UNIVERSITÀ
DEGLI STUDI
DI PADOVA

DIPARTIMENTO
DI INGEGNERIA
DELL'INFORMAZIONE

DIPARTIMENTO DI INGEGNERIA DELL'INFORMAZIONE

CORSO DI LAUREA IN BIOINGEGNERIA

"Polymeric Heart Valves: the state of the art"

Relatore: Prof. Andrea Bagno

Correlatore: Ing. Martina Todesco

Laureando: Gianluca Lezziero

ANNO ACCADEMICO 2023 – 2024

Data di laurea: 21 Ottobre 2024

Index

Abstract

Recently, with the increasing number of people suffering from cardiovascular diseases (e.g., heart valve stenosis and/or insufficiency), the attention paid to artificial heart valves has grown significantly. The development of a prosthetic device that fully replaces the functionality of the native valve remains a challenge. Polymeric heart valves have the potential to better mimic native valves, combining the durability of mechanical valves with the biocompatibility of bioprosthetic ones. Over the years, novel biomaterials (such as promising new polymers and nanocomposites), and innovative designs have been explored for possible application in developing polymeric heart valves (PHVs). In the present work, the evolution of PHVs in terms of material, design, and fabrication are illustrated, including *in vitro* and *in vivo* studies. Moreover, the drawbacks associated with the implementation of prosthetic valves are highlighted, and possible future directions for their further development are discussed.

1. Introduction

Valvular heart disease (VHD) remains a significant global health concern, affecting millions of people worldwide and causing premature mortality, disability, and reduced quality of life [1]. As the population increases and ages, the prevalence of valve-related disorders (e.g., aortic stenosis or mitral regurgitation) continues to rise, leading to a growing demand for effective and durable heart valve replacements. A report from 2024 highlights that the global prevalence of VHD for aortic and mitral valves is 13.3% and 15.5%, respectively [2]. Between 1990 and 2019, the incidence of calcific aortic valve disease, a major cause of heart failure, increased by 90% [2].

Currently, the primary treatment for VHD is the surgical heart valve replacement with either biological or mechanical valve prostheses, performed in approximately 250,000-300,000 patients worldwide per year [3]. On the other hand, these established solutions have some limitations, such as the need for lifelong anticoagulation therapy and susceptibility to structural deterioration. The decision of which type of valve must be implanted is mainly based on patient-related factors (e.g., contraindications to anticoagulation therapy, age, and place of residence).

In recent years, another type of prosthetic heart valve made of polymeric material has emerged as an alternative to both biological and mechanical devices, offering potential advantages in terms of durability, biocompatibility, and ease of manufacturing. These polymeric valves are designed to overcome the drawbacks of traditional prostheses by eliminating animal-derived proteins and reducing the risk of calcification and immune response [4]. Moreover, advancements in polymer science and materials engineering have enabled the development of novel polymeric materials with tailored properties, such as enhanced flexibility, strength, and wear resistance.

This thesis aims to explore recent developments in polymeric heart valve technology, highlighting material selection, manufacturing, design, and functional characteristics. By addressing the critical challenges associated with valve replacement, including thrombogenicity, durability, and hemodynamic performance, polymeric valves hold the potential to revolutionize the field of cardiovascular implants.

1.1 Methodological approach and scope

References for this thesis were identified through searches on PubMed and Google Scholar from 1950 until July 2024 with the following keywords: "polymeric heart valves", "artificial valves", "heart valve diseases", "polymeric material", "polymeric fabrication",

"hemocompatibility polymers", "biostable polymers", "heart valve degeneration", "heart valve treatment", "mechanical properties polymers", "heart valve anatomy", "valve layers", "valve stenosis", "valve regurgitation", "mechanical valves", "valve replacement". Articles were also identified through searches of the authors' own files and the reference lists of identified papers (excluding publications in languages other than English). Among over 100,000 results, the final reference list was created based on relevance, excluding topics regarding "biodegradable polymers" and "tissue engineering".

1.2 Native heart valves

Understanding anatomy and function of native heart valves is crucial for developing and optimizing prosthetic heart valves. Native heart valves play a fundamental role in ensuring unidirectional blood flow through the heart, preventing backflow and maintaining efficient circulation. The human heart contains four valves: aortic, mitral, tricuspid, and pulmonary valves, each with unique structure and function, depending on the specific location within the heart.

1.2.1 Anatomy

The heart is a complex muscular organ responsible for pumping the blood throughout the body. It consists of four chambers: the right and left atria, and the right and left ventricles. These chambers work in a coordinated manner to ensure the continuous flow of the blood to the lungs for oxygenation and to the rest of the body to supply oxygen and nutrients and remove carbon dioxide and catabolites. The heart contains four valves that regulate blood flow and allows it moving in the correct direction, preventing backflow (**Figure 1.1**). These valves open and close cyclically in response to pressure changes [5]. The tricuspid and mitral atrioventricular valves separate the atria from the ventricles in the right and left sides of the heart, respectively. The aortic valve separates the left ventricle from the aorta, and the pulmonary valve separates the right ventricle from the pulmonary artery. Heart valves are composed of flexible yet strong tissue structures, primarily made up of collagen, elastin, and glycosaminoglycans [5]. These components provide the mechanical properties needed for the valves to withstand the repetitive opening and closing movements during cardiac cycles.

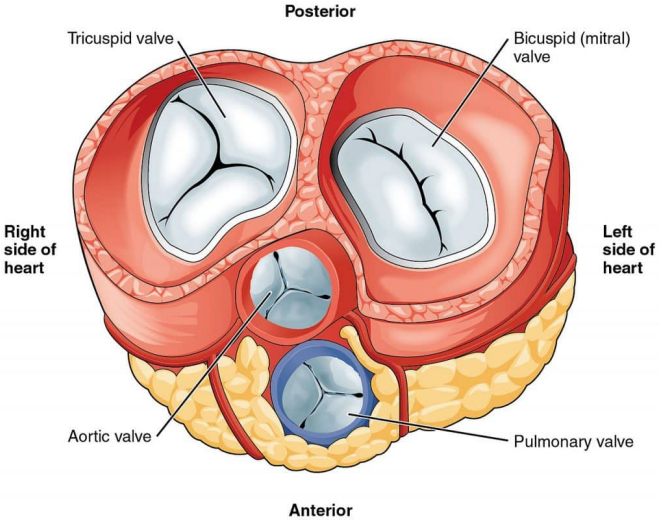


Figure 1.1. Top view of the heart with the atria and major vessels removed.

More specifically, the mitral valve is composed of several fundamental components: the mitral anulus, the valve leaflets, the chordae tendineae, and the papillary muscles [6]. The mitral annulus is a fibrous ring that provides structural support to the valve, maintaining its shape and helping it function properly during the cardiac cycle. The mitral valve has two leaflets, the anterior (or aortic) and the posterior, which open to allow the passage of the blood during diastole, and close during systole to prevent reflux. The chordae tendineae are thin strands of connective tissue that connect the valve leaflets to the papillary muscles inside the left ventricle [6]. These muscles contract during ventricular systole, tensing the chordae tendineae and keeping the valve leaflets closed, preventing prolapse and ensuring a tight closure of the valve. The tricuspid valve, on the other hand, is made up of three cusps: posterior, anterior, and septal. These leaflets are connected to the annulus fibrosus, which provides structural support to the valve. The chordae tendineae connect the valve leaflets to the papillary muscles within the right ventricle [6].

The pulmonary valve consists of three semilunar cusps: anterior, right, and left cusps, each of which inserts into a fibrous ring [7]. During ventricular systole, the pulmonary valve cusps open, allowing deoxygenated blood to flow into the pulmonary artery and then into the lungs for oxygenation; during diastole, the semilunar cusps close to prevent blood flowing back into the right ventricle [7].

The aortic valve is composed of three semilunar cusps: right, left and non-coronary cusps, inserted into a fibrous ring [7]. It is the valve most frequently affected by valvular diseases, which can be due to various factors. The aortic valve is located between the left ventricle and the aorta being responsible for ensuring the one-way flow of the blood from the ventricle to the

rest of the body, preventing reflux. During ventricular systole , the aortic valve must withstand the highest pressure within the heart, which can exceed 120 mmHg. This ongoing mechanical stress can cause structural damages over time. Other contributing factors may include aging, degeneration, calcification, and the presence of turbulent blood flows due to the position of the valve.

Heart valve leaflets are structured to withstand the dynamic environment of the heart and are mainly composed of three distinct layers. The fibrosa is the external layer, the thickest one, and is mainly composed of a dense network of collagen type I fibers [8]. Functionally, this layer provides a robust structure to resist mechanical forces during the cardiac cycle and it extends over the entire leaflet surface. With regard to the aortic valve, the ventricularis layer (or atrialis layer for the mitral and tricuspid valves) is the internal one and faces the left ventricle (or left atrium for the mitral valve and right atrium for the tricuspid valve). It is composed of a dense network of elastin fibers and collagen [8]. The physiological function of this layer is to help in minimizing large radial strains that could appear when the valve is fully opened and the forward flow is at its maximum [8]. In the middle, there is the spongiosa layer, which contains a high concentration of glycosaminoglycans (GAGs) and proteoglycans (PGs) [9]. This layer imparts flexibility and resilience to the valve leaflets and helps maintaining hydration and lubrication, crucial properties for their durability and ability to withstand the repetitive stresses imposed by the heart function [9]. All these layers are encased in a sheath of endocardial endothelial cells interlaced with valve interstitial cells [5]. These cells have a homeostatic activity that aids in the daily function of the valve. They create a barrier that prevents the adhesion of blood cells and platelets, maintaining smooth blood flow and preventing clot formation [9]. Moreover, this layer adapts to mechanical stresses imposed by the pulsatile nature of the blood flow, plays a role in modulating local inflammation (e.g., endothelial cells can release cytokines and chemokines in response to injury or inflammation), and can produce and release various substances that regulate blood vessel tone and blood flow dynamics (e.g., endothelial cells can release nitric oxide (NO), which helps maintaining optimal blood vessel dilation) [5],[8].

Mechanical and biological properties of native heart valves due to their complex structure, are the basis of research and development in the field of polymeric heart valve.

1.2.2 Valvular diseases

Understanding the diseases of native heart valves is crucial for developing effective treatment strategies and advancing in the design of prosthetic heart valves. Native heart valve diseases encompass a range of conditions that impair valve function, leading to significant

cardiovascular complications. These diseases can be due to congenital defects, degenerative changes, inflammatory processes, or infectious agents. A detail examination of these conditions, including their etiology, pathophysiology, and clinical manifestations, provides essential insights into their impact on cardiac function.

The main pathologies are herewith described, highlighting the mechanisms underlying valve dysfunction and the resulting clinical consequences.

- **Rheumatic Heart Disease (RHD)**: it is a chronic condition that mainly affects children and young adults in developing countries, where the access to adequate healthcare and antibiotic treatments is limited [10]. RHD results from acute rheumatic fever (ARF), an inflammatory disease that can arise after a preventable infection by the bacterium Strep A (Group A Streptococcus) [11]. If the infection and ARF are not treated, repeated infections can occur. ARF-associated carditis is characterized by progressive damages to the heart valves, leading to long-term complications and increased morbidity and mortality [11].

  ARF is an autoimmune response: after the infection, the immune system mistakenly attacks its own tissues, particularly heart, joints, skin, and central nervous system. This autoimmune reaction involves molecular mimicry, where the streptococcal antigens resemble human tissue proteins, leading to immune cross-reactivity [12]. The inflammation caused by ARF can affect all layers of the heart (pancarditis), but the most significant and lasting impact is on the heart valves, particularly mitral and aortic valves [12]. The inflammatory process results in swelling, necrosis, and fibrinoid degeneration of valvular tissues, followed by scarring and fibrosis, which can make the valves to become stenotic or regurgitant [12]. ARF typically presents with a combination of symptoms including fever, migratory arthritis (painful and swollen joints), carditis (inflammation of the heart), Sydenham chorea (involuntary movements), erythema marginatum, or subcutaneous nodules [12]. Carditis is the most serious manifestation. The long-term consequences of RHD include valve stenosis and/or regurgitation, with the possibility of both in one or more valves [10]. When antibiotic strategies or medications to manage the symptoms fail, valve repair or replacement surgery are necessary. It is important to highlight that in those regions of the world where the number of operations is rationed, valve replacement is often chosen over valve repair [11].
- **Heart valve stenosis**: it is a condition characterized by the narrowing of one or more of native heart valves, which restricts blood flow. The main consequences of valve

stenosis can be an increased cardiac workload, a decreased cardiac output (leading to reduced oxygen for tissues and organs), arrhythmias, and thromboembolisms. Narrowing can affect any of the heart valves, although it most commonly impacts the aortic and mitral ones. Several are the causes of valve stenosis (**Figure 1.2**): inflammatory rheumatic heart disease, degenerative calcification, congenital heart defects (e.g., congenitally bicuspid aortic valve), endocarditis, and radiation therapy [13].

As mentioned above, valve stenosis can affect all the valves, though it is rarer for the pulmonary and tricuspid ones. Pulmonary valve stenosis is almost always congenital in origin [14]. While the normal pulmonary valve is trileaflet, the congenitally stenotic valve may be unicuspid, bicuspid, or dysplastic. Tricuspid stenosis is the least common form of valvular stenosis, largely due to the low incidence of RHD, which is the main cause [14]. The mitral and aortic valves are the most frequently affected. Regarding the mitral valve, stenosis is the most frequent valvular complication of ARF. Other causes include leaflet thickening, chordal shortening and fusion, and superimposed calcification, all of which can contribute to the restriction of leaflet motion [14]. Aortic stenosis is prevalent, affecting about 5% of the population at age 65 and increasing with aging. It is the second most common valvular disease in the USA [15]. The main causes of aortic stenosis are rheumatic valve disease, calcification, and congenitally bicuspid aortic valve (often with superimposed calcific changes) [14]. Although rheumatic aortic stenosis is the most common cause worldwide, in the USA and Europe, bicuspid aortic disease accounts for about 50% of all valve replacements for aortic stenosis [14]. In most cases, the bicuspid valve results from the fusion of the left and right coronary cusps, resulting in a smaller posterior cusps and larger anterior cusps (~80% of cases), while the fusion of the non-coronary and right cusps results in a larger right cusp (~20% of cases) [14].

In general, diagnosis requires echocardiography to assess the structure and functionality of the valves, and treatment options range from medication to manage symptoms, to surgical interventions such as valve repair or replacement. Early detection and appropriate management are crucial to prevent the progression of the disease and maintain optimal heart function.

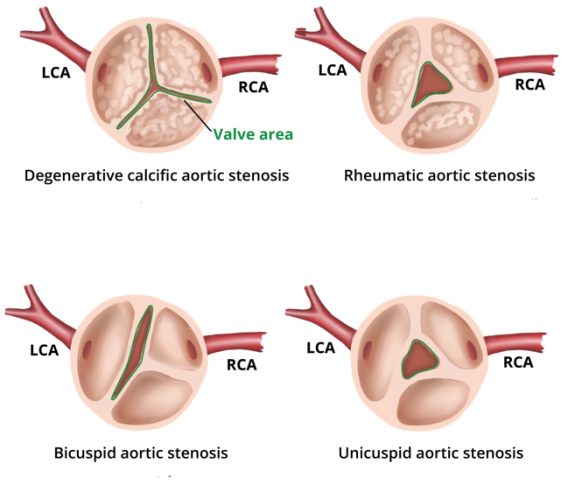


Figure 1.2. Different causes of aortic valve stenosis. In figure RCA and LCA are represented as Right Coronary Artery and Left Coronary Artery, respectively.

- **Heart valve prolapse**: it is a condition in which one of the heart valve leaflets bulges or prolapses backward during contraction. This typically affects the mitral valve, but rarely it can also involve other valves. Prolapse means that the valve does not close properly, resulting in valve regurgitation, complicated by heart failure or arrhythmia, that could also lead to sudden death [16].

  The most common case is mitral valve prolapse (MVP), which occurs in about 2-3% of the general population [17]. Specifically, it consists of a 2 mm or more displacement during systole of the body or the tip of the valve leaflet above the plane of the mitral annulus [17]. MVP is frequent in some syndromic diseases, but it is generally found in isolated, non-syndromic forms, due to different factors such as degenerative disease, congenital abnormalities, or after trauma or infections [17]. With regard to the other valves, the incidence of valve prolapse is very low, around 1% for the aortic valve [17]. Heart valves prolapse is a condition that requires careful monitoring and appropriate management to prevent complications and maintain optimal heart function.
- **Heart valve regurgitation**: also known as valve insufficiency, it occurs when a heart valve fails to close properly, allowing blood to flow backward. This condition can affect each of the four heart valves but is more common for the mitral and aortic ones. Aortic regurgitation can be mainly due to a bicuspid valve or aortic root dilation [15]. This disease is diagnosed in 8.5% of women and 13% of men, with an increasing prevalence

with aging [15]. Mitral regurgitation is also fairly common in the population, and for people aged 75 or more, it is around 10% [18].

The causes of valve regurgitation (**Figure 1.3**) can be divided into organic valve regurgitation (or primary regurgitation), which involves the structural alteration of the heart valve due to lesions or degenerative disease (e.g., mitral annular disjunction syndrome), and functional regurgitation (or secondary regurgitation), where the valve is morphologically normal, but the blood backflow is caused by abnormal changes in ventricular/atrial function and geometry (e.g., ischemic cardiomyopathy) [18]. In general, causes of valve regurgitation include degeneration, inflammation, tissue disruption, infection, trauma, iatrogenic factors, or congenital abnormalities [19].

The diagnosis of heart valve regurgitation can involve different techniques, such as 2D/3D echocardiography, cardiac magnetic resonance, or other types of imaging procedures [19]. However, symptoms caused by regurgitation can persist even after medical therapies, and in most cases of severe regurgitation, the onset of symptoms identifies patients who are already developing other heart dysfunctions and who are, therefore, at higher risk of surgical complications.

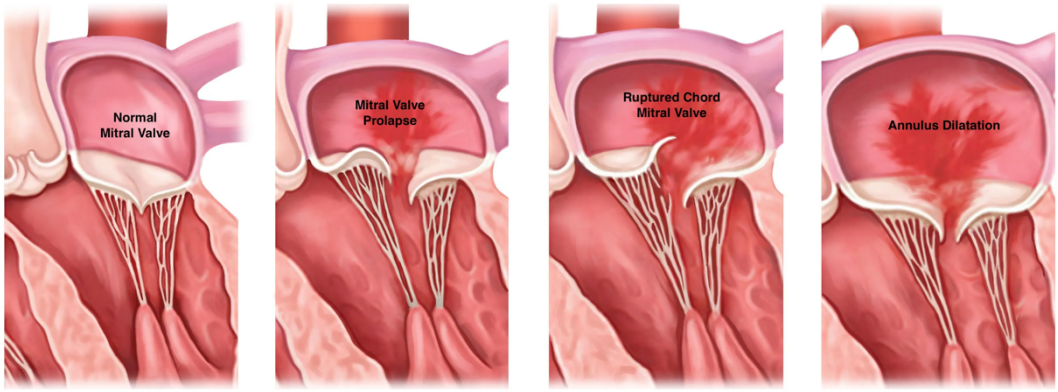


Figure 1.3. Different causes of mitral valve regurgitation.

- **Infective Endocarditis (IE)**: it is a severe microbial infection that can affect the inner layer of the heart chambers and valves or indwelling cardiac devices [20]. This condition primarily affects the heart valves. It causes a high mortality rate despite progress in diagnosis and medical therapies: about 19-82% of 5-year mortality and 6-50% in-hospital mortality [20]. The main risk factors for developing IE follow valve replacement, cardiac factors (e.g., congenital valvular abnormalities, rheumatic heart disease, degenerative valvular disease, or post-cardiac transplant of indwelling cardiac

devices), and non-cardiac risks (e.g., intravenous drug use, chronic liver disease, hemodialysis, poor dentition, or advanced age) [20].

IE development on native tissue typically starts with valvular endothelium damage or inflammation (**Figure 1.4**), when pathogens adhere directly due to fibrin deposition, or indirectly with the activation of endothelial cells, which can trigger the adsorption of the von Willebrand factor: this latter promotes platelet recruitment, leading to the formation and deposition of fibrin [20]. Fibrin and von Willebrand factor are crucial for the initial adhesion of bacteria. In the case of indwelling devices or prosthetic valves, bacterial adhesion is promoted by disturbed blood flow and/or blood protein adsorption, or due to contamination with patient's own skin flora during implantation [20]. Once adhered, bacteria form a protective structure composed of several layers and host components, such as proteins, platelets, fibrin, and extracellular DNA. In the clinical setting, this structure is called biofilm (or vegetation), and it confers several advantages to bacteria, such as strong endothelial adherence and protection against antimicrobial treatments and against immune defense [20].

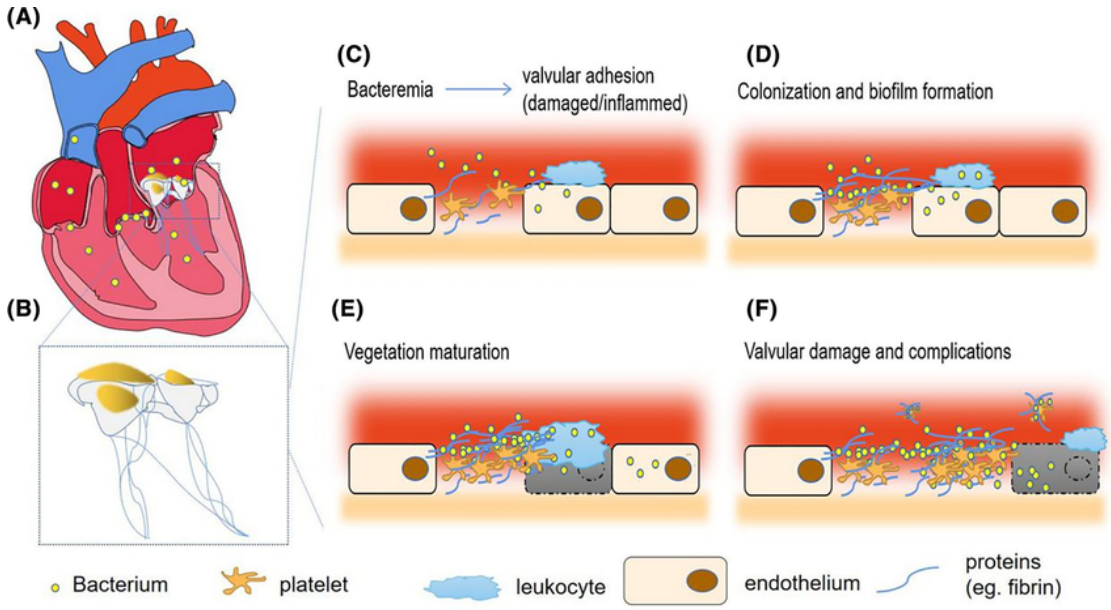


Figure 1.4. Pathogenesis of IE. *A,B*) Valve vegetations in IE. *C*) Bacteria adhesion inflamed valves and cause infection. *D*) Bacteria proliferation and biofilm formation. *E*) Progression of vegetation maturation along with valvular damage. *F*) This progression results in several clinical symptoms and complications [21].

IE treatment involves prolonged courses of intravenous antibiotics to eradicate the infection. In cases of severe valve damage, heart failure, or uncontrolled infection, surgical intervention may be necessary to repair or replace the affected valve. Prompt

and appropriate treatment is essential to prevent complications such as heart failure, stroke, or systemic embolization, even after surgical intervention where the infection can persist.

2. Current therapeutic approaches

Heart valve diseases represent significant clinical challenges due to their impact on cardiac function and patient morbidity. As the prevalence of these conditions continues to rise with an aging population, the development and implementation of effective therapeutic strategies become fundamental. Various current therapeutic approaches for heart valve diseases exist, including pharmacological treatments, minimally invasive procedures, and surgical interventions aimed at repairing or replacing diseased valves. While surgical intervention is frequently necessary, it is often considered the last option due to its invasive nature and associated risks.

2.1 Pharmacological approach

Valvular treatments depend on the type and severity of the disease. Drugs may be useful in cases of less severe valvular diseases or as a bridge to surgery for patients with more severe disease. Although drugs can address the principal issues such as stenosis or regurgitation, they do not work on all valves.

Based on the type of disease, different pharmacological treatments are proposed. For aortic stenosis, studies have been conducted with statins, bisphosphonates, and ACEIs/ARBs [22]. Statins have shown good results in reducing cholesterol levels and managing atherosclerotic cardiovascular disease, but for aortic stenosis they did not show significant effectiveness in slowing disease progression or improving outcomes in clinical trials [21]. Similarly, since bisphosphonates can inhibit vascular calcification, different studies investigated their potential to delay progression or induce regression of aortic stenosis, but with no success [21]. Enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) showed reduced calcium accumulation during studies, but they need further investigations regarding stenosis. For aortic regurgitation, the focus is on different vasodilators and beta-blockers [21]. While beta-blockers are currently under study, some vasodilators have shown good results: long-term treatment with nifedipine reduced mortality and morbidity in patients with severe aortic regurgitation; ACEIs, indirect vasodilators, showed a reduction in regurgitant volume [21]. For mitral regurgitation, ACEIs/ARBs are commonly employed for both types of MR, but are more useful in functional MR, while beta-blockers are currently under study, but with no beneficial results [21]. Regarding mitral stenosis, pharmacological therapy cannot affect valve dysfunction, but reducing heart rate to lengthen diastole can enhance symptoms and

hemodynamic abnormalities [21]. This can be achieved using beta-blockers or non-dihydropyridine calcium channel blockers.

To prevent or combat infectious diseases, antibiotics are prescribed, especially during dental procedures or other surgeries. For instance, some commonly used antimicrobials to treat IE are β-lactams, glycopeptides, and, more rarely, lipopeptides such as daptomycin [23]. Regarding RHD, as ARF is associated with group A streptococci, penicillin is commonly used, while macrolide antibiotics (e.g., erythromycin, roxithromycin, or azithromycin) are preferred for patients with allergic reactions to penicillin [24]. In recent years, other different antibiotics were approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), such as oritavancin, dalbavancin, ceftaroline, and ceftobiprole, showing good hopes for treating various infections [25].

