consortium
AVR = Aortic Valve Replacement
RSS = Reynolds Shear Stress

REFERENCES