Another pharmacological treatment is based on antithrombotic therapy, including anticoagulant and antiplatelet therapies. It is an important treatment, particularly for prosthetic heart valves recipients, for whom the risk of thromboembolic complications is greatest during the first three months after surgery, patients undergoing valve repair, or those with specific native valve conditions that predispose them to thromboembolic events [26]. Commonly used anticoagulants are vitamin K antagonists (VKAs) and direct oral anticoagulants (DOAs) [25]. VKAs inhibit the synthesis of vitamin K-dependent clotting factors; warfarin is the most used, often for life-long anticoagulant therapy following mechanical valves implantation [27]. DOACs, such as dabigatran, rivaroxaban, apixaban, or edoxaban, are used to prevent stroke in atrial fibrillation but are generally not recommended for patients with prosthetic heart valves due to the higher risk of thromboembolic events and valve thrombosis compared to warfarin [26]. Antiplatelet agents are often used in combination with anticoagulants. Aspirin is the most used, inhibiting platelet aggregation, and in most cases, the conjunction with warfarin leads to a lower risk of embolic events, but a higher risk of bleeding, compared to aspirin alone [25]. P2Y12 inhibitors are another class of antiplatelet agents, including clopidogrel, prasugrel, and ticagrelor. They are less frequently used but can be combined with aspirin in high-risk patients, particularly after valve replacement surgery [26],[27].

2.2 Surgical approach

Surgical approaches for heart valve diseases can be divided into two main groups: minimally invasive procedures and traditional surgical interventions, the choice depending on the patient's specific valve disease, overall health, and risk factors.

Minimally invasive approaches for treating heart valve diseases offer significant benefits in terms of recovery times, postoperative pain, and reduced risks of complications compared to traditional open-heart surgeries. However, these approaches are not suitable for treating complex or severe cases. The main procedures are:

- *Mitral valve Transcatheter Edge-to-Edge Repair* (M-TEER), a non-surgical treatment mainly for mitral regurgitation; it is suitable for patients who are not candidates for open-heart surgery. The M-TEER procedure involves a device to clip together the valve leaflets to reduce regurgitation (**Figure 2.1**) [28]. Specifically, a guide catheter is used in the percutaneous procedure, which is inserted typically from the right femoral vein into the left atrium. A device with a clip is then steered through the mitral valve and monitored (e.g., by echocardiography and fluoroscopy) until the mitral regurgitation is reduced [29]. In Europe, two M-TEER devices are currently approved for the treatment: the MitraClip (Abbott, North Chicago, U.S.) and PASCAL (Edwards Lifesciences, California, U.S.) systems. The choice of the device is made after a careful evaluation of the patient's disease, anatomical complexity, annular and leaflet calcification, and baseline mitral valve area [27].

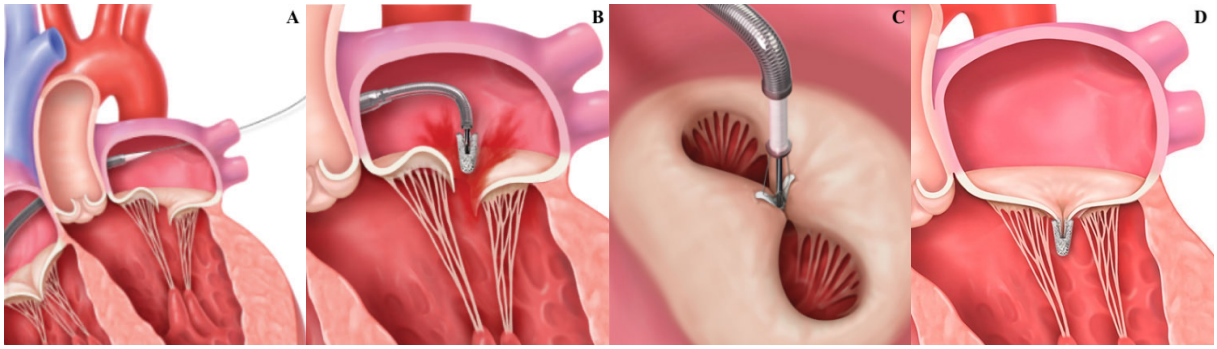


Figure 2.1. MitraClip placement procedure. *A*) Delivery system insertion. *B*) Leading the clip into left atrium to the line of coaptation. *C*) Leaflet grasping, assessment, and hemodynamics measurements. *D*) Removal of the delivery system.

- *Percutaneous Balloon Valvuloplasty* (PBV) is a minimally invasive procedure used to treat stenotic heart valves and aims to restore the normal functionality of the valve [30]. The procedure (**Figure 2.2**) involves the insertion of a guidewire through the vascular access site to the stenotic valve, threading a balloon catheter over the guidewire, and carefully positioning it across the stenotic valve [29]. The balloon is then inflated up to a specific pressure to dilate the valve. Inflation is usually done gradually and may be repeated several times to achieve the optimal dilation, avoiding excessive pressure.

Once the valve has been adequately dilated, the balloon is deflated and removed, along with guidewire and catheter [29].

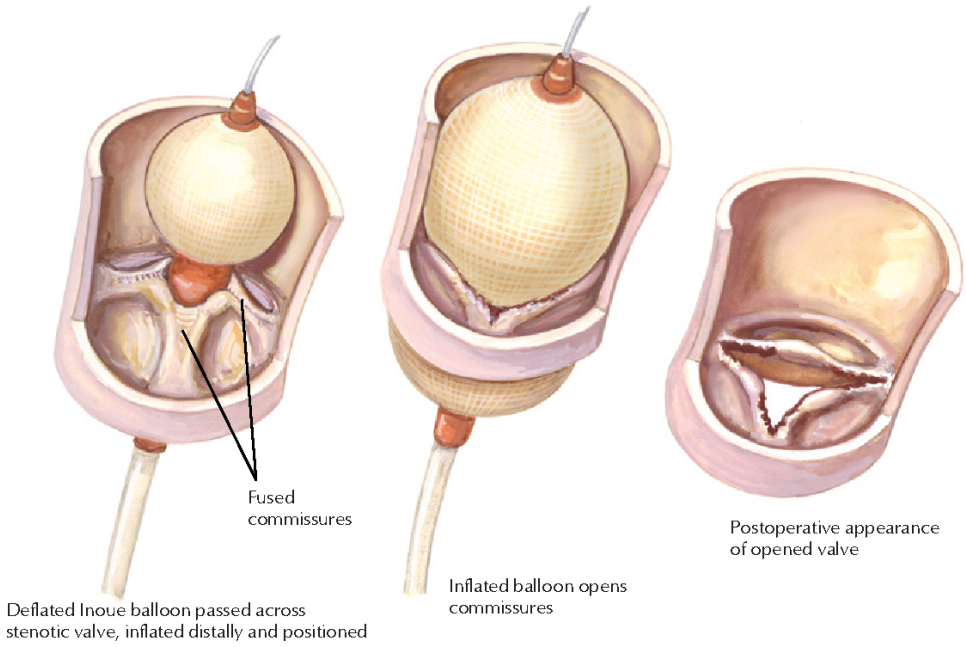


Figure 2.2. PBV procedure to treat fused commissures [31].

- *Transcatheter valve replacement* is a minimally invasive procedure used to replace a diseased heart valve without the need for open-heart surgery. This procedure can be used to treat both aortic and mitral valve diseases. Vascular access is typically performed through the femoral artery (transfemoral approach), although other access points, such as the subclavian artery or direct aortic access, may be used if the femoral route is not suitable [32]. A catheter is inserted through the access site and guided to the heart under imaging monitoring. For transcatheter aortic valve replacement (TAVR), a crimped valve mounted on a balloon-expandable or self-expanding stent is advanced through the catheter to the diseased aortic valve (**Figure 2.3**). Once in the correct position, the prosthetic valve is deployed either by inflating the balloon or allowing the stent to self-expand, pushing the diseased valve leaflets aside and anchoring the new valve in place [33]. For transcatheter mitral valve replacement (TMVR), a similar approach is used, but navigation and deployment can be more complex due to the anatomical position of the native valve [34]. This type of valve replacement offers better results and might be technically less challenging than other consolidated procedures. Nevertheless, it may come with a higher number of complications, and long-term follow-up data are limited [32].

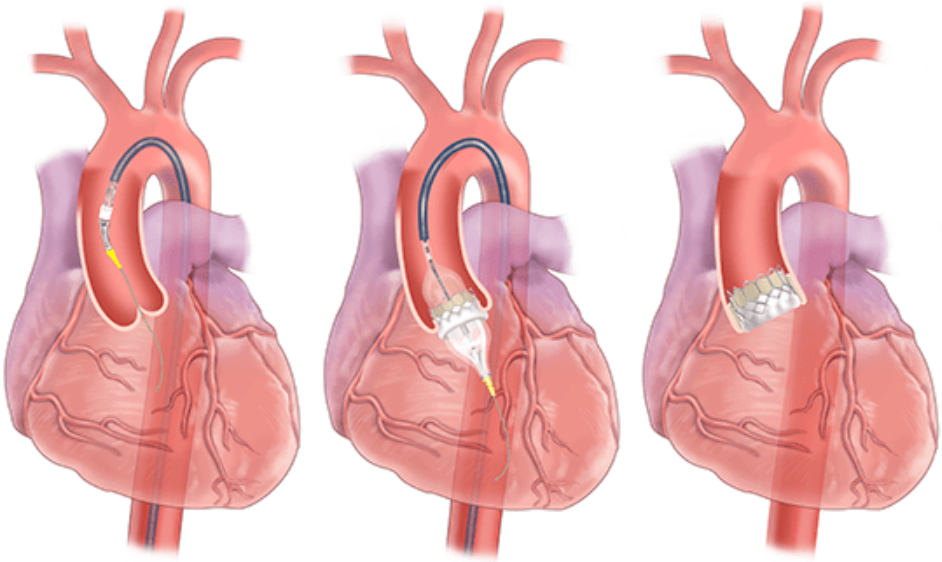


Figure 2.3. Example of TAVR procedure with a balloon-expandable stent.

Regarding traditional surgical interventions (repair and replacement), they involve open-heart surgery and remain crucial for complex and severe cases or when less invasive procedures are no suitable or have failed.

When possible, valve repair is preferred over replacement, as it preserves the patient's own valve and often results in a better heart function and a lower risk of complications. Procedures can concern different parts of the valve. Leaflet repair implies fixing the valve leaflets by removing or adding tissue to ensure their proper closure. It is often used to treat valve prolapse, deformities, or minor lesions [35]. These procedures include resection of prolapsed segments, stitching torn leaflets, and transferring or reattaching the chordae tendineae [33]. Another procedure is annuloplasty, where the valve annulus is reinforced to tighten or reshape it, leading to improved coaptation of the leaflets and a narrowed valvular orifice [33]. This can be done using different techniques, such as simple sutures, posterior annuloplasty bands, or prosthetic rings. To treat stenosis, mainly in the mitral valve, commissurotomy is required: it consists of cutting fused valve leaflets to widen the valve opening [36]. For the aortic valve, different repair techniques are employed: commissuroplasty with Cabrol sutures, root remodeling, root reimplantation, and plication are the most common procedures [37].

If the valve is too damaged to be repaired, replacement is necessary: it involves the surgical removal of the native valve and implantation of a valve prosthesis. The new valve can be of different types, each with specific features, drawbacks and advantages. The choice of the

device depends on various factors, such as patient's age, health conditions, and the specific valve that needs to be replaced.

2.3 Artificial heart valves

The prosthetic heart valves currently used in cardiac surgery are mechanical and bioprosthetic; polymeric heart valves are still undergoing several studies and investigations due to their favorable properties and promising prospective, but currently there are few clinical trials. Other types of valve replacement are homografts and autografts.

- **Homografts**: they are valves withdrawn from human donors, exhibiting several advantages: they mold well to the recipient's aortic annulus, have good resistance to infection compared to synthetic materials, do not require anticoagulation, and have excellent hemodynamic performances (especially for small sizes) [38]. This makes them particularly useful in cases of infection, such as IE. Homografts are commonly used for aortic valve replacement and are especially valuable for patients with complex valve infections or those undergoing reoperative procedures [39]. Several studies have proven that homograft replacements can significantly improve long-term outcomes in patients, but the lack of donors and the possibility of incompatibilities remain issues [38],[40].
- **Autografts**: the Ross procedure implies the use of the patient's own pulmonary valve to replace the diseased aortic valve. The pulmonary valve is then replaced with a homograft. This procedure offers more advantages than homografts, such as the potential for use in pediatric patients due to its propensity for repair and growth, internal innervation of the cusps, and higher cellular viability [38],[39]. On the other hand, the increased complexity and longer duration of the surgery complicate the replacement procedure [38]. Again, several studies showed long-term outcomes for patients, but the procedure is still characterized by limited suitability and possible complications from the graft site [40].
- **Mechanical heart valves (MHVs)**: they are made of synthetic durable materials, such as titanium and pyrolytic carbon. On average, they can normally function for up to 25 years due to their high durability, reducing the need for revision surgeries [41]. On the other hand, since they are made of non-biological materials, they require lifelong anticoagulation therapy to prevent thromboembolic events [39]. Since 1960s, different types of valve designs have been developed (**Figure 2.4**):

- *caged ball valves* have a ball that moves within a cage to open and close the orifice. The original design, i.e. the Starr-Edwards prosthesis, underwent several modifications, and more 200,000 have been implanted worldwide [42];
- *non-tilting disc valves* operate similarly to caged ball valves, but instead of using a ball, a disc opens and closes the orifice [43]. Due to their drawbacks, such as hemodynamic problems and thromboembolic complications, they were replaced by more recent tilting disc valves;
- *tilting disc valves* have a single disc that tilts to open and close the orifice. The Bjork-Shiley prosthesis was the most used in the past, with 360,000 implantations [42]. With the evolution of fabrication processes, the design was changed several times. It is no longer on the market, but other disc valves are produced (e.g., the Medtronic-Hall and the Aortech Ultracor valves) [40];
- *bileaflet valves* have two oscillating leaflets that open and close to regulate blood flow, creating two peripherical and one central orifices [41]. Since the St. Jude valve was introduced in 1977, more than 600,000 have been implanted, and currently, they are the most implanted MHVs due to their reliability and efficient blood flow dynamics [40].

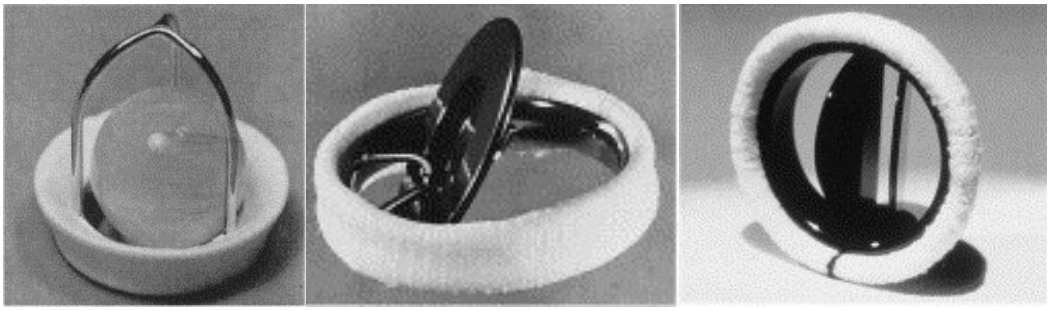


Figure 2.4. Example of MHVs: caged ball valve (*left*), tilting disc valve (*middle*), bileaflet valve (*right*) [41].

Despite the durability of MHVs, they present several drawbacks. Blood flow around the valves causes high shear stress, which can trigger platelets activation, leading to clot formation on the valve surface and increasing the chance of thromboembolic effects [41]. The use of lifelong anticoagulation therapy (e.g., warfarin) reduces the risk but increases the hemorrhagic probability. Other factors that hinder the use of MHVs include the presence of other diseases, such as thrombotic diseases or atrial fibrillation [41].

- **Bioprosthetic Heart Valves (BHVs)**: they are made of animal tissues, typically bovine pericardium or porcine heart valves (**Figure 2.5**), after chemical treatment with glutaraldehyde, which sterilizes the tissues and makes them immunologically compatible with the patient, avoiding any rejection or adverse reaction [44].

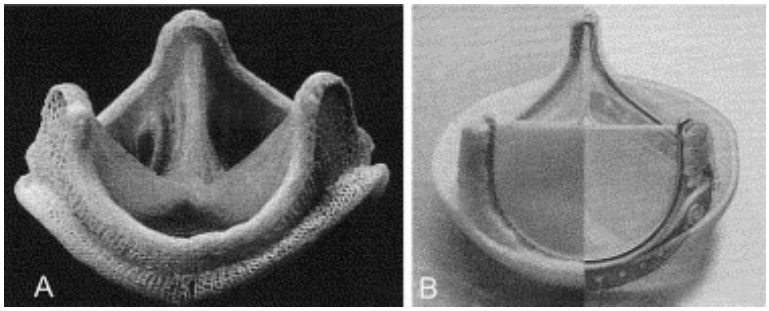


Figure 2.5. Example of BHVs with *A*) porcine, and *B*) bovine pericardial valves [45].

Unlike mechanical ones, BHVs do not require lifelong anticoagulation therapy, reducing the risk of bleeding. Additionally, they offer good hemodynamic performances similar to native valves and do not produce an audible noise, which can be a comfort factor for some patients [41]. On the other hand, they have a shorter lifespan than MHVs (typically 10-20 years), mainly due to calcification and degradation, making them not suitable for younger patients [41],[44]. Every year, tens of thousands BHVs are implanted in elderly patients, but the number of younger people with heart valve diseases is growing [42].

3. Polymeric heart valves

Polymeric heart valves (PHVs) offer an appealing alternative to current heart valve prostheses, as they can address significant limitations of both bioprosthetic and mechanical heart valves. These devices emulate the natural functioning of native heart valve leaflets while also being conducive to large-scale production.

A complete explanation and assessment of polymeric heart valves can be made according to a variety of criteria. First, they will be discussed on the basis of the specific polymers employed, the geometry used in leaflet design, the production techniques, and possible causes of failure.

3.1 The first generation of polymers for heart valves

3.1.1 Polysiloxanes

The first polymers used for the PHVs concept were polysiloxanes, commonly referred to as silicones. Polysiloxanes are characterized by alternating silicon and oxygen atoms in the molecular backbone, along with the capability of accommodating various pendant groups attached to the silicon atom. The most common form, with the repetition of the monomer $[Si(CH_3)_2O]$, is polydimethylsiloxane (PDMS) (**Figure 3.1**).

The physical properties of silicones are influenced by the polymerization degree and the degree of cross-linking among polymer chains [46]. The strong Si-O bond contributes to the high bond strength of silicones, which in turn provides them with thermal and chemical stability; additionally, biocompatibility, bio-durability and fatigue resistance make them versatile materials in medical applications [46],[47].

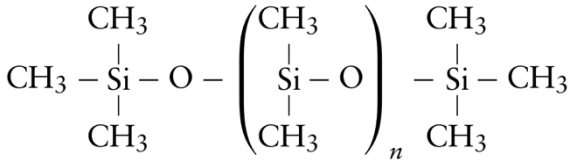


Figure 3.1. Structural formula of polydimethylsiloxane (PDMS).

One of the first flexible trileaflet valves made of silicone was developed in the 1950s by Roe et al., and tested in animals [48]. Evaluated in a dog ascending aorta model, these valves exhibited satisfactory functions in the initial stage. However, the first clinical study was unsuccessful because of post-surgery blood clot complications and high mortality rate [49]. Despite the initial failure, several endeavors to create polymeric heart valves using silicone

elastomers were made. In the 1960s, Roe produced a tricuspid aortic prosthesis from Dacron and polysiloxane (**Figure 3.2**), which was implanted in 18 patients [50]. A limited clinical trial was conducted between 1960 and 1962; however, it was discontinued due to the high mortality rate [51]. Most of the deaths occurred to clinical complications despite the correct functioning of the leaflet mechanism, although embolic complications were observed in three patients. It was reported that the prostheses were verified to be functioning well at 33 to 61 months [51].

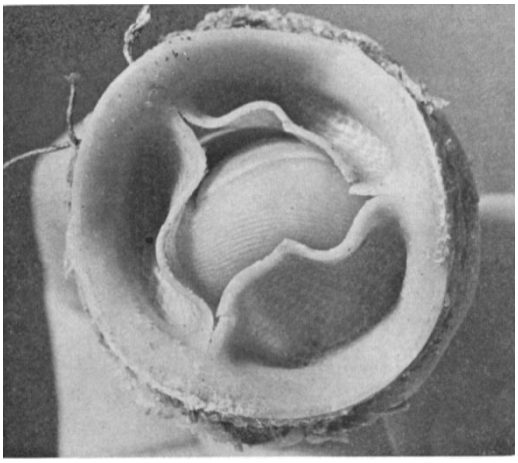


Figure 3.2. The trileaflet valve developed by Roe et al. in the open position [51].

Hufnagel et al. developed and tested trileaflet polymeric heart valves fabricated using a composite silicone rubber-polypropylene fabric, and implanted them in 20 patients [52]. A study was conducted to examine necropsies from these patients who underwent aortic valve replacement. The study concluded that although the trileaflet aortic prosthesis resembles the normal aortic valve in design, these materials are not durable enough to withstand the hemodynamic stresses in this position [52].

Mohri et al. revisited and tested trileaflet silicone valves in the 1970s (**Figure 3.3**) [53]. The study discussed the durability and performance of Silastic trileaflet aortic valves, highlighting concerns regarding water absorption and the large-scale production of these valves. It also explored the importance of vortex formation during the closing phase, that can be a way to prevent fibrin deposition or blood clot formation and identified potential thrombotic effects in animal trials. Regional heparinization was proposed as an effective solution [53].

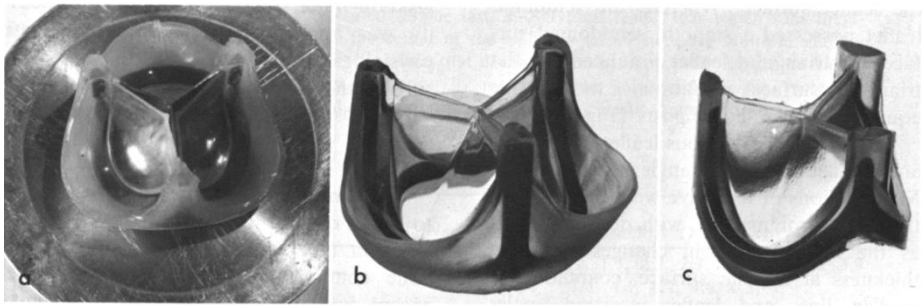


Figure 3.3. Different design of Silastic valve. *a*: valve with semidome-shaped leaflets, *b*: valve with triangular-shaped leaflets, *c*: final model of valve [53].

Despite the extensive utilization of polydimethylsiloxane-based devices and implants across various medical disciplines, these early studies showed that the durability was a critical issue that did not keep up with the pressure generated by blood flow. Other studies, even recently, demonstrated positive outcomes with the use of PDMS, either as a coating, a surface-modifying end group, or when incorporated into other polymers.

In the early 2000s, Simmons et al. illustrated the efficacy of a flexible PDMS-based polyurethane, synthetized using 20% poly(hexamethylene oxide) (PHMO) and 80% PDMS macrodiols, which exhibited excellent biostability and improved long-term biocompatibility. The functional properties were determined by both *in vivo* tests, using scanning electron microscopy (SEM) on explanted samples from sheep after 24 months, and *in vitro* tests [54]. Additionally, PDMS proved beneficial when employed as a surface modifier for polyurethane. Due to the low surface energy, siloxane groups migrate onto the surface, creating a siloxane-rich polyurethane surface [55]. This modification was shown to provide enhanced *in vivo* degradation resistance. However, under high strain conditions, it revealed pitting and cracking damages [56]. Dabagh et al. further investigated the effects of PDMS grafting onto polyurethane [57]. In a 30-day *in vitro* study, they observed that surface modification of polyurethane films prevented calcification, exhibited no cytotoxicity, but did not alter platelet adhesion due to the good blood compatibility of both polymers.

To address the long-term durability of this material, interest in the combination of PDMS and polycarbonate urethane (PCU) has grown over the years. The durability and mechanical resistance of PCU complement the advantages of PDMS, which is flexible and biocompatible. A study on PDMS-PCU has shown that PDMS tends to accumulate on the surface layer, protecting the bulk from degradation, and enhancing oxidative resistance [58]. However, high PDMS fractions may result in possible residual stress, undesirable visual defects or weak interfacial interactions. The optimal molar ratio of PCU/PDMS was found to be 90:10, which

simultaneously improved oxidation and hydrolysis resistance, while maintaining a proper mechanical performance [58]. This material can find potential use in long-term implantation applications.

Another recent study investigated the potential application of a biostable PDMS-based polyurethane-urea bearing zwitterion sulfobetaine (PDMS-SB-UU) [59]. The material was successfully synthesized, and its stability was confirmed by *in vitro* tests against 30% hydrogen peroxide and lipase for 8 weeks. It also demonstrated higher resistance to platelet adhesion and fibrinogen adsorption compared to PDMS. Additionally, PDMS-SB-UU exhibited no cytotoxicity with rat vascular smooth muscle cells or hemolysis with ovine blood [59]. PDMS-SB-UU can be utilized either as the entire matrix or as surface coating for several blood-contacting medical devices, such as prosthetic heart valves.

3.1.2 Polytetrafluoroethylene

Polytetrafluoroethylene (PTFE) (**Figure 3.4**) has another commonly used trade name, Teflon. It contains only carbon and fluorine atoms. PTFE exhibits high chemical inertia, high stability and strong mechanical properties [60]. Due to these features, PTFE is used in various biomedical applications.

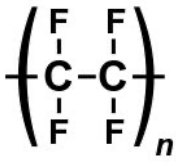


Figure 3.4. Structural formula of polytetrafluoroethylene (PTFE).

Braunwald and Morrow performed clinical trials with flexible tricuspid Teflon fabric valves, based on the Muller-Littlefield prosthesis [61]. They caried out hemodynamic assessments and postoperative clinical exams of valve function in 23 patients, who underwent the replacement of the aortic valve with flexible PTFE prosthesis. Left heart catheterizations indicated satisfactory valve function in 21 out of 23 patients. However, severe aortic regurgitation developed in 13 patients, leading to death or reoperation [62]. Examination of removed Teflon valves revealed stiffening and calcification of the fabric, causing leaflet tearing and valve regurgitation. The failure of Teflon aortic prosthesis was attributed to unsatisfactory material rather than improper design.

At the end of the 1960s, Robert W. Gore introduced a new iteration of the material, that is expanded polytetrafluoroethylene (ePTFE). ePTFE was patented in 1976 and known to the public as Gore-Tex; it is formed by mixing PTFE powder with lubricant to create a paste, which is extruded into a film or tape, then the lubricant is removed by heating, and the result is stretched at high temperature [63]. ePTFE is widely employed in biomedical applications due to its mechanical, chemical and biocompatibility properties [63]. One of the earliest applications of Teflon heart valves dates back to the late 1980s, when 12 prostheses were implanted in the tricuspid position in the sheep model [64]. In half of the valves, large calcific deposits were discovered on the inflow surfaces near the stent posts.

The application of ePTFE valves is currently limited. Medical devices made of ePTFE are not frequently used due to the considerable risk of dysfunction caused by thickening, calcification, or constriction of the valves, alongside suboptimal hemodynamic performance.

3.1.3 Polyurethane

Polyurethanes (PUs) are other polymers potentially suitable for the development of prosthetic heart valves. They are distinguished by the presence of a urethane linkage and can be synthesized through an addition reaction between an alcohol and an isocyanate (**Figure 3.5**). PUs are extensively studied due to their convenient synthesis, achievable at room temperature and under mild conditions [65]. Polyurethanes are widely used in cardiovascular applications due to advantageous mechanical and physiochemical properties. Moreover, some of them are also characterized by high biocompatibility that allows their unrestricted use in blood-contacting devices [66]. Furthermore, PUs surface exhibits excellent resistance to microbic contamination, while thrombi formation is nearly comparable to PTFE.

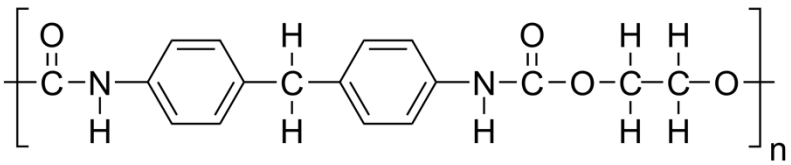


Figure 3.5. Structural formula of a polyurethane (PU).

Braunwald et al. designed and fabricated a prosthetic valve for mitral position made of flexible polyurethane, with leaflets controlled by Teflon-made chordae tendineae [67]. In 1959, they implanted these valves in 27 dogs. Despite some difficulties during the experiment, the prosthetic valve was ultimately deemed satisfactory. In 1960, the same valves were used for

complete mitral valve replacement in two human patients [68]. One patient survived the procedure but died, presumably of an arrhythmia, four months later.

In the following years, various valves with different types of PUs were tested on animals or through *in vitro* experiments. In 1988, an animal test was conducted to assess different valves made of different PUs (**Figure 3.6**) [69]. Two valves from each material were implanted in the mitral position of Jersey calves. The survival times recorded ranged between 127 and 291 days. While all explanted valves showed calcification and obstruction, these findings suggested that at least two PUs achieved survival times significantly surpassing those of bioprestheses under similar implant conditions.

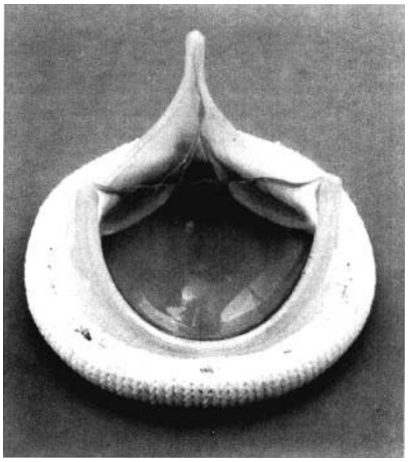


Figure 3.6. Implantable tricuspid heart valve developed by Lo et al. [69].

In 1991, Jansen et al. introduced a novel three-leaflet valve, the J-3, designed to mitigate membrane stress [70]. The J-3 valve demonstrated superior hydrodynamic performance, thereby minimizing the risk of thrombus formation. *In vitro* testing revealed excellent durability and minimal shear stresses in the downstream flow field. However, animal tests showed poor resistance to calcification [71]. In 1996 a new polyurethane tri-leaflet valve was developed, consisting of three thin polyurethane leaflets suspended within a flexible polyurethane frame [72]. The valve showed good results in hydrodynamic tests and exhibited good durability, with an equivalent lifespan of 10 years.

Bernacca et al. manufactured and evaluated several prosthetic heart valves. Initially, in 1996, they examined prosthetic heart valves made of polyetherurethane (PUE) [73]. These valves showed minimal calcification, particularly in regions of material failure, whereas bovine pericardium or porcine aortic valve biomaterials demonstrated much greater calcification under the same conditions. In 1997, they tested prosthetic heart valves made of polyetherurethaneurea

(PEUE) [74]. These valves demonstrated superior mechanical performances, particularly in term of fatigue resistance, compared to PEU valves. However, no significant improvement was observed as to calcification.

In 2003 and then in 2004, a new PCU heart valve was introduced respectively for the mitral (**Figure 3.7**) and aortic (**Figure 3.8**) positions, with the trade name ADIAM [75], [76]. PCU contains hard and soft segments, whose ratio determines material hardness. Both prostheses were designed to mimic physiological flow. The ADIAM mitral valve showed no material degradation, intrinsic calcification, or other signs of structural degradation, neither *in vivo* nor *in vitro* settings. Additionally, no thromboembolic complications were observed [75]. The ADIAM aortic valve, instead, demonstrated *in vivo* durability with no increased thromboembolic complications and no intrinsic calcification. However, *in vivo* tests on animals had some limitations due to anatomical reasons, as they increased or caused some of the above-mentioned complications [76]. Both prostheses have not reached the clinical trial phase.

Although PUs exhibit satisfactory mechanical properties, their limited biocompatibility and biostability hinder the development of an optimal PHV.

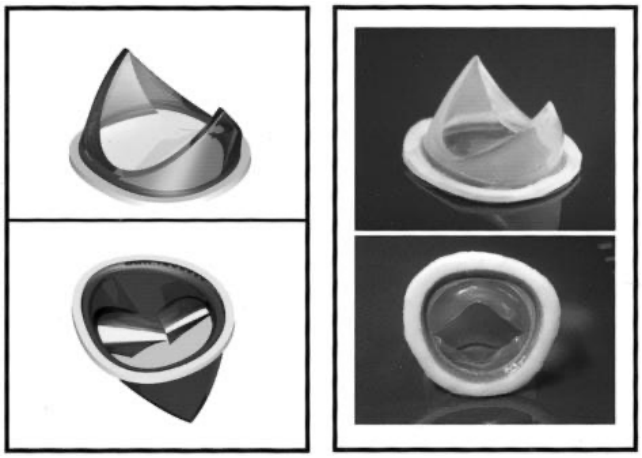


Figure 3.7. The ADIAM PCU valve with special design for mitral position: digital models of the valve (left) and the final products (right) [75].

Figure 3.8. The ADIAM PCU valve with special design for the aortic position: digital model of the valve (left) and the final product (right) [76].

3.2 Novel polymers for prosthetic heart valves

Several recently developed polymers, different in composition and structure with respect to the previously illustrated ones, are currently available for the production of PHVs with enhanced mechanical properties and improved biocompatibility.

3.2.1 POSS-PCU

The POSS-PCU is a nanocomposite polymer with superior biostability and biocompatibility compared to previous materials. This enhancement is achieved by improving the high resistance of PCU to cyclic loads through the creation of composites based on polyhedral oligomeric silsesquioxane (POSS) nanoparticles (**Figure 3.9**). It is a non-toxic polymer that possesses excellent thromboresistance and resistance to degradation [77],[78]. It was demonstrated that the presence of the POSS group protects the soft segment of the PU, responsible for its flexibility and elasticity, from oxidative and hydrolytic degradation [78].

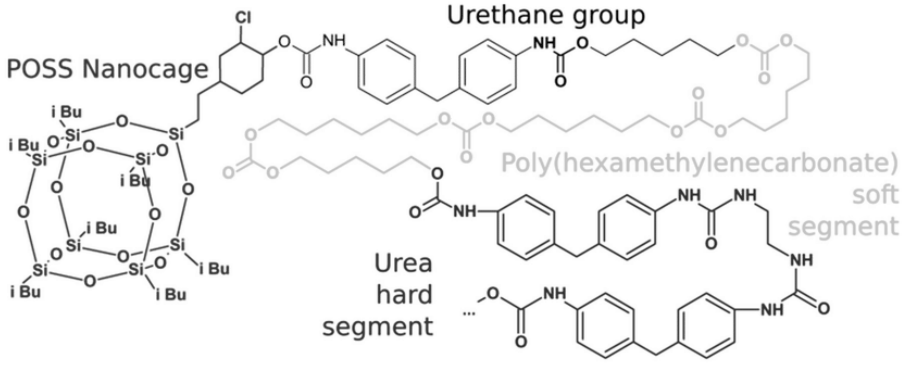


Figure 3.9. Structural formula of POSS-PCU.

A first heart valve prototype made of POSS-CPU was developed at UCL (University College of London, UK) (**Figure 3.10**), demonstrating that it possesses excellent mechanical

strength, favorable surface properties and resistance to platelet adhesion [79]. The nanocomposite was also utilized by the Rahmani's group for the development of a new semi-stented aortic valve (SSAV), optimizing the manufacturing process to enhance the precision and consistency required in heart valves by implementing an automated dipping and coating process [80]. The result was a polymeric heart valve with potential clinical application. The leaflet thickness played a fundamental role in the hydrodynamic performance of this kind of prostheses: the thinnest valve (100 μm leaflet thickness) performed better than a thicker valves or any bioprosthetic valve.

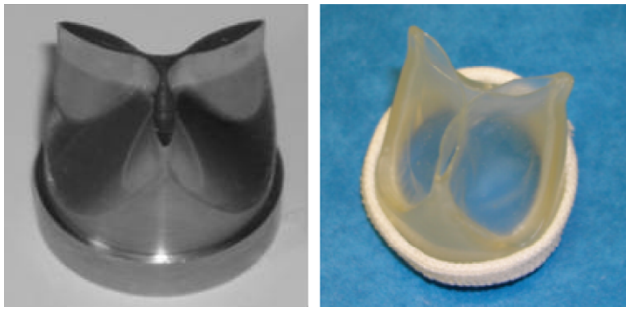


Figure 3.10. Design and prototype of the synthetic heart valve made of POSS-PCU at UCL [79].

The POSS-PCU also played a significant role in the development of transcatheter heart valves when, in 2016, the Rahmani's group developed a trileaflet valve, the TRISKELE valve (**Figure 3.11**) [81]. Utilizing new technologies to ensure repeatability and rapid production at lower costs, this valve has undergone both *in vitro* and *in vivo* testing. The *in vitro* study demonstrated the excellent hydrodynamic performance of the TRISKELE valve, which showed a significant reduction in paravalvular leakage, regardless of the presence of calcification [82]. In the *in vivo* study, the TRISKELE valve was successfully implanted in an acute preclinical ovine model with a 30-minute postoperative follow-up. It exhibited optimal hemodynamic performances after catheter removal, although the presence of regurgitation was noted [81].

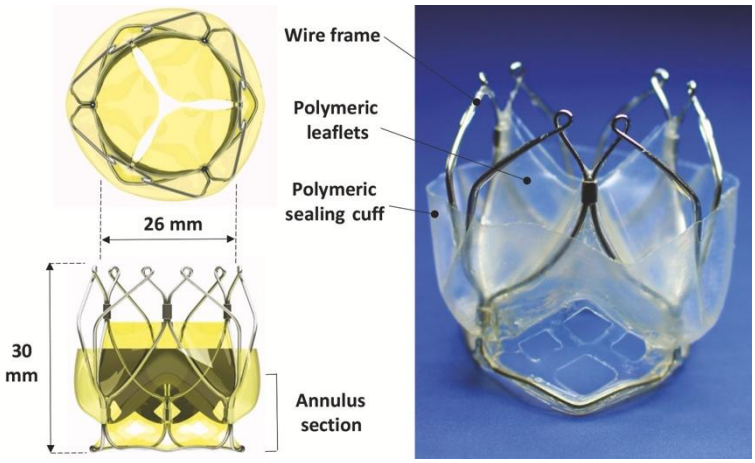


Figure 3.11. The TRISKELE valve developed by Rahmani et al. [81].

3.2.2 FGO-PCU (Hastalex)

Hastalex is a novel nanocomposite material based on the incorporation of functionalized graphene oxide (FGO) into the main chain of poly(carbonate-urea)urethane (PCU) developed by Ovcharenko et al. [83], who described in detail the synthesis of the Hastalex nanocomposite. The material finds several industrials applications, such as an antifouling agent in marine applications or as fibers in the textile industry.

The initial tests conducted by Ovcharenko's group showed mechanical properties comparable with ePTFE, yet superior tensile strength that exceeds the load of native valve tissues and blood vessels. Although possessing a great capacity for elongation under extreme loads, it exhibits a relatively rigid nature within the range of physiological loads compared to common biological materials used for manufacturing prosthetic heart valves. Hastalex has a much higher Young's modulus than ePTFE (11.3 MPa versus 1.9 MPa respectively along longitudinal direction), which is a crucial aspect in minimizing energy loss [83]. The hydrodynamic performances of Hastalex heart valves depend on leaflets design, but the high deformability and higher rigidity of this material allow the realization of thinner leaflets. Additionally, Hastalex is a hydrophobic material thanks to the presence of the functionalised graphene oxide, its properties and concentration.

In vitro test showed that Hastalex has no cytotoxic effect, but is able to promote high cell adhesion, viability, and proliferation. Moreover, *in vivo* testing on rats showed that Hastalex possesses superior resistance to calcification when compared to ePTFE and cattle-derived pericardium. Currently, only one prototype of a Hastalex-based polymer heart valve has been developed (**Figure 3.12**): despite the promising advantages in cardiovascular surgery

applications, more *in vitro* and *in vivo* tests are needed before moving towards clinical trials [83].

Figure 3.12. Valve prototype made of Hastalex [83].

3.2.3 SiPUU

Although the current generation of siloxanepolyurethanes (e.g., Elast-Eon™) possesses the necessary mechanical properties and biostability for different kinds of medical implants, biomedical applications such as heart valves require materials with improved mechanical features in addition to long-term biostability. SiPUU (**Figure 3.13**) is an improved biostable elastomeric polyurethane, composed of siloxane and polyurethane segments, often linked by urea groups. The siloxane segments provide flexibility, biocompatibility, and excellent resistance to thermal and oxidative degradation due to the silicon-oxygen backbone, the polyurethane segments improve mechanical strength and durability, while urea linkages enhance the polymer's mechanical properties and thermal stability [84]. This polymer is obtained through a two-step synthetic process. The soft segments of SiPUU are made from 20:80 (w/w) mixture of 4,4'-methylenediphenyl diisocyanate (MDI) linked with poly(hexamethylene oxide) and ⟨α,ω-bis(6-hydroxyethoxypropyl) polydimethylsiloxane: this combination has proven to be ideal for long-term biostability and good mechanical properties [85]. The hard segments are composed of MDI and a mixture of 1,2-ethanediamine (EDA) and 1,3-bis(4-hydroxybutyl)-1,1,3,3-tetramethyldisiloxane (BHTD) in varying molar ratios, and it has been shown how the tear resistance and mechanical strength increased by increasing the amount of EDA [86]. An *in vitro* degradation study showed that SiPUU is resistant to oxidation, even after undergoing chemical modifications, while retaining its good mechanical properties [87].

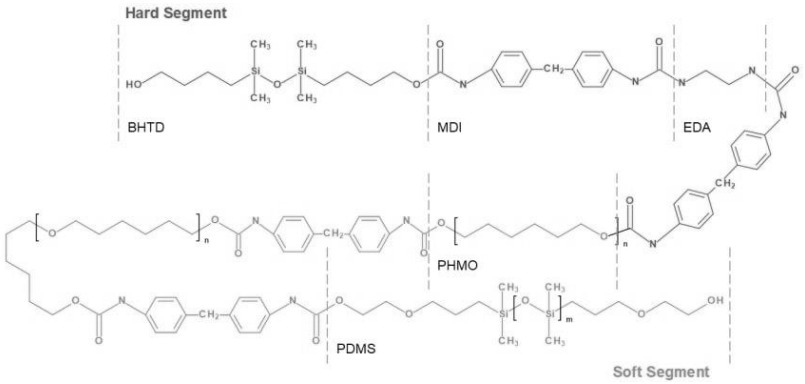


Figure 3.13. Structural formula of SiPUU.

A SiPUU heart valve prototype (**Figure 3.14**) was developed by Millson et al. [88]. The SiPUU (LifePolymer, LP, Foldax, USA) valve, with the trade name of "Tria Valve", consists of a radio-visible polyetheretherketone (PEEK) stent, two or three specifically designed leaflets (depending on valve anatomical destination), and a polytetrafluoroethylene felt sewing ring. Tria valves were tested in accordance with the ISO 10993 standards, identifying no significant risk of toxicity or tissue injury [88]. *Ex vivo* thrombogenicity assay demonstrated nearly undetectable levels of platelet adhesion and fibrin deposition on polymer surfaces; moreover, Tria valves showed exceptional hemocompatibility in two different large animal models. For sheep, eight sterilized Tria valves were successfully implanted in the aortic position for a 140-day period: minimal inflammation adjacent to the aorta and the suture were observed, with no hemorrhagic evidence, thrombotic formation or mineralization effect. A minimal amount of fibrous tissue coverage was demonstrated for the control leaflets, but no endothelialization was observed, while no significant health problems were observed for the sheep during the observation period [88]. These studies have shown that the material exhibits ideal properties for polymeric heart valve.

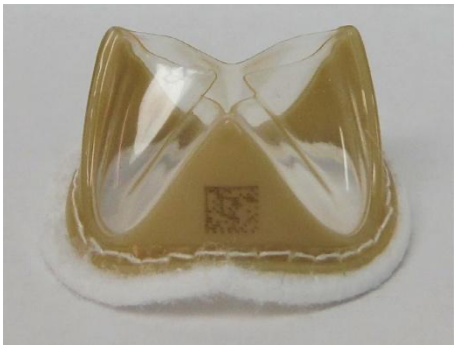


Figure 3.14. Foldax Tria aortic valve developed by Jenney et al. [88].

In 2021, a study was published to provide a preliminary evaluation of the clinical effectiveness and safety of the Tria aortic heart valve by Foldax Inc., the only company authorized by the FDA for this trial [89]. 15 valves were implanted in 15 patients to assess clinical effectiveness endpoints (improvement in EOA[1], improvement of NYHA classification[2], rate of adverse events, hemodynamic parameters) and primary safety endpoints (thromboembolic events, major hemorrhage, all-cause and valve-related death, other valve-related events like reoperation or explantation) within one year after implantation [89]. One patient was withdrawn intraoperatively due to valvular regurgitation. There were two deaths (on postoperative days 60 and 90) unrelated to the valve or procedure: one due to bleeding after elective surgery to remove a renal tumor, and the other due to hemodynamic collapse and cardiac arrest probably caused by pulmonary embolism after discontinuation of warfarin in a morbidly obese subject. Additionally, there was one lacunar stroke on postoperative day 172. Another patient, 92 days postoperatively, experienced acute myocardial infarction caused by thrombotic obstruction of the right coronary artery. The Tria LP heart valve showed significant improvements in transvalvular gradients, EOA values, and NYHA functional class up at one year follow up [89]. Safety outcome measures appeared comparable to those reported for bioprosthetic heart valves.

In 2024, Foldax Inc. conducted a study in India: the Tria LP valve was implanted in the mitral position in 67 patients aging from 19 to 67 years, with the majority suffering from rheumatic heart disease [90]. Imaging of the valve 30 days after surgery showed no sign of leaflets calcification and/or deterioration. The trial is still ongoing, and the valves will be assessed at six months and one year for safety, hemodynamic performance, and durability.

Regarding transcatheter heart valves, in 2018 Steven J. Yakubov announced the development of a transcatheter Tria heart valve, manufactured by Foldax Inc. The transcatheter Tria is made of LifePolymer material and its design has been optimized to increase durability and hemodynamics. The valve has been investigated *in vivo*, implanting it in the aortic position of four animals. The results showed good hemodynamics, absence of thrombotic or fibrotic events after 30 days, and clean leaflets after 90 days [90].

[1] EOA, effective orifice area

[2] The New York Heart Association (NYHA) Classification provides a simple way of classifying the extent of heart failure. It classifies patients in one of four categories based on their limitations during physical activity.

3.2.4 SIBS *and* xSIBS

Poly(styrene-*block*-isobutylene-*block*-styrene) (SIBS) (**Figure 3.15**) is a thermoplastic block copolymer discovered in the early 1990s, whose physical properties overlap those of silicon rubber and polyurethane. It remained unknown until the introduction of Boston Scientific Corporation's (BSC) Drug Eluting TAXUS Coronary Stent in 2002 [91]. Due to its chemical composition, SIBS maintains oxidative, hydrolytic, and enzymatic stability throughout its lifespan in the body, making it biostable and associated with a relatively low foreign body reaction. SIBS is synthetized via sequential polymerization of styrene and isobutylene monomers to form block copolymers, typically utilizing living anionic polymerization techniques. Its hardness can be varied by changing the amount of styrene [91]. However, the thermoplastic nature of SIBS means that it has poor creep properties, susceptibility to stress cracking [91] and fatigue failure [92]; it has poor gas permeability (which renders it more difficult to sterilize with ethylene oxide) and it is not gamma-ray sterilizable [91]. Thus, one of the critical aims of the researcher is to enhance the physical properties of the material, principally via fiber reinforcement.

Gallocher et al. tried to reinforce SIBS with polypropylene, resulting in a significant improvement of mechanical properties, but unexpectedly high platelet deposition was observed on tissue samples [92]. The same results were observed with the reinforcement of SIBS with polyethylene terephthalate (PET, Dacron) fibers as done by Wang et al. [93]: in this case, the valve failed in animal test because of material failure and calcification. An improved version of this polymer, named xSIBS (**Figure 3.15**), was developed by Innovia LLC, aiming to eliminate the significant dynamic creep of the thermoplastic SIBS that has limited its suitability for PHVs [94]. SIBS was modified to enhance its mechanical properties, resulting in a flexible, tear-resistant material with improved hydrodynamic performance, reduced thrombogenicity, and increased durability [95]. xSIBS is an excellent candidate as a material also for prosthetic transcatheter heart valves.

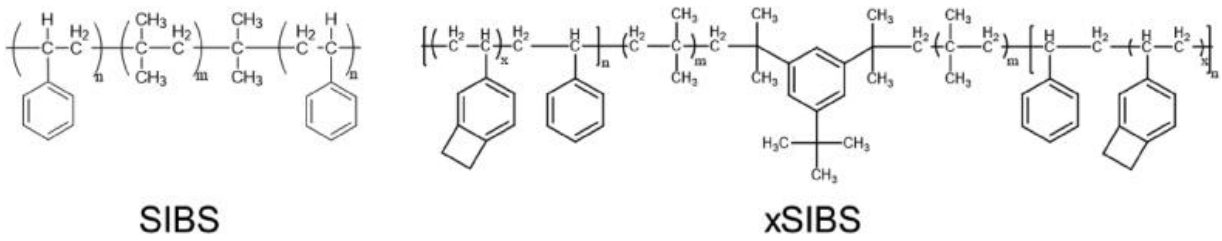


Figure 3.15. Structural formula of SIBS and xSIBS.

The design of the SIBS valve underwent several improvements to ensure adequate hemodynamic performance and durability. At the beginning, Innovia LLC developed a polymeric trileaflet heart valve using SIBS (**Figure 3.16 A**). The valve design was changed several times, transitioning from a low to a medium profile. Moreover, the leaflet geometry was converted from a spherical to a cylindrical design, and the leaflet reinforcement was changed from low-density to high-density Dacron with the same nominal thickness. Furthermore, the leaflet fabrication process was enhanced from dip coating to casting. These modifications have significantly improved valve durability by reducing the incidence of SIBS failure [96]. However, all these changes were not enough to get the approval for the clinical use. *In vivo* studies on animals showed Dacron fatigue failure, calcification and SIBS leaflet coating cracking.

These issues were partially solved by using xSIBS and an optimized design (**Figure 3.16 B**) [97]. A novel xSIBS heart valve was developed by Claiborne et al. [97] with changes in the geometry. The leaflet shape was modified from cylindrical to hemispherical, and a flat leaflet profile was designed to maximize the coaptation surface. Additionally, to minimize the stress during the cardiac cycle, the radial cross-sectional profile of the leaflets was modified from uniform to variable thickness [97]. The optimization of the valve's configuration and leaflets geometry was performed using parametric DTE[3] methodology, which includes a series of simulations comparing the original Innovia valve, a benchmark biological valve, and the novel xSIBS valve. Enhanced performances were observed in the optimized valve in terms of durability, hemodynamic and thrombogenic resistance [97]. This optimized PHV was later called as the "first-generation" Polynova surgical aortic valve.

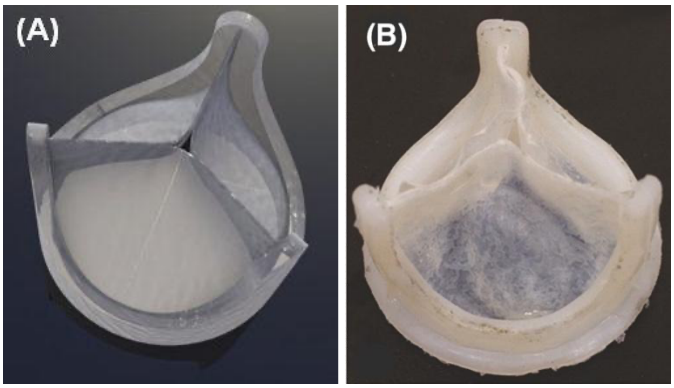


Figure 3.16. *A*) original Innovia SIBS-Dacron PHV [97]; *B*) optimized xSIBS valve prototype [94].

[3] DTE, dynamic tensile extrusion

SIBS and xSIBS have also gained traction in the development of TAVR. In 2009, Claiborne et al. developed a SIBS trileaflet heart valve mounted on a Nitinol self-expanding stent [98]. The leaflet thickness and optimal valve geometry were determined through a series of *in vitro* tests, proving to be capable of resisting migration and crushing forces exceeding those expected *in vivo*.

In 2018, Rotman et al. developed a novel polymeric aortic heart valve for TAVR made of xSIBS [99]. This new valve was derived from the SAVR valve previously described, with modifications regarding the fabrication process and enhancements in the leaflet design, resulting in improved mechanical properties and durability. Rotman's group proceeded with an *in vitro* study of the new valve [100]. The EOA remained stable with a gradual decrease in transvalvular pressure gradient and regurgitation. Additionally, calcification was significantly reduced, and following crimping testing, no tears or surface damage were observed [100].

Despite better performances, the Polynova TAVR valve exhibits the highest overall regurgitant fraction compared to the previous valves, indicating the need for further optimization. In 2022, Kovarovic et al. introduced a "second-generation" polymeric TAVR valve [101]. The stent frame underwent redesign to decrease the crimped volume compared to its predecessor, while also generating higher radial forces within the intended range of use to prevent crimping damage. Additionally, leaflets were optimized for larger-size device, further reducing cyclic stresses. This second generation polymeric TAVR valve is currently undergoing *in vitro* hydrodynamic testing and subsequent *in vivo* animal trials [101].

A novel advancement in the development of PHVs is the introduction of carbon nanofillers (CNTs) into SIBS [102]. In an initial study, CNTs were dispersed in chloroform using sonication following the addition of a SIBS solution at different ratios. The optimal results were observed for SIBS films containing 4-6 wt% of CNT, which demonstrated higher tensile strength and conductivity compared to the original polymer, although with increased stiffness [102]. Subsequently, it was demonstrated that using dodecylamine (DDA) to modify CNTs, characterized by a long non-polar alkane chain, significantly improved the dispersion of nanotubes in SIBS compared to unmodified CNTs [103]. As a result of this modification, the tensile strength increased and *in vitro* tests demonstrated higher biocompatibility with no toxicity toward blood components, but high concentration of CNTs can lead to platelet aggregation, potentially causing thrombosis. Consequently, it was demonstrated that SIBS with higher molecular weight, reinforced with 1-2 wt% of modified CNTs, is one of the most promising materials for creating cardiovascular implants like heart valve prostheses [103].

3.2.5 PVA *and* PVA-BC

Poly(vinyl alcohol) (PVA) is a hydrophobic polymer known for its advantageous properties, including excellent physico-mechanical characteristics, non-toxicity, biocompatibility, and high swelling capacity, making it highly suitable for various biomedical applications [104]. PVA is synthetized through the radical polymerization of vinyl acetate, resulting in poly(vinyl acetate) (PVAc), which is subsequently hydrolyzed to yield PVA (**Figure 3.17**). The polymer can be crosslinked either chemically or physically, but the physical crosslinking offers the advantage of eliminating residual amount of toxic crosslinking agents compared to chemical methods [104]. Furthermore, by adding filler such as particle or fibers into PVA and making PVA-based blends, desirable mechanical properties can be achieved. This enables the replication of different human tissue texture and properties, enhancing its potential for biomedical applications.

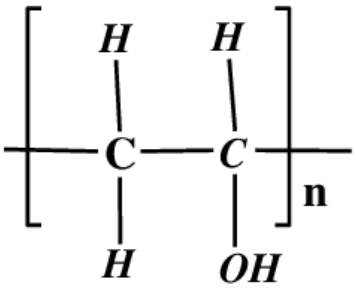


Figure 3.17. Structural formula of poly(vinyl alcohol) (PVA).

The exploration of PVA for medical purposes originated between the 1950s and 1960s. However, its specific use in the biomedical field has become more prominent in recent decades. In the early 2000s, Wan et al. showed that the tensile properties of PVA hydrogel can be adjusted via freeze/thaw cycling to closely align with the physiological range of the porcine aortic root [105]. They successfully developed a prototype of an expandable artificial heart valve stent using an injection molding technique with PVA hydrogel subjected to four freeze/thaw cycles [105]. In the same years, Jiang et al. developed a novel tricuspid valve made completely of polyvinyl alcohol cryogel (PVA-C) [106]. In their study, they examined two different leaflet designs (**Figure 3.18**), resulting in two different areas in the central orifice. The cylindrical stent was fabricated from PVA-C. The opening and closing phases of the valve prototype were successfully demonstrated using a cyclic flow tester. A unique advantage of the PVA-C heart valve is its ability to be temporally compressed into a small ball, facilitating the

insertion into the chest cavity through a small incision [106]. This feature is particularly suitable for heart valve replacement via closed heart surgery, with the potential to reduce blood hemolysis and the incidence of bleeding complications, while ensuring an unobstructed central orifice during opening.

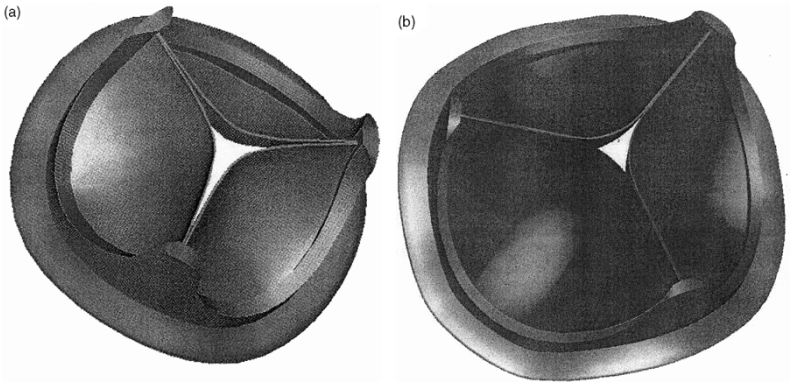


Figure 3.18. CAD models of the heart valve with two different leaflets geometry, highlighting the different area in the central orifice [106].

In the following years, several PVA-based nanocomposites were developed and studied for biomedical applications, to improve the mechanical properties and leaflets functionality. Wan et al. reinforced PVA with bacteria cellulose (BC) (**Figure 3.19**) [107], a nanomaterial with valuable characteristics for biomedical applications, including polyfunctionality, hydrophilicity and biocompatibility [108]. They produced multiple samples of the PVA-BC nanocomposite with varying concentrations of PVA and BC. The incorporation resulted in a material with higher mechanical strength and higher stiffness compared to PVA alone and it can be tailored to possess mechanical properties almost identical to those of cardiovascular tissues such as heart valve leaflets [107],[109]. Despite these promising results, there are no current studies on the long-term *in vitro* or *in vivo* performances of this nanocomposite. However, other researcher demonstrated the potential use of this material for the development of a TAVR prototype, but further discussion will be provided later.

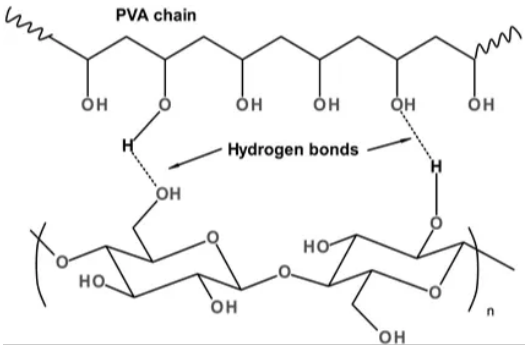


Figure 3.19. Structural formula of PVA-BC.

Another material with promising properties for biomedical applications is the Graphene Oxide/Polyvinyl Alcohol (GO/PVA) composite [110]. GO/PVA composite hydrogel is commonly prepared by a freeze/thaw method. Compared to pure PVA hydrogel, it showed increased tensile strength, breaking elongation, and compressive strength. The incorporation of GO into PVA hydrogel affect positively the toxicity of PVA to osteoblast cells and therefore GO/PVA hydrogels should have many potential applications as biomaterials [110]. It is worthy to note that among the methods for increasing the biocompatibility of blood contacting devices, the surface of these devices can be altered by applying a hydrogel coating [111]. PVA can also be a promising polymer for long-term blood contacting PHV valves, considering issues of fatigue resistance.

As mentioned before, PVA is also used as a material for the development of transcatheter heart valve. Mohammadi et al. proposed a novel tricuspid percutaneous valve, composed of leaflets made entirely from PVA-BC nanocomposite [112]. The valve's geometry was adjusted to prevent sharp warping of the leaflets and eliminate the central opening orifice area when the valve is fully closed. It was combined with a Nitinol stent and Dacron cover, and a specific cavity mold was designed for the fabrication of the valve [112]. Indeed, this model is considered for the mitral position, which currently lacks commercial implementation due to its significant technical challenges such as low risk of paravalvular regurgitation, preventing migration to the left ventricle, and providing low profile with sufficient anchoring [113].

3.2.6 LLDPE *and* HA-LLDPE

Linear low-density polyethylene (LLDPE) (**Figure 3.20**) is a type of polyethylene (PE) with a linear polymer chain structure and a relatively low density compared to the other types of PE. LLDPE is made through copolymerization of ethylene with long-chain olefins. This structure provides the material with different properties, such as high tensile and tear resistance, low

bending stiffness, and low shear stress sensitivity, allowing its use in biomedical applications [114]. However, LLDPE does not provide sufficient biocompatibility for long-term blood interaction. Some studies have shown how hyaluronan (hyaluronic acid, HA) into LLDPE can lead to improvements to the first polymer. HA is a naturally occurring polysaccharide found in tissue and body fluids of vertebrates and in some bacteria. Its structure contributes to viscoelastic property, hydrophilicity, and lubrication [115].

Prawel et al. conducted a study to evaluate the possible use of HA-LLDPE as a material for flexible heart valve leaflets [116]. HA-LLDPE materials were manufactured using the swelling method, a fast and simple technique that did not alter the mechanical properties of the LLDPE. The presence of HA reduced the static water contact angles for all the material samples [116]. HA-LLDPE was used to make a trileaflet heart valve, which was assessed in a pulsatile flow loop system, demonstrating promising hemodynamic performance. Subsequently, the researchers evaluated the hemocompatibility of the material [117]. The surface was determined to be cytocompatible, showing no significant cellular necrosis. Whole blood clotting assay indicated that the HA-LLDPE surface significantly reduced clotting under static conditions due to a reduction of the intrinsic pathway activation and platelet adhesion/activation [117]. The study demonstrated the material's potential for cardiovascular applications.

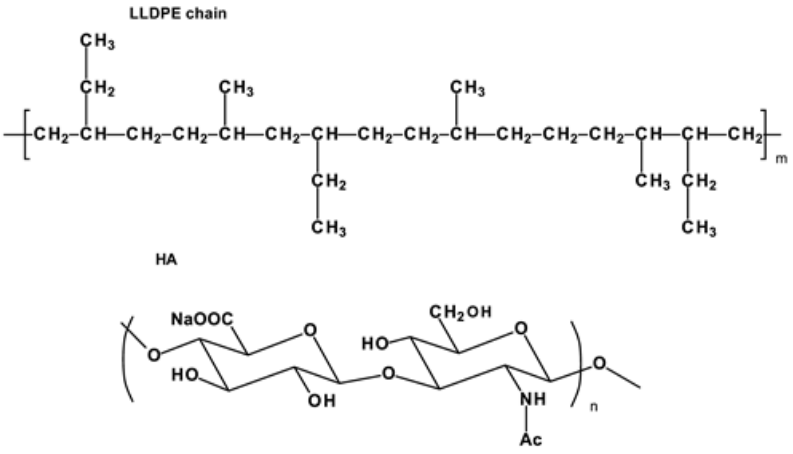


Figure 3.20. Structural formula of LLDPE and HA chain.

Yousefi et al. tested different LLDPE valve prototypes to find the best design able to improve the hemodynamic characteristics [118]. The alteration of the aspect ratio between stent height and diameter, as well as the leaflet arch length variation, leads to the creation of nine different valve configurations. The researchers focused their study on configurations that ensure full commissure coaptation. To this purpose, they added short leaflet arches to valves with

medium aspect ratios and omitted leaflet arches in valve with higher aspect ratios [118]. Consequently, six out of the nine configurations were analyzed (**Figure 3.21**). The study revealed that incorporating leaflet arches and adopting a higher HV profile offer several advantages. Firstly, they result in a significant decrease in the RSS (Principal Reynolds Shear Stress), yielding to better leaflet coaptation and reducing regurgitation percentage. However, it is important to note that a high stent profile might delay the reattachment of flow in the aorta and marginally increase the RSS. This increase could potentially lead to higher levels of hemolysis and blood damage. Furthermore, the introduction of the leaflet arches leads to a substantial improvement in leaflet kinematics and heart valve hemodynamics by refining the low-profile design of the heart valve [118].

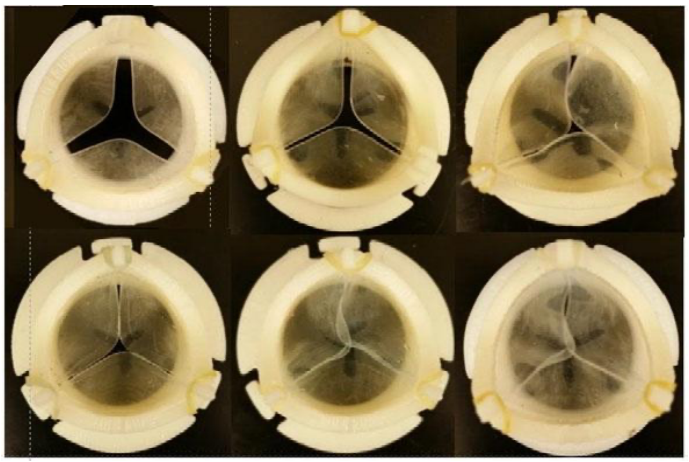


Figure 3.21. Top view of the six heart valves investigated by Yousefi et al. [118].

In recent years, HA-LLDPE has also played a role for transcatheter heart valves. A novel HA-LLDPE based transcatheter heart valve, the HA-TAV, was developed and compared against two others commercially available TAVRs: the Medtronic Evolut and the Edwards SAPIEN 3 [119]. The hemodynamic parameters measured indicate that the HV-TAV surpasses basic requirements and stand on par with the leading valves. Additionally, turbulent flow characterization in the HA-TAV demonstrates enhancements compared to the leading commercially available valves [119]. However, to evaluate the expected long-term durability of the novel valve, an accelerated fatigue test is necessary.

3.2.7 SEPS *and* SEBS

SEPS and SEBS are thermoplastic elastomers characterized by distinct chemical composition and versatile properties. SEPS, or poly(styrene-*b*-ethylene/propylene-*b*-styrene) (**Figure 3.22**),

is a styrenic block copolymer (SBC) with hydrogenated isoprene unit as the mid-block [120]. It is a non-toxic material known for its thermal and oxidation stability, making it widely used in industrial applications as well as in medical tubing, films, and stoppers. However, its poor creep resistance and poor surface hydrophilicity lead to inferior biocompatibility when compared with other polymers [121]. SEBS, or poly(styrene-*b*-ethylene/butylene-*b*-styrene) (**Figure 3.23**), is an SBC with hydrogenated butadiene unit as the mid-block [122]. Despite its poor creep resistance on prolonged use, this material has good thermal, chemical and UV resistance due to the presence of the saturated ethylene butylene unit [121]. As regards calcification, a recent study indicates that a styrene block copolymer exhibits significantly lower susceptibility to calcification *in vitro* compared to a polyurethane valve [123].

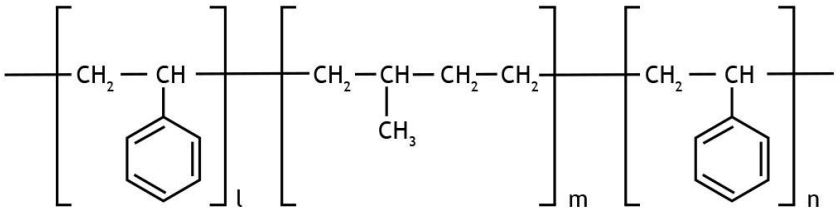


Figure 3.22. Structural formula of SEPS.

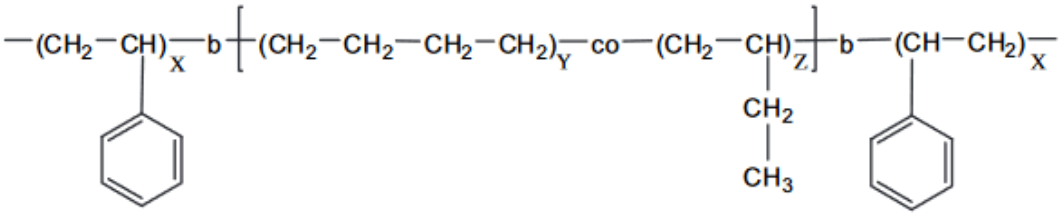


Figure 3.23. Structural formula of SEBS.

Recently, Stasiak et al. developed and tested a novel polymeric heart valve, named Poli-Valve, manufactured by injection moulding SEPS and SEBS (**Figure 3.24**) [124]. The two styrenic triblock copolymers were provided by Kraton Co (Houston, Texas). Taking inspiration from the native valve, where collagen fibers are aligned to withstand stresses during loading, the researcher used oriented styrene cylinders in block copolymer to reinforce the polymeric leaflets. They performed *in vitro* and *in vivo* tests on various valve prototypes. The final design includes a stiffer support structure made of SEBS29, and softer leaflets made of SEBS20, featuring cylindrically shaped leaflets with a concave leading-edge profile [124]. The prototype's performance surpassed the ISO standards *in vitro*, exhibiting excellent

hydrodynamics and good durability equivalent to a 30-year life span. A brief *in vivo* study demonstrated excellent hemodynamics and biocompatibility, but further investigations are required [124].

Figure 3.24. Different views of prototype Poli-Valve J6 made of SEBS [124].

3.2.8 Other nanocomposites

In recent decades, many nanocomposites have been created, studied, and tested for biomedical applications, with promising results. With specific regards to the heart valves, some of these nanocomposites have shown excellent results when in contact with blood or subjected to high stress. In 2011, Volpato et al. used carboxyl-functionalized multi-walled carbon nanotubes (MWCNTs) as fillers in a polyamide 6 (PA 6) matrix to investigate the fabrication and the mechanical properties resulting from the addition of CNTs [125]. The PA6/MWCNT composite was produced by electrospinning, a technique that allows the dispersion and alignment of the MWCNTs within the polymer matrix, resulting in the formation of surface roughness. The researchers highlighted the encouraging results, noting that the fiber diameter, network morphology, and mechanical properties can be adjusted to mimic specific target tissues that need to be replaced [125].

Another nanocomposite that has been studied is a poly(lactic-co-glycolic acid) (PLGA) material enriched with carbon nanofibers (CNF) [126]. The study, at specific weights ratios of CNFs (50:50), showed that nanoscale roughness increases cardiomyocytes growth, and also enhances tensile strength and conductivity properties. Additionally, it was demonstrated that PLGA density can alter cardiomyocyte adhesion and proliferation, closely resembling native heart tissue [126].

Poly(propylene fumarate) (PPF), a linear aliphatic unsaturated polyester, has played an important role in biomedical applications due to its extensive investigation. With regard to cardiovascular applications, two studies were reported: one study synthesized a novel segment polyurethane (SPU) with PPF as the soft segments, resulting in a material with a regular structure, controllable deformation recovery ability, and degradation rate [127]. The PPFU elastomer exhibited good mechanical properties, improved tensile strength, low cytotoxicity, and good biocompatibility, even though further studies are needed before any clinical application. The other study demonstrated that single-walled carbon nanotubes (SWNTs), particularly ultra-short SWNTs (US-tubes), are excellent reinforcing agents due to their superior mechanical properties [128]. This led to the development of a novel US-tube/PPF nanocomposite, which showed excellent biocompatibility and versatile surface chemistry, allowing the functionalization of the external surface with a variety of chemical moieties. Such modifications could enhance mechanical properties, hemocompatibility, or allow for *in vivo* monitoring of the degradation rate [128].

Graphene Oxide is another component often used for the creation of nanocomposites. In 2012, Su-xing et al. developed a range of functional graphene oxide based on the biomimetic monomer MPC (GO-g-pMPC) and then prepared polyurethane (PU)/functional graphene oxide nanocomposite films (PU/GO-g-pMPC) [129]. Mechanical results and TEM observations confirmed the successful synthesis. Additionally, the material demonstrated improved resistance to nonspecific protein adsorption and platelet adhesion, indicating good hemocompatibility [129]. The following year, Jin et al. synthesized a novel exfoliated polyethylene/modified graphene oxide nanocomposite (PE/GO-MPC) via melt intercalation (F). At 0.2 wt% GO-MPC content, there was a significant increase in tensile strength and elongation at break. The material also exhibited excellent hemocompatibility and antimicrobial activity against specific bacteria [130]. Both nanocomposites require further study, but they are both expected to eventually be used in biomedical applications.

4. Fabrication processes

For the production of a heart valve, manufacturing techniques can greatly vary depending on the desired mechanical properties or the specific 3D shapes needed for valve leaflets and geometrical configuration. Numerous chemical and mechanical processing steps may be required, but some common techniques for polymers can be considered. The choice of the most convenient technique largely depends on the type of polymer: thermoplastics can be processed using heat or solvents (if they are sufficiently soluble), while thermosetting materials require molding techniques.

4.1 Injection molding

Injection molding is a widely used manufacturing method for creating polymeric heart valves due to its precision and efficiency in forming complex structures [131]. The process begins with the preparation of the polymer, typically in granules, which is heated to a fluid state. The melted polymer is then injected under high pressure into a mold cavity designed to exactly reproduce shape and dimension of the desired object, for example the heart valve leaflet structures. The polymer is packed tightly into the mold to ensure it fills all the details and contours of the cavity. Once injected, the mold and the polymer are cooled. After cooling, the mold is opened, and the newly formed desired object is carefully removed [124]. The resulting product may undergo further processes to remove any imperfection or excess materials. This method offers relatively inexpensive and highly reproducible manufacture.

Stasiak et al. manufactured the novel Poli-valve PHV using inject molding of styrenic triblock copolymers with a cylindrical microstructure (**Figure 4.1**) [124]. The injection process was conducted through a channel that narrowed from a 2 mm diameter to 0.4 mm, minimizing the size of the sprue. Channel reduction also facilitated the spontaneous detachment of the sprue, leaving only about 1 mm of excess material on the heart valve leaflet's surface. The resulting valve exhibited excellent mechanical properties, hemocompatibility, and promising results in short-term *in vivo* tests [124]. This molding process had a role in the manufacturing of one-piece VAD valve. Sacristàn et al. opted for an injection process using four separate piece molds to realize the valve, aiming to reduce production cost: it resulted in variability of leaflet thickness [132]. Later, an evaluation study showed that this valve had limited hemodynamic performance mainly due to its stenotic characteristics [133].

Figure 4.1. Aluminium mould inserts for the J6 valve [124].

On the other hand, by utilizing a multistep approach where different polymers are introduced into the mold at various time, multimaterial structures can be developed [131]. Weber et al. proposed a novel multiple-step injection molding process to produce multicomponent heart valves made of fibrin and elastin-like recombinant gels (**Figure 4.2**) [134]. The researchers demonstrated the potential to imitate the structure of native heart valves by incorporating different scaffold, cell types, components for both leaflets and wall.

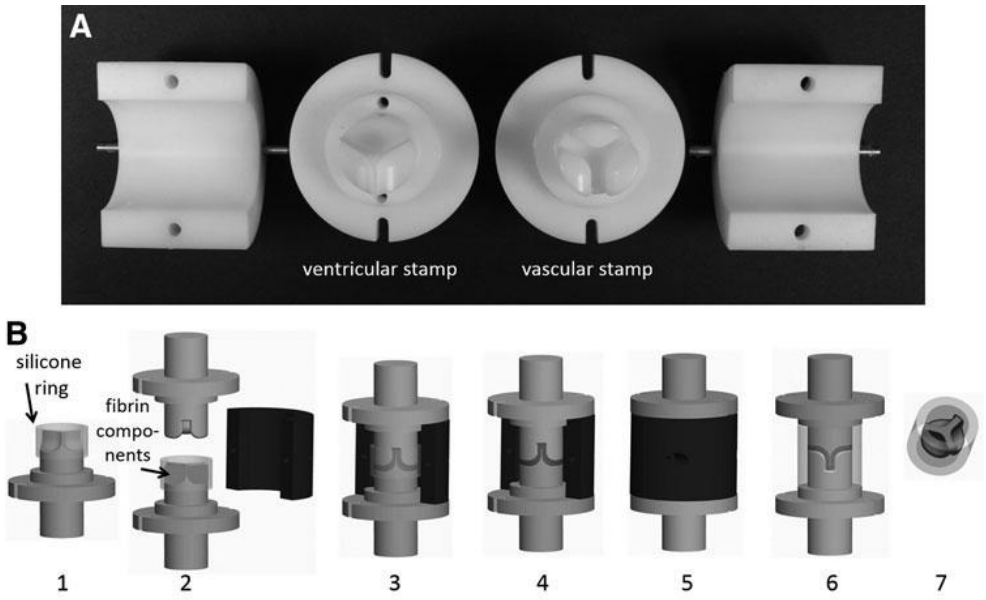


Figure 4.2. *A*) molds component for ventricular and vascular stamp, and shells. *B*) schematic representation of the molding procedure: 1) assemble of ventricular stamp and silicone ring to define the mold volume; 2) assemble of vascular stamp to obtain the leaflets; 3) polymerization of the fibrin gel; 4) careful removal of the silicon ring; 5) assemble of the second shell to define the wall volume; 6) the shells are disassembled; 7) careful removal of the valve [134].

However, practical limitations exist for molding methods that aim to produce multilayer structures with varying properties and cell types [131]. These include the need to open and close

the mold multiple times, leading to potential complications and discrepancies in manufacturing, as well as the fact that each material will exhibit isotropic properties, in contrast to the anisotropic components of native heart valves.

4.2 Compression molding

Compression molding is a manufacturing process primarily used for forming thermosetting plastics and some thermoplastics. The process (**Figure 4.3**) involves the placement of a pre-measured amount of polymer into an open, heated mold cavity. The mold is then closed, and heat and pressure are applied, causing the material to flow and conform to the shape of the cavity. The heat makes the curing process easier, transforming the polymer into a rigid, durable component [135]. This method is commonly used to produce large, relatively simple parts and is valued for its ability to mold intricate details with minimal material waste. To enable the successful manufacture of a component, various process parameters and mold features have to be optimized, such as the amount of material, temperatures, pressure, and the duration of process [135]. This technique enables the manufacture of leaflets with controlled thickness and the desired mechanical and physical properties. However, for medical applications, improving the surface quality of additively manufactured parts after the building process is still critical because, for example, in heart valves, surface topography can influence thrombus development.

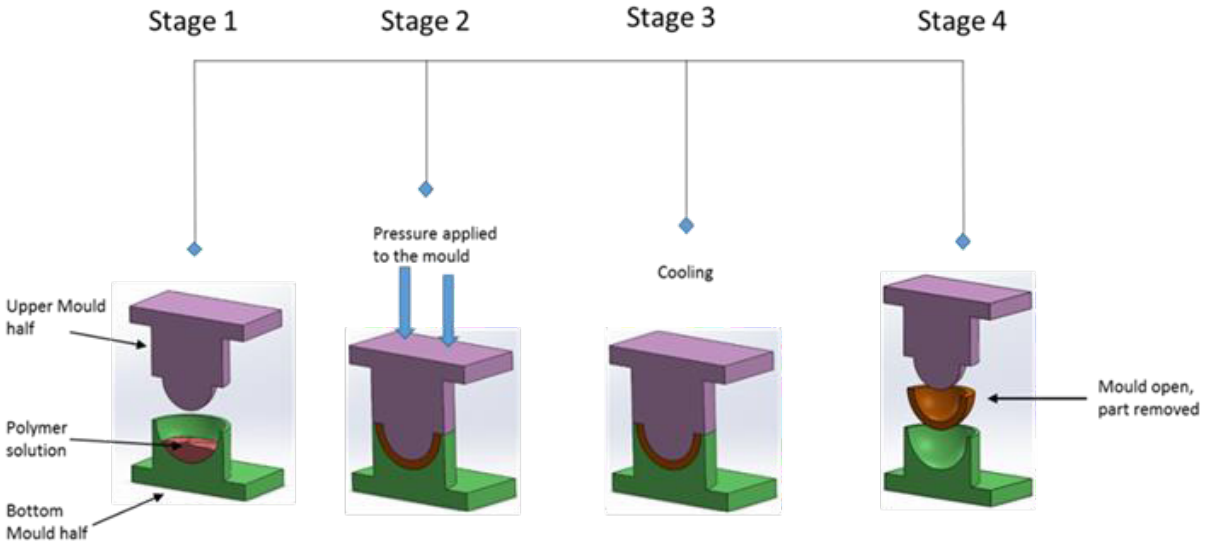


Figure 4.3. Steps of the compression-moulding procedure [135].

This was one of the first methods used for the fabrication of prosthetic heart valves. Early silicone valves were formed in one-piece by heating the mold up to 180 ºC under high pressure

and curing at 200 ºC for 4 hours [48]. These valves exhibited satisfactory short-term *in vivo* functionality [136]. Later, Roe et al. addressed some issues by casting thermocompression molds with different materials for the leaflets and sewing ring [51], achieving better results in clinical applications, with four patients surviving several months [50]. In 2013, Claiborne et al. developed a novel trileaflet polymeric heart valve made of xSIBS using a custom compression molding process [94]. The mold was coated with dry Teflon release agent, filled with the polymer, compressed with approximately 1 ton at 260 ºC for 30 minutes, and then cooled to room temperature before valve removal [94]. More recently, Masheane et al. developed a novel compression molding process for polymeric heart valve, using additive manufacturing technologies to produce white resin molds (**Figure 4.4**) [135]. They established parameters such as a 1:15 weight-to-volume solution, solution preheating at 89 ºC, and mold holding pressure of 0.25 MPa for 3 hours at 35 ºC, to manufacture a prototype polyurethane heart valve, resulting in a reproducible and well-controlled process.

Figure 4.4. Two valve prototypes fabricated with polyurethane: the valve on the right shows how the compression speed has a role in developing and entrapping air bubbles [135].

4.3 Dip molding

Dip molding is a manufacture process, also known as dip coating, used to create thin-walled, hollow parts by dipping a mold or mandrel into a polymer solution. This process is known for its simplicity and cost-effectiveness; it is suitable for producing items with uniform wall thickness and smooth surfaces. The process follows several straightforward steps. First, a mold or mandrel with, for example, the desired leaflet geometry is immersed into the polymeric solution, typically heated to a temperature ranged from 60 to 80 ºC [137]. After removal, a layer of solution adheres to the mold. Thereafter, the solvent is removed by heating leaving a thin solid polymeric film on the mold. These steps can be repeated to achieve the desired polymer thickness. The valve frame (or stent) can be dipped together with the mold initially or in

subsequent steps, facilitating a seamless transition and strong bond between the leaflets and the frame, even when using different materials [137].

The dip molding process necessitates precise control over several variables, including solution viscosity, polymer concentration, mold orientation during dipping and drying, mold shape and surface roughness, dipping speed, and temperature [137]. Moreover, due to the fluid state of the polymer, adjustments of any of these parameters can impact leaflet thickness and uniformity, and can potentially introduce defects such as air bubbles [137].

Since the 1990s, this process has been used for manufacturing polymeric heart valves. In 1992, Jensen et al. produced a novel polyurethane trileaflet heart valve by means of the dip coating method (**Figure 4.5**), achieving optimal results during *in vitro* tests in terms of durability and biocompatibility, and encouraging results in animal tests also [71]. In 1996, in order to develop a novel polyurethane heart valve, Mackay et al. well-controlled the dip process and formed valve leaflets integrated with their supporting frame in a single step, producing a valve comparable to the bioprosthetic ones [72]. In the early 2000s, Daebritz et al. used a dropping technique to deposit PCU onto the mold in a controlled way, enabling variation of the thickness across the leaflets. Then, they coated the entire valve, including the stent made of a harder PCU, ensuring a durable bond between the leaflets and the stent [75],[119],[138]. More recently, Rahmani et al. realized a semi-stented aortic valve prototype with a novel automatic dip coating process to improve reproducibility [80]. Furthermore, the researchers used the automatic enhanced manufacturing process based on dip coating controlled by robots to develop a novel TRISKELE valve, suitable for a perfectly controlled and reproducible process to manufacture the valve components [81].

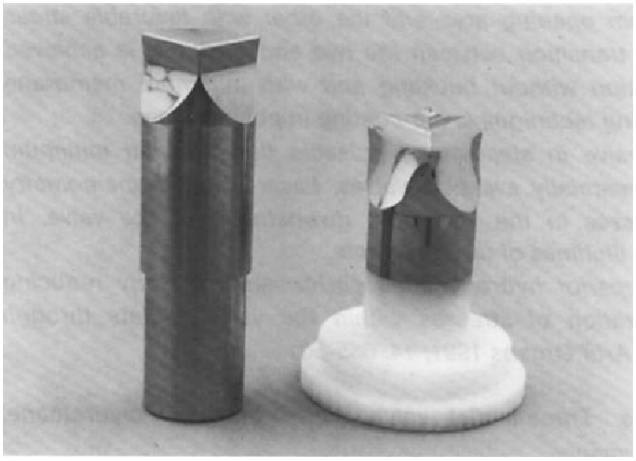


Figure 4.5. Dipping mold of the J-3 valve: leaflets geometry with one-dimensionally curved leaflets (left) and with minimal surface leaflets (right) [70].

4.4 Melt blending

Melt blending is a process used to mix different polymers or polymeric composites in their liquid state to achieve a homogeneous material with enhanced properties. It is often used as preliminary step before other processing techniques such as injection or compression molding. A composite is a material whose structure consists in two or more macroscopically identifiable components that work together to attain better properties [139]. As mentioned in the material sections (*Paragraph 3.2*), composites are increasingly used for heart valves. Melt blending is the preferred method for preparing polymer nanocomposites with a thermoplastic or elastomeric polymeric matrix. The process (**Figure 4.6**) begins with the selection of base polymers and any additional material or filler, for example nanoparticles, that are intended to enhance specific properties like mechanical strength, flexibility, or biocompatibility. The selected materials are heated to their melting point in an extruder (or in a similar device). Once melted, they are mixed thoroughly to ensure a uniform distribution of all components. The mixing can be controlled to achieve the desired characteristics such as viscosity and homogeneity. After mixing, the melted blend is cooled and solidified, through a different type of molding process, like injection or compression molding [140].

The main advantage of this method is that production rates and throughputs can be high. Since it does not require organic solvents, melt blending produces less chemical waste compared to other processes [141]. Despite the increasing use of composites and nanocomposites for the production of PHVs, many natural polymers cannot be melt-processed: they may degrade before or upon melting, or they may contain components that are unable to withstand high-temperature processing, such as proteins or drugs [141].

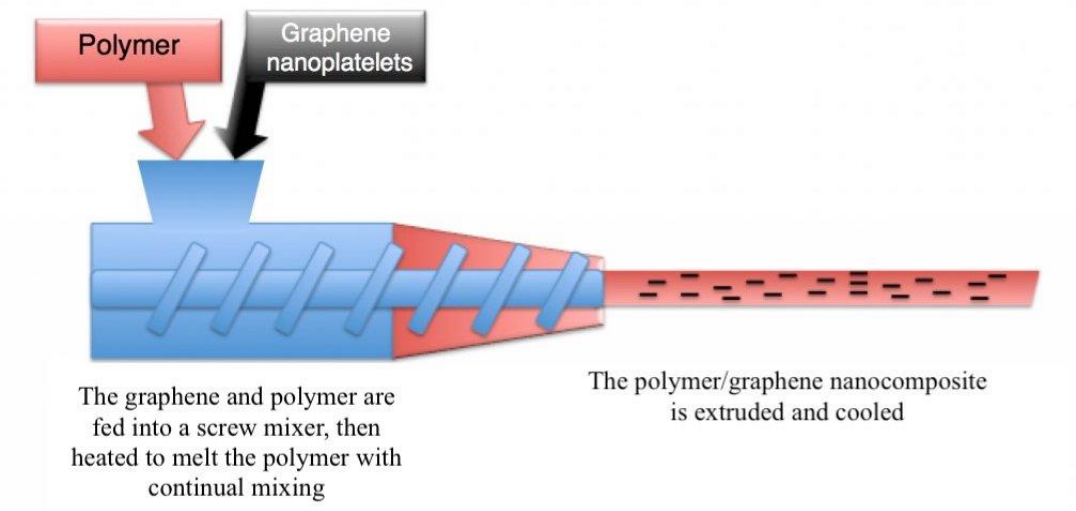


Figure 4.6. Scheme of melt blending procedure (e.g., with Graphene).

4.5 Additive manufacturing

Additive Manufacturing (AM), also known as 3D Printing, is an advanced technique used to produce a wide range of objects. In particular, for biomedical applications, AM allows the production of complex devices and implants, including patient-specific items. Regarding PHVs, AM involves building the structure layer by layer from a digital model. This process allows creating intricate designs that closely mimic the natural anatomy of heart valves, enabling the production of highly detailed components. The layer-by-layer construction method facilitates the incorporation of complex geometry and specific material properties, essential for the functional and mechanical performance required in heart valve applications.

AM includes different techniques that can be used depending on the desired product and its intended properties. The three primary types are:

- *Fused deposition modeling* (FDM): it is an AM extrusion process (**Figure 4.7**) that involves feeding a filament feedstock (polymer blend) through an electric motor-controlled pinch roller into a heated extrusion head. The filament melts as it moves through the head and is extruded through a nozzle [142]. The print head's planar x-y motion, combined with the z-motion of the building stage, allows the layer-by-layer deposition of the fused material. A second nozzle can deposit temporary supporting material. This technique is inexpensive, fast, and relatively simple, and can be expanded to multi-material printing using multiple nozzles [142]. However, it is limited to thermoplastic polymers with good viscosity properties, and due to the heated process, cells or temperature-sensitive biological agents cannot be incorporated [141]. The final printed items can exhibit a layer-by-layer effect, particularly on sloping surface, which may reduce surface smoothness and require further refinement steps.

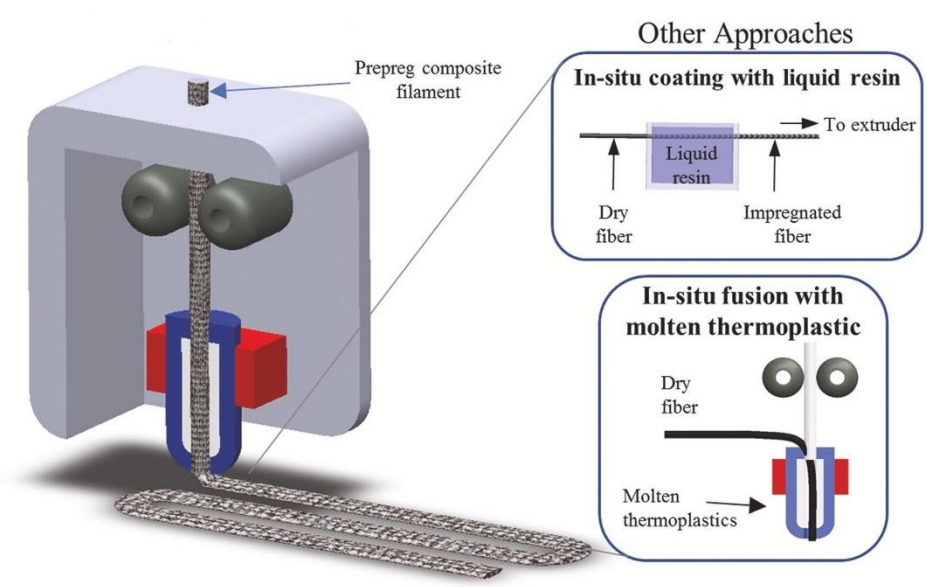


Figure 4.7. Three approaches to fabricate composite using fused filament fabrication: a nozzle is heated to melt the thermoplastic filament before being selectively deposited [142].

- *Stereolithography* (SLA): the manufacture of 3D objects by SLA relies on the spatially controlled solidification of a liquid resin through photopolymerization [143]. A digital light projector with a computer-driven building stage or a computer-controlled laser beam illuminates a pattern on the resin's surface (**Figure 4.8**). The resin in the pattern solidifies to a defined depth, determined by the energy of the UV beam/light, which can be controlled by changing the power of the light source or the scanning speed, causing it to adhere to a support platform. After photopolymerization of the first layer, the platform is moved away from the surface, and the newly exposed layer is coated with liquid resin. A pattern is then cured in this second layer. Since the curing depth exceed platform step height slightly, it ensures good adherence to the previous layer [143]. These steps are repeated to construct a solid, three-dimensional object. After excess resin is drained and washed off, the desired structure is obtained. Typically, the conversion of reactive groups in this structure is incomplete, and post-curing with (stroboscopic) UV light is often performed to enhance its mechanical properties. Compared to other AM techniques, SLA has the highest print quality in terms of part complexity and shape accuracy [141]. Complex internal features and cell viability can be achieved. However, the main limitations of this process are due to the limited availability and the high cost of photopolymerizable materials.

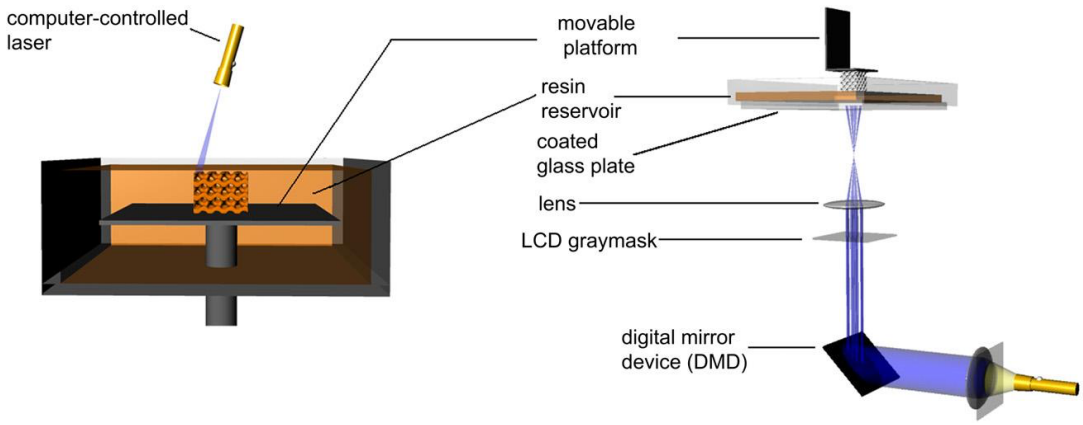


Figure 4.8. Representation of two types of stereolithography setups: a bottom-up system with a scanning laser (left) and a top-down setup with digital light projection (right) [143].

- *Selecting laser sintering* (SLS): it is an AM technique where a machine uses fine powder material to fabricate a 3D object based on a digital model (**Figure 4.9**). The powder is selectively heated by a laser beam to a point where the surface tension of individual particles is overcame, causing them to fuse together solidifying layer-by-layer [144]. To minimize thermal distortion, the entire base is preheated just below the material's melting point. The laser scans the powder surface, fusing particles to form each solid layer. After each layer is finished, the base is lowered, a new layer of powder is spread by a roller, and the sintering process is repeated. The powder in excess remains in place to support the next layer. Once the object fabrication is completed, the excess powder is removed and recycled [144]. This eliminates the need for a support structure and allows for intricate geometry. SLS offers high accuracy and material versatility, but fabricated parts often require post-processing to improve surface quality. Polymers in fabricated parts may shrink or warp due to thermal distortion, and bioactive molecules cannot be incorporated due to the high temperature used [141].

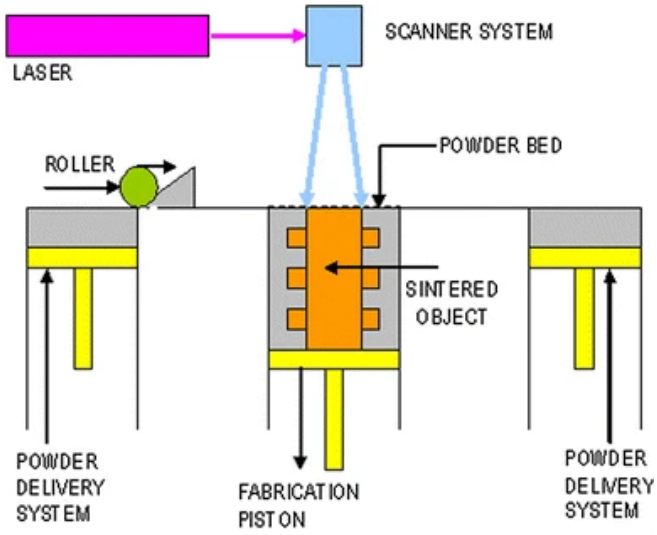


Figure 4.9. Scheme of selecting laser sintering technique [144].

AM technologies have the potential to revolutionize the manufacture of heart valves by enabling the creation of personalized, complex constructs. Improving printing resolutions, expanding the rage of printable materials, and integrating multiple 3D printing technologies with other manufacturing techniques, will pave the way toward the production of clinically usable and durable heart valves [145]. Although the majority of applications and studies of these processes have been concentrated in the field of tissue engineered heart valves (TEHVs), recent attention has also focused on producing new valve prototypes or individual component of PHVs. For instance, in 2021, Cavallo et al. proposed a novel polyurethane-based self-expandable trileaflet aortic valve, with the stent printed using a fused deposition modelling (FDM) 3D printer: promising results in terms of valve crimping capabilities, durability, fluid dynamic performance, and hemocompatibility were obtained [146]. In 2023, a novel 3D-printable heart valve was proposed by Schröter et al. By modifying the lateral profile of the triangular leaflets and 3D printing in silicon, they obtained a prototype that exhibited overall characteristics comparable to those of both currently adopted biological and mechanical prostheses [147].

4.6 Solvent casting

Solvent casting is a widely used technique in biomedical applications due to its simplicity and effectiveness in creating thin films, complex structures, and membranes. This process involves several steps (**Figure 4.10**) [148]. First, the desired polymer is dissolved in an appropriate solvent to create a homogeneous polymer solution. The choice of the solvent depends on polymer's solubility and the desired properties of the final product. For hydrophilic polymers, water is a

common solvent used in solution casting, while for hydrophobic polymers, organic solvents such as tetrahydrofuran (THF), dimethyl sulfoxide (DMSO), and dichloromethane (DCM) are typically used [141]. The polymer solution is then poured into a mold that defines the shape of the desired object. The polymer is left to dry by solvent evaporation: as the solvent evaporates, the polymer precipitates and forms a solid film. The thickness and uniformity of the film can be controlled by adjusting the concentration of the polymer solution and evaporation conditions [148]. Once solidified, the polymer is carefully removed from the mold. Post-processing steps, such annealing or cross-linking, may be applied to enhance the mechanical properties and stability of the material. The solvent used in solvent casting significantly affects the mechanical and physical properties of the resultant films [141].

This process has played a role in manufacturing various PHVs over the years. Some of the already mentioned polymers, like polyurethane and SIBS, have been used for the fabrication of heart valves through this process. For instance, the Angioflex heart valve, made of polyurethane, showed excellent results in calcification tests compared to other prosthetic heart valves [149]. For SIBS valves, a study demonstrated that solvent casting with a 25 µm SIBS coating thickness provide optimal biocompatibility, as evidenced by *in vitro* and *in vivo* tests [150]. More recently, SIBS has been studied to improve its applicability in PHVs. The material, dissolved in chloroform, exhibited the ability to replicate native leaflet functions with minimal risk of perforations, leaflet stress accumulation, ruptures, and tears [151].

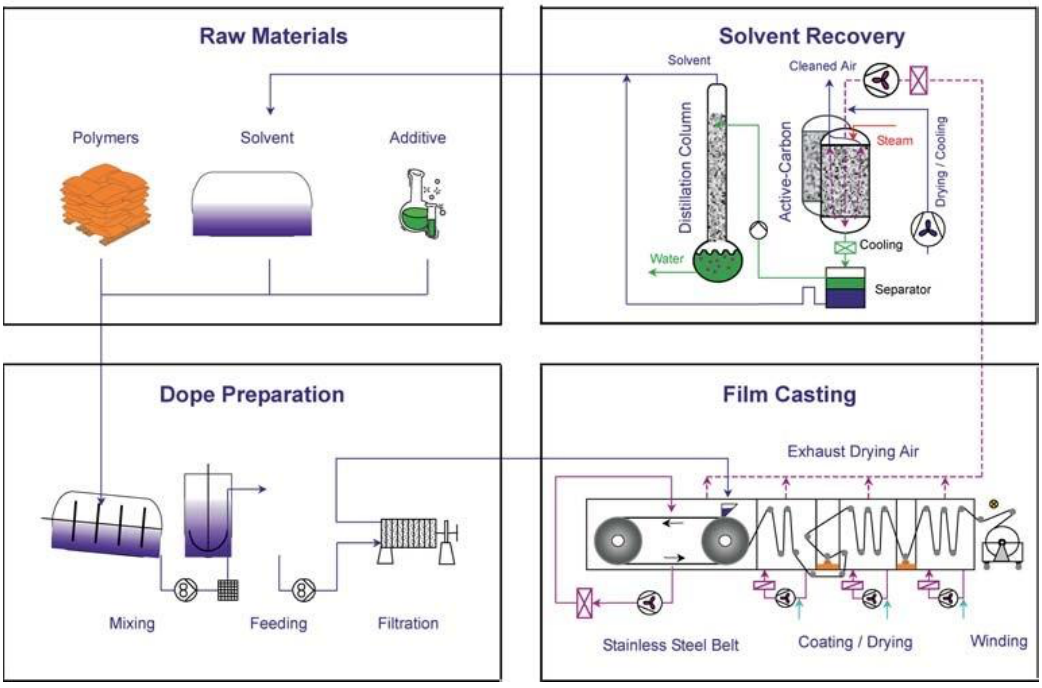


Figure 4.10. Scheme of the production of solvent cast films [148].

4.7 Electrospinning

Electrospinning is a versatile and precise method for fabricating nanofibers, widely utilized across numerous scientific fields, especially in biomedical applications. This technique allows producing extremely thin polymer or composite fibers, typically ranging in diameter from micrometers to nanometers, through the application of a high-voltage electric field to a polymer solution.

While electrospinning employs different methods, it generally revolves around three key elements (**Figure 4.11**): a syringe with a nozzle tip connected to a high-voltage direct current (HVDC) source, a grounded collecting screen that can be configured in various arrangements, and a flow rate regulator [152]. The HVDC source generates an electric current that facilitate the extrusion of a positively charged liquid jet (i.e., polymer solution, melt, or emulsion) from the nozzle tip. As this jet stream expands, it naturally fragments into numerous uniform fibers that are randomly oriented, which are subsequently collected on the negatively charged collector. This process results in a fibrous scaffold, widely used in bioengineering for its ability to mimic the native structure of the extracellular matrix and enhance cellular activities, owing to its substantial surface area-to-volume ratio [152].

Numerous natural biopolymers have been used in electrospinning by optimizing the solvent system and fabrication parameters. However, due to the presence of organic solvent and high voltage, cells cannot be directly used in the process [131]. This process is widely exploited in tissue engineering for polymeric heart valves, particularly for scaffold fabrication, but it does not have a significant impact on the fabrication of purely synthetic, non-degradable, and implantable valves.

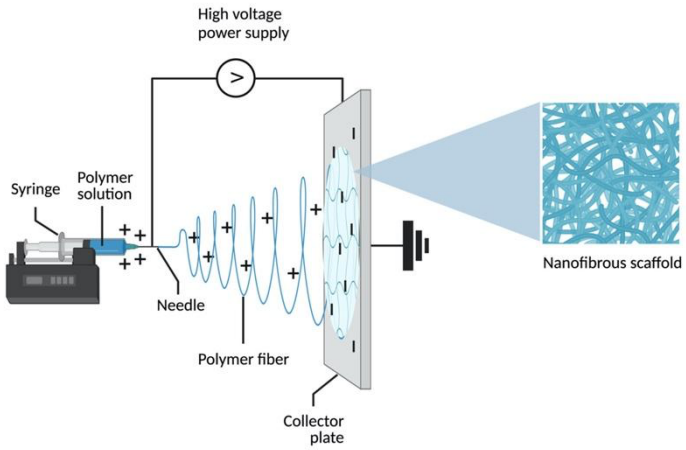


Figure 4.11. Schematic diagram of the manufacture of electrospun nanoscaffolds [152].

5. General consideration on design and geometry

The choice of the design is a crucial step in the development of artificial heart valves. Unlike bioprosthetic valves, polymeric valves can be virtually designed in any shape, which underscores the importance of structural design strategies. In particular, the geometry of the leaflets significantly influences the performance and durability of the valve. Studies have demonstrated that a geometry designed to mimic physiological flow patterns improves hemodynamics and reduces the risk of thrombosis [153], while abnormal flow patterns can increase forces on the arterial wall, leading to dilatation and potential aneurysm development. Furthermore, leaflet geometry can impact the rate of calcification [73].

There are several key requirements in heart valve design. Firstly, the valve must fit well within the host anatomy. The leaflets should offer minimal resistance to forward flow and rapidly open at a minimal variation of systolic transvalvular pressure. They must also ensure adequate sealing in the closed position to prevent/reduce backward flow. Furthermore, efforts should be made to minimize damage to blood cells and thrombogenic effects, while keeping stress peaks in the valve components as low as possible throughout the cardiac cycle to ensure durability and minimal changes of the geometric features [154]. A geometry that closely matches the natural valve configuration is desirable. Various designs have been proposed throughout the development of PHVs, but none can match the complexity of the natural valve.

Until the early 2000s, valve designs have substantially relied on experimental methods to assess their performance, often based on relatively straightforward mathematical equations that describe the geometry. In recent years, computational methods have significantly advanced for predicting the performance of any specific valve design. Numerical simulations, such as structural finite element analysis (FEA), computational fluid dynamics (CFD), and the integration of fluid-structure interaction (FSI) physics, have become pivotal in optimizing valve designs and enhancing various valve performance metrics [137]. FSI models, the latest computational tool, combine solid structural physics, with fluid flow physics, encompassing their highly nonlinear interaction. This distinguishes them from traditional computational fluid dynamics simulations, which typically assume fixed solid structures, and conventional structural finite element simulations, which often simplify the fluid effects to a fixed pressure distribution.

As regard PHVs, over the years, both bileaflet and trileaflet valves have been studied and developed, but the majority of the investigations have focused on the trileaflet design. This is

because trileaflet configurations are geometrically similar to natural pulmonary and aortic valves, which are the mostly diseased valves due to their workload.

5.1 Valve design over the years

The bileaflet mitral valve was one of the first artificial heart valves developed by Braunwald et al. in 1959 [67]. The valve was made of Dacron fabric enriched with PU in a mold, and its shape was obtained from casts of human and animal valves. Regarding bileaflet valves, a more recent study proposed a novel polymeric valve made of PCU [155]. This valve featured an oval stent with two asymmetric struts supporting a small posterior leaflet and a large anterior one, mimicking the natural mitral valve morphology. It featured a flat leaflet configuration and variable leaflet thicknesses (between 100-300 μm), encouraging physiological flow patterns [155]. *In vitro* and *in vivo* tests showed promising results, such as no thrombi formation, negligeable regurgitation, and no signs of structural damage or calcification. However, the valve never reached the clinical phase.

As for trileaflet valves, many designs have been studied over the years. In 1958, Roe and Moore proposed a design with cone-shaped leaflets, showing minimal resistance to systolic flow and promising hemodynamics and physiological efficacy [48], [136]. Furthermore, in 1977 Ghista and Reul proposed an optimised design to achieve smooth washout, good coaptation, and minimal leaflet stress [156]. After an analytical study defined by Chong, based on subtending angles and principal curvature radii [157], the optimised design facilitated the tangential flow and mutual support of leaflets throughout the closure rim, achieving *in vitro* durability of more than 350 million cycles [156]. In 1982, Wisman et al. proposed a trileaflet PHV made of segmented polyurethane [158]. The valve was composed of hemicylindrical leaflets and a flexible support: it showed good efficiency in *in vitro* tests, but dystrophic calcification and thrombosis arised in animal tests [158]. Later, other studies have been proposed, such as the one on the valve geometry using a cylindrical model, which showed important considerations regarding reduced dilatation pressure and low bending strains [159]. In 1994, Lean and Fisher proposed a novel design for a polyurethane heart valve [160]. They started by analyzing previous leaflet geometries and demonstrated that increasing the radius of curvature at the base of the leaflets would enhance opening characteristics. A new geometry, termed ‘alpharabola’, was proposed, which has a variable radius of curvature and a varied leaflet thickness, leading to a reduced opening pressure of over 40% and a minimal pressure differential [160]. In 1995, Mackay et al. developed a novel polyurethane valve that comprised a cylindrical support frame and, in the closed position, a leaflet shape defined by conic sections:

hyperbolic in the circumferential and elliptical in the radial direction [72]. Furthermore, hyperbolic parameters were adjusted to allow efficient coaptation with minimal stretching of the leaflets. The valve showed good hydrodynamic performance and durability without any signs of failure [72]. In 2001, the same researchers proposed a novel design for a trileaflet heart valve with conical geometry for the leaflet region next to the frame and a spherical upper leaflet region, allowing for facilitated opening and closing, good coaptation, and stable closed position [161]. The valve showed an improved hydrodynamic function, with a higher EOA and a reduced regurgitation, and the pulsatile flow results showed a lower total energy loss. Later, in 2003, Jiang et al., during the development of a heart valve made of PVA, proposed two novel designs based on the hyperbolic geometries of Mackay's group, defining the shape of the leaflet using a hyperbolic revolution around an axis and the revolution around an axis of an arc subtending two straight lines [106]. The second one provided better control of the central opening and leaflet curvature, but both designs experienced gaps between adjacent leaflets and a large central orifice when the valve closes [106].

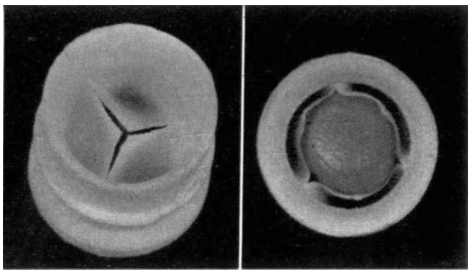
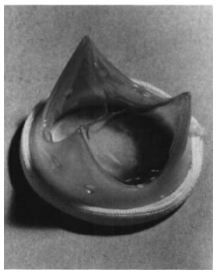
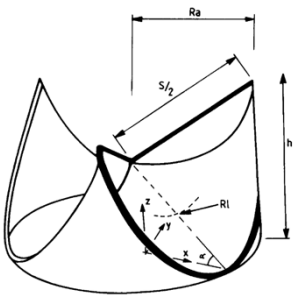
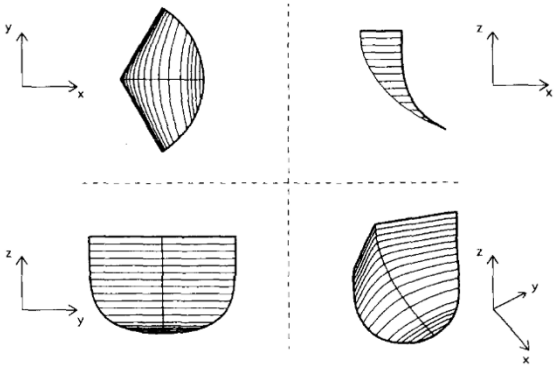
After the early 2000s, as mentioned above, researchers started using more efficient computational methods to develop better designs for heart valves. In 2008, Mohammadi et al. developed a novel PVA-BC heart valve, and by using Bezier surfaces (a spline that could be easily altered by manipulating control points in CAD software) combined with structural FEA and including material properties (i.e., the elastic moduli in orthogonal directions), they were able to analyze and select the optimal geometry, addressing the shortcomings of previous hyperboloid designs [162]. Even though fluid flow was not accounted for in this analysis, the structural simulations demonstrated favorable opening and closing dynamics as well as stress distributions within the physiological range for native aortic valves [162]. In 2010, Burriesci et al. proposed a novel polymeric heart valve design optimized by means of FEA [163]. The geometry, specifically conceived to minimize stress amplitudes in the leaflet and maximize the geometric orifice area, was defined as a ruled surface between the intersection of the stent cylinder with a plane and an arc joining the commissures. *In vitro* tests proved a larger EOA compared to Mackay's ellipto-hyperbolic geometry, as well as reductions in regurgitation and transvalvular pressure drop [163]. Different studies have proven that a larger EOA, exhibited by valves with the thinnest leaflets, is preferable due to a lower pressure differential, regurgitation, and energy loss [80]. This design was later used by Rahmani et al. for developing the novel TRISKELE transcatheter aortic valve [82]. Another important study based on structural FEA was conducted by Li and Sun, who investigated around 500 distinct leaflet designs by means of simulations of TAV closure under nominal circular deployment and

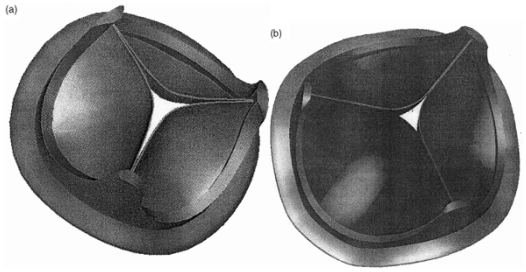
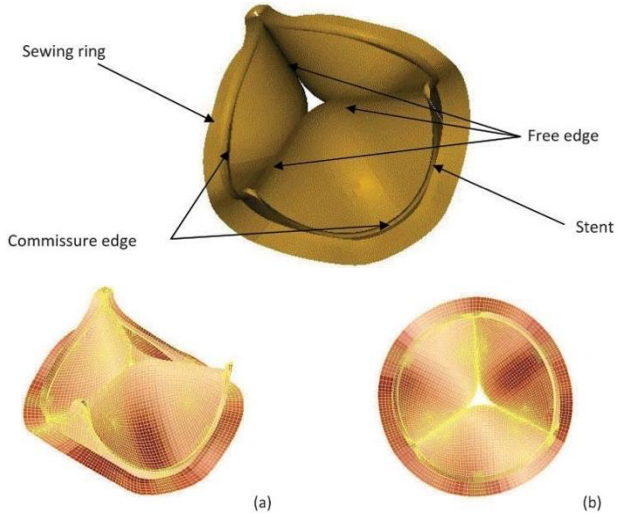
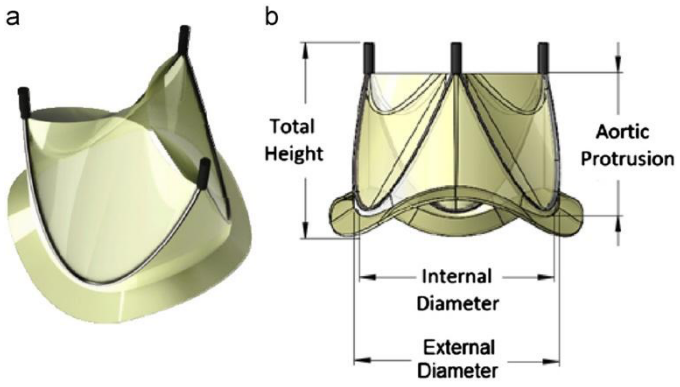
physiological loading conditions. This study was aimed to observe how variations in leaflet geometry affect valve peak stresses in both circular and elliptical configurations [164]. The optimization study led to the identification of an optimal leaflet design capable of reducing peak stress on the TAV leaflets by approximately 5% compared to the original design.

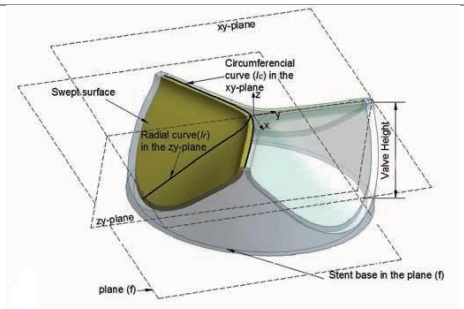
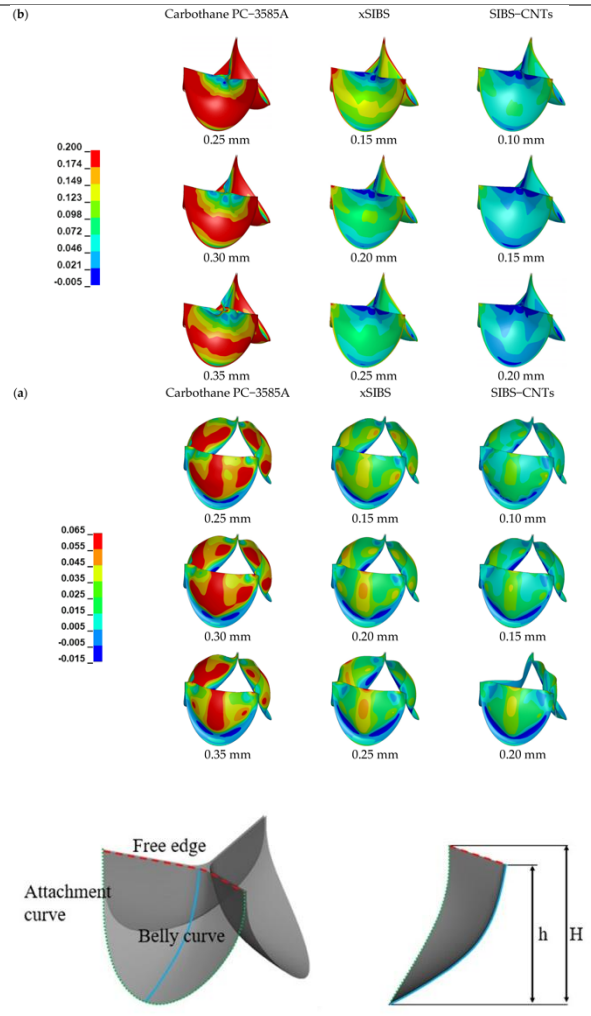
In recent years, trileaflet heart valve designs based on simulations incorporating nonlinear fluid-structure interaction physics, have become increasingly widespread. In 2015, Gharaie and Morsi utilized an FSI model to optimize and evaluate the performance of their design [165]. They compared previously published data with predicted results to validate the FSI model, developing a design characterized by two curves (radial and circumferential). These curves were optimized to achieve reduced stress concentration in the leaflets and minimal regurgitation. The optimized valve prototype demonstrated high hemodynamic performance with absence of damaging stress concentration during the entire cardiac cycle [165]. In 2018, Ghosh et al. developed a polymeric SAVR valve using the FSI technique with a boundary-fitted method, the Arbitrary Lagrangian-Eulerian (ALE) method, which deforms the fluid cells according to the structural motion [166]. The valve showed a large opening area and a high flow rate, while wall shear stress distribution and mechanical stress magnitudes were stable, demonstrating the enhanced performance of the prototype. Later, in 2021, Farokhi et al. developed a double-coupled fluid-structure interaction model using ALE and steered adaptive mesh (SAM) to investigate the impact of valve elasticity and valve positions on hemodynamics and solid parameters [167]. The simulation results indicated that a lower elastic modulus causes an increase in the EOA. Furthermore, the results of valve position showed that, when the valve is closer to the sinuses, a greater EOA and lower stresses imposed on the leaflet are achievable [167]. On the other hand, Zhou et al. studied the correlation between valve thickness and material properties [168]. They utilized the FSI analysis to obtain a more accurate solution of the stress and strain distribution, EOA, and regurgitation fraction of the valves with varying thicknesses across three different materials: Carbothane PC-3585A, xSIBS, and SIBS-CNTs. For each valve, they found specific optimal constraints for valve thickness based on the elastic modulus of each material: a smaller elastic modulus like the one of Carbothane PC-3585A allowed the production of a ticker valve (> 0.3mm); vice versa, with an elastic modulus greater than that of xSIBS (2.8 MPa), excellent results can be obtained with a thickness less than 0.2 mm [168].

A summary of the evolution of polymeric heart valves over the last decades is illustrated in **Table 5.1**.

Table 5.1. Illustrates the evolution of polymeric heart valve over the last decades.

Design	Description	Reference
	One of the first designs for polymeric valves, with cone-shaped leaflets and made of Silicon	Roe et al. [136]
	Polyurethane trileaflet valve composed of three hemicylindrical leaflets, each with a 10 mm diameter respect to the flow axis, and an orifice diameter of 23.5 mm	Wisman et al. [158]
	3D illustration of the cylindrical trileaflet heart valve, showing the angle of inclination, the radius of curvature, the radius of the aortic root, and the height of the valve	Lockie et al. [159]
	Leaflets geometry of a polyurethane heart valve: in the closed position, the leaflet shape is characterized by conic section: hyperbolic in the circumferential (x-y plane) and elliptical in the radial direction (x-z plane)	Mackay et al. [72]

	Design of heart valves with leaflet geometry defined by *a*) hyperboloid of revolution around an axis and *b*) revolution around an axis of an arc subtending two straight lines. The difference in the area of the central orifice is underlined	Jiang et al. [106]
	Optimized geometry of a trileaflet valve made of PVA-BC, without gaps between the two adjacent leaflets and a middle orifice area < 5% of the total orifice area in the closed position (top). A view of the FE model of the valve in an a) isometric view and b) top view	Mohammadi et al. [162]
	SSAV prototype made of POSS-PCU, *a*) isometric view, *b*) specifics, with internal diameter of 21 mm, external diameter of 22 mm, aortic protrusion of 14 mm and total height of 20 mm	Rahmani et al. [80]

 	3D model of the leaflet (up) and the discretization of the optimized valve (bottom). Design characterized by two curves (circumferential and radial), optimized to achieve the maximum GOA, minimal regurgitation, and less damage concentration in the leaflets	Gharaie and Morsi [165]
	MIPE distribution of the three materials analyzed, showing that Carbothane had strain higher than the others, especially in the closed phase. In the opening phase, as the thickness increases, the strain in the middle of the valve belly increases and disappears on both sides. Following the closed phase, high strains at commissure points and along the attachment curve diminishes with increasing thickness. The geometry valve model used is showed (bottom)	Zhou et al. [168]

6. Complications associated with the use of PHVs

From an optimistic perspective on the clinical use of PHVs, it is crucial to consider the complications observed *in vitro* and *in vivo* studies over the years. These studies have shown increasingly better prevention measures, which may lead to possible clinical exploitation in the future. Despite advances in surgery and valve design, the replacement of a diseased native valve with a prosthetic one is not yet a definitive cure for patients. The native disease is often supplanted by prosthetic valve disease, with clinical outcomes influenced by prosthetic valve hemodynamics, durability, complications related to the device, and patient response. Many of these complications can be prevented, or their impact minimized, with careful medical management, periodic monitoring of valve functionality, or, in the case of polymeric valves, through modifications in material structure, surface properties, or valve design. For artificial heart valves, the complications and criteria are the following:

- **Hemocompatibility**: it is one of the major issues limiting the clinical applicability of blood-contacting biomaterials. Adverse interactions between material and blood must be extensively analyzed to prevent the activation and/or destruction of blood components. The protein layer initially adsorbed on the biomaterial surface primarily triggers adverse reactions, such as coagulation activation via the intrinsic pathway, leukocyte activation leading to inflammation, and platelet adhesion and activation, which can result in decreased blood cells and/or thrombus formation [169]. Prior to clinical application, the hemocompatibility of blood-contacting materials has to be investigated, as outlined in ISO 10993-4 (**Table 6.1**). This standard describes five categories for the analysis: thrombosis, coagulation, platelets, hematology, and immunology. To perform the requested analyses, various *in vitro* models are used to incubate blood with the biomaterial [169]. These models provide information on changes in platelets, erythrocytes, and leukocytes, the generation of activation products in plasma, and the adsorption of proteins or deposition of cells on the material surface. Both blood and biomaterial surface are analyzed before and after incubation.

  Initially, the primary limitation of these *in vitro* models is the absence of an endothelium. The endothelium produces anti-thrombotic components and cytokines and expresses adhesion molecules for monocytes, thrombocytes, and neutrophils, playing a crucial role in the interaction between circulating blood and injured vessel wall [169]. In recent years, the use of microfluidic devices has allowed for the simultaneous determination of platelet and coagulation activation under defined physiological or pathological wall

shear rates, using only a small amount of blood. Additionally, the combination with fluorescence microscopy allows for real-time optical imaging of fibrin fiber formation and platelet adhesion.

Table 6.1. Common tests to assess materials interaction with blood (ISO 10993-4:2017).

Tests by categories	
Haemolysis	Material-induced
	Mechanical-induced
Thrombosis (*in vivo, ex vivo*)	Gross analysis, percentage occlusion, light microscopy, SEM
***In vitro* thrombosis**	
Coagulation	Thrombin, fibrin assays, PTT assay
Platelet activation	Platelet count (% loss) and some indicator of activation or SEM
Haematology	Complete blood count, leucocyte activation
Complement system	SC5b-9 (Ca3 optional)

- **Thrombosis**: it is an *in vivo* phenomenon that results in partial or complete occlusion of a blood vessel or device due to coagulation. Events such as intraoperative stroke, transient ischemic attacks, sudden death, and myocardial infarction may be due to prosthesis-generated thromboemboli or other causes [170]. As discussed in the materials section (*Paragraph 3.2*), proteins adsorption on the material has a crucial effect to determine the level of thrombogenicity of any given material: this represents a critical area of investigation for the development of novel PHVs. Unlike mechanical valves, PHVs significantly reduce thrombotic risk and, as a consequence, the amount of anticoagulation required [171]. This reduction is important because anticoagulation often results in bleeding episodes, which can cause death, stroke, reoperation, or hospitalization. Indeed, recipient of mechanical prostheses require lifelong anticoagulation, typically with vitamin K antagonists (e.g., warfarin), which brings significant challenges, including frequent blood analyses, possible drug-drug interactions, dietary and activity restrictions, medication costs, and the need to travel long distances for anticoagulation monitoring [172]. PHVs thrombogenicity is evaluated by means of *in vitro* and *in vivo* models designed to mimic human conditions and comprehensively examine blood-implant interactions. ISO 10993-4 provides detailed requirements for such tests.

- **Calcification**: valve calcification (**Figure 6.1**) involves the gradual accumulation of calcium salts over and inside valvular tissue, potentially leading to various complications. While PHVs are designed to be less prone to calcification than bioprosthetic ones, they are not entirely exempt, prompting numerous studies aimed at minimizing or eliminating this event. Calcific deposits commonly occur in the commissural and basal regions of the cusp. This phenomenon can lead to adverse outcomes in both pre-clinical studies and long-term implantation. Growing calcific masses can block the leaflets, causing structural valve deterioration and potentially resulting in stenosis or regurgitation [173]. Calcification can be either passive, when calcium ions accumulate and disrupt the material, or active, driven by inflammatory responses to antigens present in prosthetic tissues, leading to accelerated tissue mineralization [171]. PHVs have a distinct advantage over traditional bioprestheses because they lack animal-derived proteins, such as Neu5Gc and αGal: this may lead to longer durability [171]. As mentioned earlier, calcific susceptibility can be assessed using both *in vitro* and *in vivo* testing. Sheep are preferred for *in vivo* tests due to their accelerated and enhanced calcium metabolism, creating the "worst-case-scenario" for valvular calcification [171].

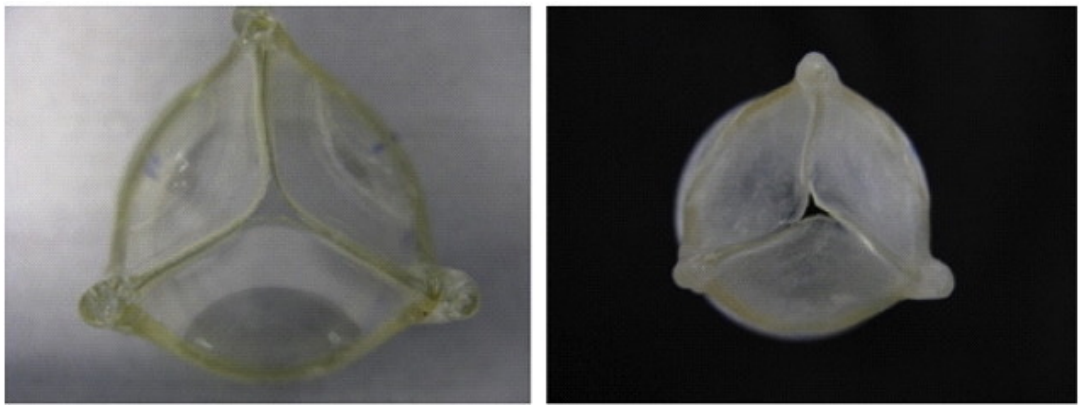


Figure 6.1. Polyurethane (Angioflex) valve before (left) and after (right) a calcification test [149].

- **Infection**: infection of the valve or surrounding tissues (prosthetic valve endocarditis) is a severe complication that may necessitate antibiotic treatment and eventually valve replacement. The risk of endocarditis associated with PHVs has not been extensively studied, necessitating further research to clearly define these risks compared to bioprosthetic and mechanical valves. Generally, this complication is more prevalent within the first two years after surgery, and it is more common in patients whose valves

were replaced due to damage inflicted by previous infective endocarditis, often involving the same microorganisms responsible for the initial infection [174]. Further complications related to infective endocarditis include congestive heart failure, embolization, and paravalvular abscesses.

- **Mechanical complications**: some complications related to PHVs can be categorized as mechanical issues. Due to the repetitive opening and closing cycles, these valves are susceptible to fatigue failure that, over time, can lead to the development of cracks and eventually structural failure (**Figure 6.2**). As previously mentioned, developing proper valve geometry is a crucial step, along with conducing appropriate fatigue tests, often under conditions more severe than those for a native valve. Additionally, cyclic application of mechanical stress can cause wear and tear, leading to thinning of valve leaflets and potential rupture. This scenario depends on the given material or, once again, on the leaflets design. Achieving the right balance between stiffness for structural support and flexibility for proper functioning is challenging, because inadequate flexibility can impair valve motion, while insufficient stiffness can compromise structural integrity.

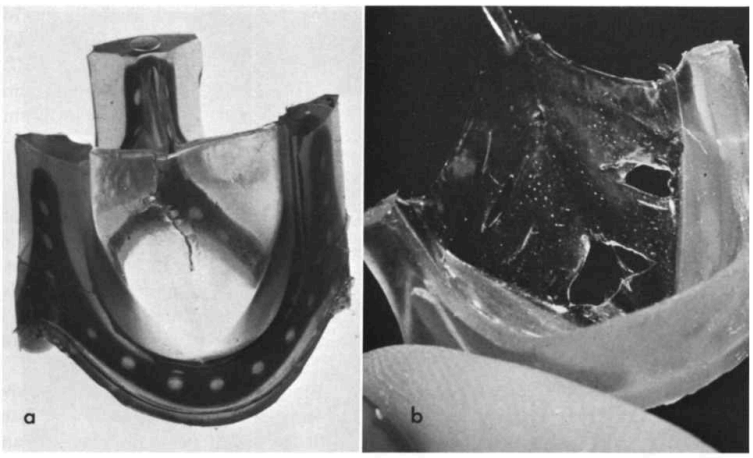


Figure 6.2. Example of leaflet tear: *a*) leaflet tear due to fatigue test; *b*) leaflet tear due to incorrect manufacturing process [53].

- **Hydrodynamical complications**: some problems with PHVs function can be categorized as hydrodynamic issues. Poor valve design can lead to various problems related to blood flow dynamics or blood components integrity. Improper valve design can result in incomplete closure of the valve leaflets, leading to backflow of blood or regurgitation, which compromise the efficiency of the heart's pumping action. It can

cause stenosis, reducing the effective orifice area and thus impeding blood flow though the valve. Furthermore, it can cause high shear stress, that can lead to hemolysis (i.e., the destruction of red blood cells), which can cause anemia and other complications. The criteria and possible tests are outlined in ISO 5840-3 and ISO 10993-4.

7. Modification techniques

PHVs are designed to offer improved durability compared to bioprosthetic valves, and higher biocompatibility and functionality than mechanical devices. However, as discussed in the previous section, they still face different challenges, and no approved clinical application is currently in progress. Over the years, various strategies have been explored to enhance PHVs performances: they will be briefly illustrated herewith.

7.1 Endothelialization

One promising approach to mitigate clot formation is endothelialization, which implies the formation of a monolayer of endothelial cells (ECs) on the blood-contacting surfaces [175]. In the native heart, the endothelial layer is selectively permeable, allowing substances such as oxygen, chemicals, and white blood cells to pass through. Healthy ECs help create and sustain an anti-proliferative and anti-thrombotic environment throughout the blood vessel, promoting the laminar flow of plasma and blood components. The absence of a healthy endothelium, for example after the implantation of a prosthetic vascular graft, can result in thrombus formation and intimal hyperplasia, leading to vessel occlusion. Similarly, the endothelial layer in a heart valve maintains the necessary anti-thrombotic and anti-degenerative environment: any other surface causes blood coagulation [175].

Endothelialization can be achieved through various approaches [175]:

- biological modifications: techniques such as coating, covalent grafting, or immobilization of various cell-adhesive biomolecules (e.g., proteins and bioactive peptides) on the biomaterial surface;
- cellular engineering:
    - cellular therapy: infusion of endothelial progenitor cells (EPCs) from circulating blood making them to adhere, migrate, and proliferate on device surfaces;
    - pharmacological therapy: activation of EPCs in a similar manner influenced by specific drugs;
    - gene therapy: deliver specific genes into endothelial cells can potentially stimulate the production of factors that promote anti-thrombotic properties and can improve the integration of the implanted device with the surrounding tissue.

Regarding PHVs, *in vivo* endothelialization has not been directly reported in the scientific literature, but various materials have been investigated [176]. Not all polymers are prone to endothelial cell adhesion and proliferation, often necessitating surface modification techniques.

On the other hand, the nature of polymers offers some advantages, such as the ability to design surfaces with specific micro or nanostructures to mimic the natural extracellular matrix to facilitate cell adhesion. Additional approaches include *in vitro* pre-seeding the valve with ECs before implantation, culturing valves in a bioreactor that simulates physiological conditions to enhance cell adhesion and growth, or incorporating into the polymeric matrix specific drugs that are slowly released to promote endothelialization over time.

7.2 Surface modification and functionalization

Functionalization and surface modification of polymers are strategies suitable to enhance properties and performances of the prosthetic valves, particularly in terms of biocompatibility, durability, and functionality.

Surface modifications involve the alteration of surface properties without necessarily adding new chemical functionalities. On the other hand, functionalization applies specific chemical groups or molecules to the surface to impart new functionalities, endothelialization being an example thereof.

One extensively studied surface modification technique involves the incorporation of polyethylene glycol (PEG) [177]. PEG-coated surfaces create tightly bound layers of water that prevent protein adsorption, significantly reducing possible thrombus formation. However, incorporating PEG into polymers has some drawbacks, such as non-biodegradability, triggering the complement pathway (that results in immunological responses), and causing hypersensitivity reactions [177]. Other surface modifications, such as incorporation of poly(vinyl chloride) (PVC), poly(2-ethyl-2-oxazoline), polyethylene oxide (PEO), titanium oxides/nitrides, polysulfone (PSF), and poly(ethylene), have been attempted to increase hemocompatibility but with limited long-term success [177], [178].

For polymeric materials, several techniques have been used over the years to modify surface characteristics:

- physical treatments: processes such as plasma treatment, ion implantation, or ultraviolet (UV) irradiation, can change surface characteristics like roughness, wettability, and energy [179]. Some studies have developed promising materials using UV irradiation and plasma treatment, enhancing biocompatibility and bactericidal activity [180];
- coatings: the application of thin layers of biocompatible materials such as polymers, ceramics, or metals can improve hemocompatibility and reduce thrombogenicity [179]. Benson et al. proposed a coating with two covalently linked hyperbranched polymer thin films, one adhering to the surface and one preventing protein adsorption, showing

promising preliminary results in terms of durability and cell adhesion [181]. Recent studies have proposed drug-releasing multilayer coatings to decrease the use of anticoagulation drug (**Figure 7.1**) [182], and hydrogel coatings that enhance hydrophilicity and blood compatibility, maintaining platelet resistance after multiple stretching and bending cycles [183].

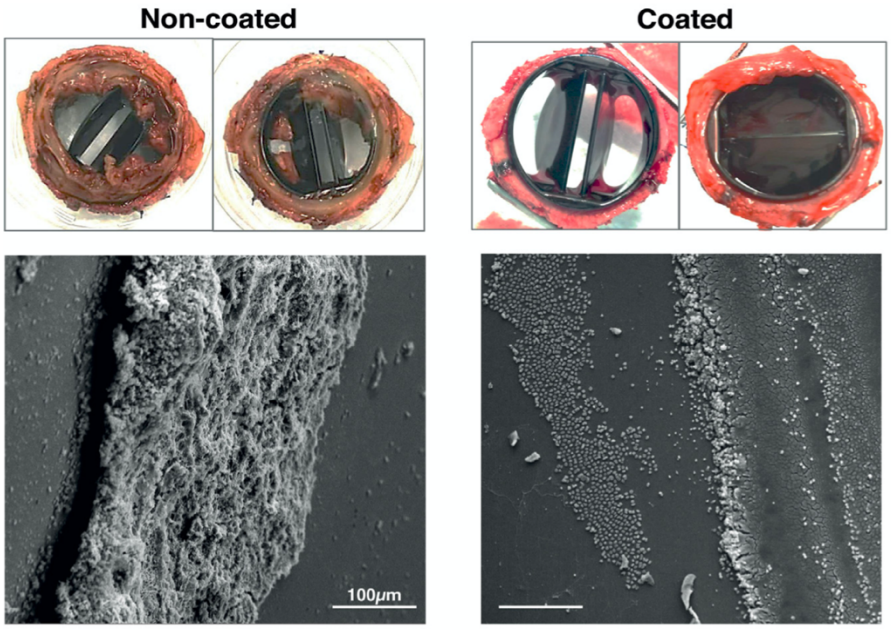


Figure 7.1. Artificial heart valve before (left) and after (right) coating process to achieve antithrombotic feature, showing explanted valves one month after surgery and a clot section (TEM images) [182].

- topographical modifications: creating micro- or nano-scale patterns on the surface can influence cell behavior and protein adsorption without adding chemical substances [179]. Altering surface roughness can affect blood cell adhesion [184], and surfaces with specific micro-structures similar to native tissues have shown higher super hydrophobicity and blood compatibility than smooth surfaces (**Figure 7.2**) [185]. A recent study by Vigano et al. highlighted that surface nanotexture can minimize thrombogenicity, although further specific studies are needed [186].
- chemical grafting: covalent bonding of bioactive molecules such as peptides, proteins, or growth factors, to the surface can promote specific cellular responses or inhibit unwanted reactions [180]. These responses are crucial for the successful application of tissue-engineered heart valves.

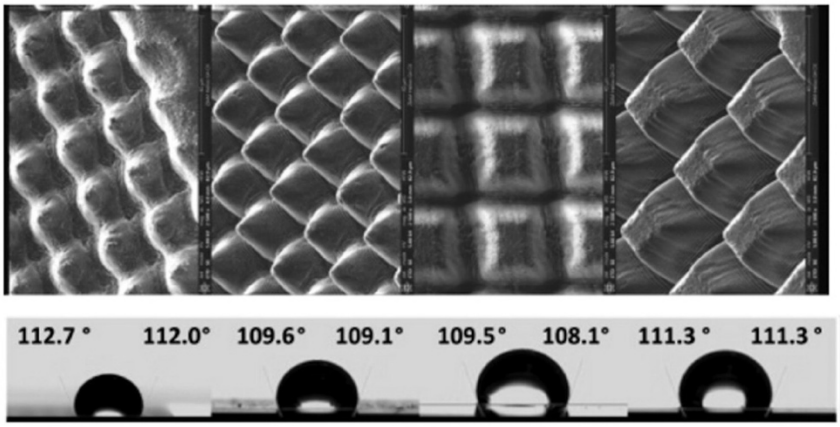


Figure 7.2. Four different textures obtained from laser irradiation, leading to different water contact angles. A lower contact angle indicates a more hydrophilic surface, which promotes higher blood compatibility [186].

Conclusions

Polymeric heart valves offer a promising alternative to traditional prosthetic devices, with significant potential to improve the quality of life for patients. Despite the wide range of materials, manufacturing technologies, and valve designs presented in this work, the requirements for biostability and mechanical properties, the complexity of the valve model in an anisotropic environment, and the complex structure and functioning of the native valve to be replaced, the research advancements and technological developments on this field are slow and challenging. However, what was thought impossible years ago, it has now become possible, with polymers like SiPUU successfully exploited for the production of PHVs already under clinical trials. Compared to previous studies, the most recent research demonstrated satisfactory hemodynamics and *in vitro* durability, along with reduced calcification and thrombogenic potential *in vivo*. The biggest challenge for PHVs is the successful demonstration of long-term *in vivo* durability, but with the introduction of new materials and new technological solutions, the clinical translation of PHVs with successful outcomes will be possible soon.

Bibliography

[1] S. Coffey *et al.*, «Global epidemiology of valvular heart disease», *Nat. Rev. Cardiol.*, vol. 18, fasc. 12, pp. 853–864, dic. 2021, doi: 10.1038/s41569-021-00570-z.
[2] S. S. Martin *et al.*, «2024 Heart Disease and Stroke Statistics: A Report of US and Global Data From the American Heart Association», *Circulation*, vol. 149, fasc. 8, feb. 2024, doi: 10.1161/CIR.0000000000001209.
[3] S. Azari *et al.*, «A systematic review of the cost-effectiveness of heart valve replacement with a mechanical versus biological prosthesis in patients with heart valvular disease», *Heart Fail. Rev.*, vol. 25, fasc. 3, pp. 495–503, mag. 2020, doi: 10.1007/s10741-019-09897-9.
[4] C. D. Resor e D. L. Bhatt, «Polymeric Heart Valves: Back to the Future?», *Matter*, vol. 1, fasc. 1, pp. 30–32, lug. 2019, doi: 10.1016/j.matt.2019.06.003.
[5] R. B. Hinton e K. E. Yutzey, «Heart Valve Structure and Function in Development and Disease», *Annu. Rev. Physiol.*, vol. 73, fasc. 1, pp. 29–46, mar. 2011, doi: 10.1146/annurev-physiol-012110-142145.
[6] R. H. Anderson, S. Y. Ho, e A. E. Becker, «Anatomy of the human atrioventricular junctions revisited», *Anat. Rec.*, vol. 260, fasc. 1, pp. 81–91, set. 2000, doi: 10.1002/1097-0185(20000901)260:1<81::AID-AR90>3.0.CO;2-3.
[7] M. Misfeld e H.-H. Sievers, «Heart valve macro- and microstructure», *Philos. Trans. R. Soc. B Biol. Sci.*, vol. 362, fasc. 1484, pp. 1421–1436, ago. 2007, doi: 10.1098/rstb.2007.2125.
[8] M. S. Sacks, W. David Merryman, e D. E. Schmidt, «On the biomechanics of heart valve function», *J. Biomech.*, vol. 42, fasc. 12, pp. 1804–1824, ago. 2009, doi: 10.1016/j.jbiomech.2009.05.015.
[9] H. Tseng e K. J. Grande-Allen, «Elastic fibers in the aortic valve spongiosa: A fresh perspective on its structure and role in overall tissue function», *Acta Biomater.*, vol. 7, fasc. 5, pp. 2101–2108, mag. 2011, doi: 10.1016/j.actbio.2011.01.022.
[10] V. Y. F. He *et al.*, «Long-Term Outcomes From Acute Rheumatic Fever and Rheumatic Heart Disease: A Data-Linkage and Survival Analysis Approach», *Circulation*, vol. 134, fasc. 3, pp. 222–232, lug. 2016, doi: 10.1161/CIRCULATIONAHA.115.020966.
[11] F. Peters, G. Karthikeyan, J. Abrams, L. Muhwava, e L. Zühlke, «Rheumatic heart disease: current status of diagnosis and therapy», *Cardiovasc. Diagn. Ther.*, vol. 10, fasc. 2, pp. 305–315, apr. 2020, doi: 10.21037/cdt.2019.10.07.
[12] D. Sika-Paotonu, A. Beaton, A. Raghu, A. Steer, e J. Carapetis, «Acute Rheumatic Fever and Rheumatic Heart Disease».
[13] S. M. Shah, J. Shah, S. M. Lakey, P. Garg, e D. P. Ripley, «Pathophysiology, emerging techniques for the assessment and novel treatment of aortic stenosis», *Open Heart*, vol. 10, fasc. 1, p. e002244, mar. 2023, doi: 10.1136/openhrt-2022-002244.
[14] H. Baumgartner *et al.*, «Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice», *Eur. J. Echocardiogr.*, vol. 10, fasc. 1, pp. 1–25, gen. 2009, doi: 10.1093/ejechocard/jen303.
[15] D. R. Ancona, «Epidemiology of aortic valve stenosis (AS) and of aortic valve incompetence (AI): is the prevalence of AS/AI similar in different parts of the world?».
[16] C. Delwarde *et al.*, «Genetics and pathophysiology of mitral valve prolapse», *Front. Cardiovasc. Med.*, vol. 10, p. 1077788, feb. 2023, doi: 10.3389/fcvm.2023.1077788.
[17] A. Singh *et al.*, «An Extremely Rare Case of Isolated Aortic Valve Prolapse Causing Aortic Regurgitation in the Absence of Any Other Pre-existing Cardiovascular or Non-cardiovascular Condition», *Cureus*, set. 2023, doi: 10.7759/cureus.46144.
[18] B. Del Forno *et al.*, «Mitral valve regurgitation: a disease with a wide spectrum of therapeutic options», *Nat. Rev. Cardiol.*, vol. 17, fasc. 12, pp. 807–827, dic. 2020, doi: 10.1038/s41569-020-0395-7.
[19] W. A. Zoghbi *et al.*, «Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation», *J. Am. Soc. Echocardiogr.*, vol. 30, fasc. 4, pp. 303–371, apr. 2017, doi: 10.1016/j.echo.2017.01.007.

[20] J. J. P. Kouijzer, D. J. Noordermeer, W. J. Van Leeuwen, N. J. Verkaik, e K. R. Lattwein, «Native valve, prosthetic valve, and cardiac device-related infective endocarditis: A review and update on current innovative diagnostic and therapeutic strategies», *Front. Cell Dev. Biol.*, vol. 10, p. 995508, ott. 2022, doi: 10.3389/fcell.2022.995508.
[21] W. Hu, X. Wang, e G. Su, «Infective endocarditis complicated by embolic events: Pathogenesis and predictors», *Clin. Cardiol.*, vol. 44, fasc. 3, pp. 307–315, mar. 2021, doi: 10.1002/clc.23554.
[22] J. S. Borer e A. Sharma, «Drug Therapy for Heart Valve Diseases», *Circulation*, vol. 132, fasc. 11, pp. 1038–1045, set. 2015, doi: 10.1161/CIRCULATIONAHA.115.016006.
[23] L. M. Baddour *et al.*, «Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications: A Scientific Statement for Healthcare Professionals From the American Heart Association», *Circulation*, vol. 132, fasc. 15, pp. 1435–1486, ott. 2015, doi: 10.1161/CIR.0000000000000296.
[24] A. P. Ralph e B. J. Currie, «Therapeutics for rheumatic fever and rheumatic heart disease», *Aust. Prescr.*, vol. 45, fasc. 4, pp. 104–112, ago. 2022, doi: 10.18773/austprescr.2022.034.
[25] A. Oliva *et al.*, «New Antimicrobials and New Therapy Strategies for Endocarditis: Weapons That Should Be Defended», *J. Clin. Med.*, vol. 12, fasc. 24, p. 7693, dic. 2023, doi: 10.3390/jcm12247693.
[26] «Anticoagulation for Valvular Heart Disease - American College of Cardiology».
[27] D. R. R. Brandt, «Prosthetic heart valves: Part 2 - Antithrombotic management».
[28] J. Hausleiter, T. J. Stocker, M. Adamo, N. Karam, M. J. Swaans, e F. Praz, «Mitral valve transcatheter edge-to-edge repair», *EuroIntervention*, vol. 18, fasc. 12, pp. 957–976, gen. 2023, doi: 10.4244/EIJ-D-22-00725.
[29] «Percutaneous approach for valve repair».
[30] Z. G. Turi, «The 40th Anniversary of Percutaneous Balloon Valvuloplasty for Mitral Stenosis: Current Status», *Struct. Heart*, vol. 6, fasc. 5, p. 100087, ott. 2022, doi: 10.1016/j.shj.2022.100087.
[31] T. M. Bashore, «Percutaneous Balloon Valvuloplasty», *VALVULAR HEART Dis.*.
[32] H. Mahmaljy, A. Tawney, e M. Young, «Transcatheter Aortic Valve Replacement.», in *StatPearls*, Treasure Island (FL): StatPearls Publishing, 2024.
[33] M. Vinayak *et al.*, «Transcatheter Aortic Valve Replacement: Current Status and Future Indications», *J. Clin. Med.*, vol. 13, fasc. 2, p. 373, gen. 2024, doi: 10.3390/jcm13020373.
[34] Z. Xiling *et al.*, «Transcatheter Mitral Valve Repair or Replacement: Competitive or Complementary?», *J. Clin. Med.*, vol. 11, fasc. 12, p. 3377, giu. 2022, doi: 10.3390/jcm11123377.
[35] H. V. Schaff e A. Nguyen, «Contemporary techniques for mitral valve repair—the Mayo Clinic experience», *Indian J. Thorac. Cardiovasc. Surg.*, vol. 36, fasc. S1, pp. 18–26, gen. 2020, doi: 10.1007/s12055-019-00801-6.
[36] M. J. Antunes, «Closed mitral commissurotomy—a cheap, reproducible and successful way to treat mitral stenosis», *J. Thorac. Dis.*, vol. 12, fasc. 3, pp. 146–149, mar. 2020, doi: 10.21037/jtd.2019.12.118.
[37] L. G. Svensson, «The art of aortic valve repair», *JTCVS Tech.*, vol. 7, pp. 121–125, giu. 2021, doi: 10.1016/j.xjtc.2021.01.030.
[38] K. Niwaya, C. J. Knott-Craig, K. Santangelo, M. M. Lane, K. Chandrasekaran, e R. C. Elkins, «Advantage of autograft and homograft valve replacement for complex aortic valve endocarditis», *Ann. Thorac. Surg.*, vol. 67, fasc. 6, pp. 1603–1608, giu. 1999, doi: 10.1016/S0003-4975(99)00402-6.
[39] F. Santini *et al.*, «Pulmonary autograft versus homograft replacement of the aortic valve: A prospective randomized trial», *J. Thorac. Cardiovasc. Surg.*, vol. 113, fasc. 5, pp. 894–900, mag. 1997, doi: 10.1016/S0022-5223(97)70262-9.
[40] I. El-Hamamsy *et al.*, «Long-term outcomes after autograft versus homograft aortic root replacement in adults with aortic valve disease: a randomised controlled trial.», *Lancet Lond. Engl.*, vol. 376, fasc. 9740, pp. 524–531, ago. 2010, doi: 10.1016/S0140-6736(10)60828-8.
[41] T. Kumar, A. Singh, S. Thakre, S. Acharya, S. Shukla, e S. Kumar, «Scientific Evolution of Artificial Heart Valves: A Narrative Review», *Cureus*, lug. 2023, doi: 10.7759/cureus.42131.
[42] P. Bloomfield, «Choice of heart valve prosthesis», *Heart*, vol. 87, fasc. 6, pp. 583–589, giu. 2002, doi: 10.1136/heart.87.6.583.
[43] V. L. Gott, D. E. Alejo, e D. E. Cameron, «Mechanical heart valves: 50 years of evolution»,

Ann. Thorac. Surg., vol. 76, fasc. 6, pp. S2230–S2239, dic. 2003, doi: 10.1016/j.athoracsur.2003.09.002.
[44] R. A. Manji, A. H. Menkis, B. Ekser, e D. K. C. Cooper, «The future of bioprosthetic heart valves.», *Indian J. Med. Res.*, vol. 135, fasc. 2, pp. 150–151, 2012.
[45] I. Vesely, «The evolution of bioprosthetic heart valve design and its impact on durability», *Cardiovasc. Pathol.*, vol. 12, fasc. 5, pp. 277–286, set. 2003, doi: 10.1016/S1054-8807(03)00075-9.
[46] M. Zare, E. R. Ghomi, P. D. Venkatraman, e S. Ramakrishna, «Silicone-based biomaterials for biomedical applications: Antimicrobial strategies and 3D printing technologies», *J. Appl. Polym. Sci.*, vol. 138, fasc. 38, p. 50969, ott. 2021, doi: 10.1002/app.50969.
[47] A. Colas e J. Curtis, «2.3 SILICONE BIOMATERIALS: HISTORY AND CHEMISTRY».
[48] B. B. ROE e D. MOORE, «Design and fabrication of prosthetic valves.», *Exp. Med. Surg.*, vol. 16, fasc. 2–3, pp. 177–182, 1958.
[49] B. B. Roe, M. F. Burke, e H. Zehner, «THE SUBCORONARY IMPLANTATION OF A FLEXIBLE TRICUSPID AORTIC VALVE PROSTHESIS», *J. Thorac. Cardiovasc. Surg.*, vol. 40, fasc. 5, pp. 561–567, nov. 1960, doi: 10.1016/S0022-5223(19)32578-4.
[50] B. B. Roe, P. B. J. Kelly, J. L. Myers, e D. W. Moore, «Tricuspid leaflet aortic valve prosthesis.», *Circulation*, vol. 33, fasc. 4 Suppl, pp. I124-130, apr. 1966, doi: 10.1161/01.cir.33.4s1.i-124.
[51] B. B. Roe, «Late follow-up studies on flexible leaflet prosthetic valves», *J. Thorac. Cardiovasc. Surg.*, vol. 58, fasc. 1, pp. 59–61, lug. 1969, doi: 10.1016/S0022-5223(19)42628-7.
[52] M. C. Fishbein, W. C. Roberts, A. Golden, e C. A. Hufnagel, «Cardiac pathology after aortic valve replacement using Hufnagel trileaflet prostheses: a study of 20 necropsy patients.», *Am. Heart J.*, vol. 89, fasc. 4, pp. 443–448, apr. 1975, doi: 10.1016/0002-8703(75)90149-0.
[53] H. Mohri, E. A. Hessel, R. J. Nelson, H. N. Anderson, D. H. Dillard, e K. A. Merendino, «Design and durability test of Silastic trileaflet aortic valve prostheses», *J. Thorac. Cardiovasc. Surg.*, vol. 65, fasc. 4, pp. 576–582, apr. 1973, doi: 10.1016/S0022-5223(19)40740-X.
[54] A. Simmons *et al.*, «Long-term in vivo biostability of poly(dimethylsiloxane)/poly(hexamethylene oxide) mixed macrodiol-based polyurethane elastomers», *Biomaterials*, vol. 25, fasc. 20, pp. 4887–4900, set. 2004, doi: 10.1016/j.biomaterials.2004.01.004.
[55] P. A. Gunatillake, D. J. Martin, G. F. Meijs, S. J. McCarthy, e R. Adhikari, «Designing Biostable Polyurethane Elastomers for Biomedical Implants», *Aust. J. Chem.*, vol. 56, fasc. 6, p. 545, 2003, doi: 10.1071/CH02168.
[56] A. B. Mathur *et al.*, «In vivo biocompatibility and biostability of modified polyurethanes», *J. Biomed. Mater. Res.*, vol. 36, fasc. 2, pp. 246–257, ago. 1997, doi: 10.1002/(SICI)1097-4636(199708)36:2<246::AID-JBM14>3.0.CO;2-E.
[57] M. Dabagh, M. J. Abdekhodaie, e M. T. Khorasani, «Effects of polydimethylsiloxane grafting on the calcification, physical properties, and biocompatibility of polyurethane in a heart valve», *J. Appl. Polym. Sci.*, vol. 98, fasc. 2, pp. 758–766, ott. 2005, doi: 10.1002/app.22132.
[58] Z. Li *et al.*, «Simultaneous Improvement of Oxidative and Hydrolytic Resistance of Polycarbonate Urethanes Based on Polydimethylsiloxane/Poly(hexamethylene carbonate) Mixed Macrodiols», *Biomacromolecules*, vol. 19, fasc. 6, pp. 2137–2145, giu. 2018, doi: 10.1021/acs.biomac.8b00234.
[59] S. Kim *et al.*, «A biostable, anti-fouling zwitterionic polyurethane-urea based on PDMS for use in blood-contacting medical devices», *J. Mater. Chem. B*, vol. 8, fasc. 36, pp. 8305–8314, 2020, doi: 10.1039/D0TB01220C.
[60] A. J. T. Teo, A. Mishra, I. Park, Y.-J. Kim, W.-T. Park, e Y.-J. Yoon, «Polymeric Biomaterials for Medical Implants and Devices», *ACS Biomater. Sci. Eng.*, vol. 2, fasc. 4, pp. 454–472, apr. 2016, doi: 10.1021/acsbiomaterials.5b00429.
[61] W. H. Muller, W. D. Warren, J. F. Dammann, J. R. Beckwith, e J. E. Wood, «Surgical Relief of Aortic Insufficiency by Direct Operation on the Aortic Valve», *Circulation*, vol. 21, fasc. 4, pp. 587–597, apr. 1960, doi: 10.1161/01.CIR.21.4.587.
[62] N. S. Braunwald e A. G. Morrow, «A LATE EVALUATION OF FLEXIBLE TEFLON PROSTHESES UTILIZED FOR TOTAL AORTIC VALVE REPLACEMENT», *J. Thorac. Cardiovasc. Surg.*, vol. 49, fasc. 3, pp. 485–496, mar. 1965, doi: 10.1016/S0022-5223(19)33284-2.
[63] Y. Roina, F. Auber, D. Hocquet, e G. Herlem, «EPTFE -based biomedical devices: An

overview of surgical efficiency», *J. Biomed. Mater. Res. B Appl. Biomater.*, vol. 110, fasc. 2, pp. 302–320, feb. 2022, doi: 10.1002/jbm.b.34928.
[64] F. Nistal *et al.*, «In vivo experimental assessment of polytetrafluoroethylene trileaflet heart valve prosthesis», *J. Thorac. Cardiovasc. Surg.*, vol. 99, fasc. 6, pp. 1074–1081, giu. 1990, doi: 10.1016/S0022-5223(20)31464-1.
[65] F. M. De Souza, P. K. Kahol, e R. K. Gupta, «Introduction to Polyurethane Chemistry», in *ACS Symposium Series*, vol. 1380, R. K. Gupta e P. K. Kahol, A c. di, Washington, DC: American Chemical Society, 2021, pp. 1–24. doi: 10.1021/bk-2021-1380.ch001.
[66] S. K. Jaganathan, E. Supriyanto, S. Murugesan, A. Balaji, e M. K. Asokan, «Biomaterials in Cardiovascular Research: Applications and Clinical Implications», *BioMed Res. Int.*, vol. 2014, pp. 1–11, 2014, doi: 10.1155/2014/459465.
[67] N. S. Braunwald, T. Cooper, e A. G. Morrow, «COMPLETE REPLACEMENT OF THE MITRAL VALVE», *J. Thorac. Cardiovasc. Surg.*, vol. 40, fasc. 1, pp. 1–11, lug. 1960, doi: 10.1016/S0022-5223(19)32638-8.
[68] N. S. Braunwald, «It will work: the first successful mitral valve replacement.», *Ann. Thorac. Surg.*, vol. 48, fasc. 3 Suppl, pp. S1-3, set. 1989, doi: 10.1016/0003-4975(89)90615-2.
[69] H. B. Lo *et al.*, «A tricuspid polyurethane heart valve as an alternative to mechanical prostheses or bioprostheses.», *ASAIO Trans.*, vol. 34, fasc. 3, pp. 839–844, set. 1988.
[70] J. Jansen, S. Willeke, B. Reiners, P. Harbott, H. Reul, e G. Rau, «New J-3 flexible-leaflet polyurethane heart valve prosthesis with improved hydrodynamic performance.», *Int. J. Artif. Organs*, vol. 14, fasc. 10, pp. 655–660, ott. 1991.
[71] J. Jansen e H. Reul, «A synthetic three-leaflet valve.», *J. Med. Eng. Technol.*, vol. 16, fasc. 1, pp. 27–33, feb. 1992, doi: 10.3109/03091909209021954.
[72] T. G. Mackay, D. J. Wheatley, G. M. Bernacca, A. C. Fisher, e C. S. Hindle, «New polyurethane heart valve prosthesis: design, manufacture and evaluation», *Biomaterials*, vol. 17, fasc. 19, pp. 1857–1863, ott. 1996, doi: 10.1016/0142-9612(95)00242-1.
[73] G. M. Bernacca, T. G. Mackay, R. Wilkinson, e D. J. Wheatley, «Calcification and fatigue failure in a polyurethane heart valve», *Biomaterials*, vol. 16, fasc. 4, pp. 279–285, mar. 1995, doi: 10.1016/0142-9612(95)93255-C.
[74] G. M. Bernacca, T. G. Mackay, R. Wilkinson, e D. J. Wheatley, «Polyurethane heart valves: Fatigue failure, calcification, and polyurethane structure», *J. Biomed. Mater. Res.*, vol. 34, fasc. 3, pp. 371–379, mar. 1997, doi: 10.1002/(SICI)1097-4636(19970305)34:3<371::AID-JBM12>3.0.CO;2-J.
[75] S. H. Daebritz *et al.*, «Introduction of a Flexible Polymeric Heart Valve Prosthesis With Special Design for Mitral Position», *Circulation*, vol. 108, fasc. 10_suppl_1, set. 2003, doi: 10.1161/01.cir.0000087655.41288.dc.
[76] S. Daebritz *et al.*, «Introduction of a flexible polymeric heart valve prosthesis with special design for aortic position1», *Eur. J. Cardiothorac. Surg.*, vol. 25, fasc. 6, pp. 946–952, giu. 2004, doi: 10.1016/j.ejcts.2004.02.040.
[77] R. Y. Kannan *et al.*, «The Antithrombogenic Potential of a Polyhedral Oligomeric Silsesquioxane (POSS) Nanocomposite», *Biomacromolecules*, vol. 7, fasc. 1, pp. 215–223, gen. 2006, doi: 10.1021/bm050590z.
[78] R. Y. Kannan, H. J. Salacinski, M. Odlyha, P. E. Butler, e A. M. Seifalian, «The degradative resistance of polyhedral oligomeric silsesquioxane nanocore integrated polyurethanes: An in vitro study», *Biomaterials*, vol. 27, fasc. 9, pp. 1971–1979, mar. 2006, doi: 10.1016/j.biomaterials.2005.10.006.
[79] A. G. Kidane, G. Burriesci, M. Edirisinghe, H. Ghanbari, P. Bonhoeffer, e A. M. Seifalian, «A novel nanocomposite polymer for development of synthetic heart valve leaflets», *Acta Biomater.*, vol. 5, fasc. 7, pp. 2409–2417, set. 2009, doi: 10.1016/j.actbio.2009.02.025.
[80] B. Rahmani, S. Tzamtzis, H. Ghanbari, G. Burriesci, e A. M. Seifalian, «Manufacturing and hydrodynamic assessment of a novel aortic valve made of a new nanocomposite polymer», *J. Biomech.*, vol. 45, fasc. 7, pp. 1205–1211, apr. 2012, doi: 10.1016/j.jbiomech.2012.01.046.
[81] B. Rahmani *et al.*, «A new transcatheter heart valve concept (the TRISKELE): feasibility in an acute preclinical model», *EuroIntervention*, vol. 12, fasc. 7, pp. 901–908, set. 2016, doi: 10.4244/EIJV12I7A148.
[82] B. Rahmani *et al.*, «In Vitro Hydrodynamic Assessment of a New Transcatheter Heart Valve

Concept (the TRISKELE)», *J Cardiovasc. Transl. Res.*, vol. 10, fasc. 2, pp. 104–115, apr. 2017, doi: 10.1007/s12265-016-9722-0.
[83] E. A. Ovcharenko *et al.*, «A New Nanocomposite Copolymer Based On Functionalised Graphene Oxide for Development of Heart Valves», *Sci. Rep.*, vol. 10, fasc. 1, p. 5271, mar. 2020, doi: 10.1038/s41598-020-62122-8.
[84] L. S. Dandeniyage *et al.*, «Morphology and surface properties of high strength siloxane poly(urethane-urea)s developed for heart valve application», *J. Biomed. Mater. Res. B Appl. Biomater.*, vol. 107, fasc. 1, pp. 112–121, gen. 2019, doi: 10.1002/jbm.b.34101.
[85] L. S. Dandeniyage, P. A. Gunatillake, R. Adhikari, M. Bown, R. Shanks, e B. Adhikari, «Development of high strength siloxane poly(urethane-urea) elastomers based on linked macrodiols for heart valve application», *J. Biomed. Mater. Res. B Appl. Biomater.*, vol. 106, fasc. 5, pp. 1712–1720, lug. 2018, doi: 10.1002/jbm.b.33970.
[86] L. S. Dandeniyage, R. Adhikari, M. Bown, R. Shanks, B. Adhikari, e P. A. Gunatillake, «Hard segment composition, morphology, tensile properties and biostability of linked-macrodiol based siloxane poly(urethane urea)», *Mater. Today Commun.*, vol. 18, pp. 110–118, mar. 2019, doi: 10.1016/j.mtcomm.2018.11.011.
[87] L. S. Dandeniyage *et al.*, «*In vitro* oxidative stability of high strength siloxane poly(urethane-urea) elastomers based on linked-macrodiol», *J. Biomed. Mater. Res. B Appl. Biomater.*, vol. 107, fasc. 8, pp. 2557–2565, nov. 2019, doi: 10.1002/jbm.b.34346.
[88] C. Jenney *et al.*, «Assessment of a Siloxane Poly(urethane-urea) Elastomer Designed for Implantable Heart Valve Leaflets», *Adv. NanoBiomed Res.*, vol. 1, fasc. 2, p. 2000032, feb. 2021, doi: 10.1002/anbr.202000032.
[89] D. J. Kereiakes *et al.*, «Preliminary Evaluation of a Novel Polymeric Valve Following Surgical Implantation for Symptomatic Aortic Valve Disease», *JACC Cardiovasc. Interv.*, vol. 14, fasc. 24, pp. 2754–2756, dic. 2021, doi: 10.1016/j.jcin.2021.08.071.
[90] «Foldax web site», Foldax Inc. [Online]. Disponibile su: https://www.foldax.com/
[91] S. J. Yakubov, J. Wittel, e G. Johnson, «CRT-700.20 Foldax TRIA TAVI: A Novel-Polymer Transcatheter Aortic Valve: Pilot Chronic Ovine Model Study», *JACC Cardiovasc. Interv.*, vol. 15, fasc. 4, pp. S59–S60, feb. 2022, doi: 10.1016/j.jcin.2022.01.228.
[92] L. Pinchuk, G. J. Wilson, J. J. Barry, R. T. Schoephoerster, J.-M. Parel, e J. P. Kennedy, «Medical applications of poly(styrene-block-isobutylene-block-styrene) ("SIBS")», *Biomaterials*, vol. 29, fasc. 4, pp. 448–460, feb. 2008, doi: 10.1016/j.biomaterials.2007.09.041.
[93] S. L. Gallocher, A. F. Aguirre, V. Kasyanov, L. Pinchuk, e R. T. Schoephoerster, «A novel polymer for potential use in a trileaflet heart valve», *J. Biomed. Mater. Res. B Appl. Biomater.*, vol. 79B, fasc. 2, pp. 325–334, nov. 2006, doi: 10.1002/jbm.b.30546.
[94] Q. Wang, A. J. McGoron, R. Bianco, Y. Kato, L. Pinchuk, e R. T. Schoephoerster, «In-vivo assessment of a novel polymer (SIBS) trileaflet heart valve.», *J. Heart Valve Dis.*, vol. 19, fasc. 4, pp. 499–505, lug. 2010.
[95] T. E. Claiborne, J. Sheriff, M. Kuetting, U. Steinseifer, M. J. Slepian, e D. Bluestein, «In Vitro Evaluation of a Novel Hemodynamically Optimized Trileaflet Polymeric Prosthetic Heart Valve», *J. Biomech. Eng.*, vol. 135, fasc. 2, p. 021021, feb. 2013, doi: 10.1115/1.4023235.
[96] L. Pinchuk, «Chapter 11 The use of poly(styrene-block-isobutylene-block-styrene) and analogs for long-term implant applications».
[97] T. E. Claiborne *et al.*, «Thrombogenic Potential of Innovia Polymer Valves versus Carpentier-Edwards Perimount Magna Aortic Bioprosthetic Valves», *ASAIO J.*, vol. 57, fasc. 1, pp. 26–31, gen. 2011, doi: 10.1097/MAT.0b013e3181fcbd86.
[98] T. E. Claiborne *et al.*, «Toward Optimization of a Novel Trileaflet Polymeric Prosthetic Heart Valve via Device Thrombogenicity Emulation», *ASAIO J.*, vol. 59, fasc. 3, pp. 275–283, mag. 2013, doi: 10.1097/MAT.0b013e31828e4d80.
[99] T. Claiborne, D. Bluestein, e R. T. Schoephoerster, «Development and Evaluation of a Novel Artificial Catheter-Deliverable Prosthetic Heart Valve and Method for *in Vitro* Testing», *Int. J. Artif. Organs*, vol. 32, fasc. 5, pp. 262–271, mag. 2009, doi: 10.1177/039139880903200503.
[100] O. M. Rotman *et al.*, «Novel Polymeric Valve for Transcatheter Aortic Valve Replacement Applications: In Vitro Hemodynamic Study», *Ann. Biomed. Eng.*, vol. 47, fasc. 1, pp. 113–125, gen. 2019, doi: 10.1007/s10439-018-02119-7.

[101] O. M. Rotman, B. Kovarovic, M. Bianchi, M. J. Slepian, e D. Bluestein, «In Vitro Durability and Stability Testing of a Novel Polymeric Transcatheter Aortic Valve», *ASAIO J.*, vol. 66, fasc. 2, pp. 190–198, feb. 2020, doi: 10.1097/MAT.0000000000000980.
[102] B. Kovarovic, R. Helbock, K. Baylous, O. M. Rotman, M. J. Slepian, e D. Bluestein, «Visions of TAVR Future: Development and Optimization of a Second Generation Novel Polymeric TAVR», *J. Biomech. Eng.*, vol. 144, fasc. 6, p. 061008, giu. 2022, doi: 10.1115/1.4054149.
[103] M. A. Rezvova *et al.*, «Biocompatible Nanocomposites Based on Poly(styrene-block-isobutylene-block-styrene) and Carbon Nanotubes for Biomedical Application», *Polymers*, vol. 12, fasc. 9, p. 2158, set. 2020, doi: 10.3390/polym12092158.
[104] M. A. Rezvova *et al.*, «Biomaterials Based on Carbon Nanotube Nanocomposites of Poly(styrene-b-isobutylene-b-styrene): The Effect of Nanotube Content on the Mechanical Properties, Biocompatibility and Hemocompatibility», *Nanomaterials*, vol. 12, fasc. 5, p. 733, feb. 2022, doi: 10.3390/nano12050733.
[105] N. Afghan, «Mechanical Properties of Poly (vinyl alcohol) Based Blends and Composites».
[106] W. K. Wan, G. Campbell, Z. F. Zhang, A. J. Hui, e D. R. Boughner, «Optimizing the tensile properties of polyvinyl alcohol hydrogel for the construction of a bioprosthetic heart valve stent», *J. Biomed. Mater. Res.*, vol. 63, fasc. 6, pp. 854–861, gen. 2002, doi: 10.1002/jbm.10333.
[107] H. Jiang, G. Campbell, D. Boughner, W.-K. Wan, e M. Quantz, «Design and manufacture of a polyvinyl alcohol (PVA) cryogel tri-leaflet heart valve prosthesis», *Med. Eng. Phys.*, vol. 26, fasc. 4, pp. 269–277, mag. 2004, doi: 10.1016/j.medengphy.2003.10.007.
[108] L. E. Millon e W. K. Wan, «The polyvinyl alcohol–bacterial cellulose system as a new nanocomposite for biomedical applications», *J. Biomed. Mater. Res. B Appl. Biomater.*, vol. 79B, fasc. 2, pp. 245–253, nov. 2006, doi: 10.1002/jbm.b.30535.
[109] S. J. Eichhorn *et al.*, «Current international research into cellulosic fibres and composites», *J. Mater. Sci.*, vol. 36, fasc. 9, pp. 2107–2131, 2001, doi: 10.1023/A:1017512029696.
[110] M. V. Vellayappan *et al.*, «Tangible nanocomposites with diverse properties for heart valve application», *Sci. Technol. Adv. Mater.*, vol. 16, fasc. 3, p. 033504, giu. 2015, doi: 10.1088/1468-6996/16/3/033504.
[111] L. Zhang *et al.*, «High strength graphene oxide/polyvinyl alcohol composite hydrogels», *J. Mater. Chem.*, vol. 21, fasc. 28, p. 10399, 2011, doi: 10.1039/c0jm04043f.
[112] Z. Xiao, Q. Li, H. Liu, Q. Zhao, Y. Niu, e D. Zhao, «Adhesion mechanism and application progress of hydrogels», *Eur. Polym. J.*, vol. 173, p. 111277, giu. 2022, doi: 10.1016/j.eurpolymj.2022.111277.
[113] H. Mohammadi, D. Goode, G. Fradet, e K. Mequanint, «Proposed percutaneous aortic valve prosthesis made of cryogel.», *Proc. Inst. Mech. Eng. [H]*, vol. 233, fasc. 5, pp. 515–524, mag. 2019, doi: 10.1177/0954411919837302.
[114] D. Goode, R. Dhaliwal, e H. Mohammadi, «Transcatheter Mitral Valve Replacement: State of the Art», *Cardiovasc. Eng. Technol.*, vol. 11, fasc. 3, pp. 229–253, giu. 2020, doi: 10.1007/s13239-020-00460-4.
[115] M. A. Rezvova, K. Y. Klyshnikov, A. A. Gritskevich, e E. A. Ovcharenko, «Polymeric Heart Valves Will Displace Mechanical and Tissue Heart Valves: A New Era for the Medical Devices», *Int. J. Mol. Sci.*, vol. 24, fasc. 4, p. 3963, feb. 2023, doi: 10.3390/ijms24043963.
[116] S. P. James *et al.*, «Glycosaminoglycan and Synthetic Polymer Materials for Blood-contacting applications». 18 novembre 2020.
[117] D. A. Prawel *et al.*, «Hemocompatibility and Hemodynamics of Novel Hyaluronan–Polyethylene Materials for Flexible Heart Valve Leaflets», *Cardiovasc. Eng. Technol.*, vol. 5, fasc. 1, pp. 70–81, mar. 2014, doi: 10.1007/s13239-013-0171-5.
[118] R. Simon-Walker, J. Cavicchia, D. A. Prawel, L. P. Dasi, S. P. James, e K. C. Popat, «Hemocompatibility of hyaluronan enhanced linear low density polyethylene for blood contacting applications», *J. Biomed. Mater. Res. B Appl. Biomater.*, vol. 106, fasc. 5, pp. 1964–1975, lug. 2018, doi: 10.1002/jbm.b.34010.
[119] A. Yousefi, D. L. Bark, e L. P. Dasi, «Effect of Arched Leaflets and Stent Profile on the Hemodynamics of Tri-Leaflet Flexible Polymeric Heart Valves», *Ann. Biomed. Eng.*, vol. 45, fasc. 2, pp. 464–475, feb. 2017, doi: 10.1007/s10439-016-1674-7.
[120] M. Heitkemper, H. Hatoum, e L. P. Dasi, «In vitro hemodynamic assessment of a novel

polymeric transcatheter aortic valve», *J. Mech. Behav. Biomed. Mater.*, vol. 98, pp. 163–171, ott. 2019, doi: 10.1016/j.jmbbm.2019.06.016.
[121] B.-H. Tsai, T.-A. Lin, C.-H. Cheng, e J.-C. Lin, «Studies of the Sulfonated Hydrogenated Styrene–Isoprene–Styrene Block Copolymer and Its Surface Properties, Cytotoxicity, and Platelet-Contacting Characteristics», *Polymers*, vol. 13, fasc. 2, p. 235, gen. 2021, doi: 10.3390/polym13020235.
[122] P. Maji e K. Naskar, «Styrenic block copolymer-based thermoplastic elastomers in smart applications: Advances in synthesis, microstructure, and structure–property relationships—A review», *J. Appl. Polym. Sci.*, vol. 139, fasc. 39, p. e52942, ott. 2022, doi: 10.1002/app.52942.
[123] F. Lin, C. Wu, e D. Cui, «Synthesis and Characterization of Crystalline Styrene- *b* -(Ethylene-*co* -Butylene)- *b* -Styrene Triblock Copolymers», *J. Polym. Sci. Part Polym. Chem.*, vol. 55, fasc. 7, pp. 1243–1249, apr. 2017, doi: 10.1002/pola.28489.
[124] N. C. Kekec *et al.*, «Calcification resistance of polyisobutylene and polyisobutylene-based materials», *Polym. Adv. Technol.*, vol. 30, fasc. 7, pp. 1836–1846, lug. 2019, doi: 10.1002/pat.4616.
[125] J. R. Stasiak *et al.*, «Design, development, testing at ISO standards and *in vivo* feasibility study of a novel polymeric heart valve prosthesis», *Biomater. Sci.*, vol. 8, fasc. 16, pp. 4467–4480, 2020, doi: 10.1039/D0BM00412J.
[126] F. Zomer Volpato, S. L. Fernandes Ramos, A. Motta, e C. Migliaresi, «Physical and *in vitro* biological evaluation of a PA 6/MWCNT electrospun composite for biomedical applications», *J. Bioact. Compat. Polym.*, vol. 26, fasc. 1, pp. 35–47, gen. 2011, doi: 10.1177/0883911510391449.
[127] T. J. Webster, Stout, Yoo, e Santiago-Miranda, «Mechanisms of greater cardiomyocyte functions on conductive nanoengineered composites for cardiovascular application», *Int. J. Nanomedicine*, p. 5653, nov. 2012, doi: 10.2147/IJN.S34574.
[128] B. Hu, C. Ye, e C. Gao, «Synthesis and characterization of biodegradable polyurethanes with unsaturated carbon bonds based on poly(propylene fumarate)», *J. Appl. Polym. Sci.*, vol. 132, fasc. 24, p. app.42065, giu. 2015, doi: 10.1002/app.42065.
[129] B. Sitharaman *et al.*, «In vivo biocompatibility of ultra-short single-walled carbon nanotube/biodegradable polymer nanocomposites for bone tissue engineering», *Bone*, vol. 43, fasc. 2, pp. 362–370, ago. 2008, doi: 10.1016/j.bone.2008.04.013.
[130] S. Jin *et al.*, «Synthesis and anticoagulation activities of polymer/functional graphene oxide nanocomposites via Reverse Atom Transfer Radical Polymerization (RATRP)», *Colloids Surf. B Biointerfaces*, vol. 101, pp. 319–324, gen. 2013, doi: 10.1016/j.colsurfb.2012.07.004.
[131] S. Jin, D. Xu, N. Zhou, J. Yuan, e J. Shen, «Antibacterial and anticoagulation properties of polyethylene/geneO-MPC nanocomposites», *J. Appl. Polym. Sci.*, vol. 129, fasc. 2, pp. 884–891, lug. 2013, doi: 10.1002/app.38708.
[132] F. Oveissi, S. Naficy, A. Lee, D. S. Winlaw, e F. Dehghani, «Materials and manufacturing perspectives in engineering heart valves: a review», *Mater. Today Bio*, vol. 5, p. 100038, gen. 2020, doi: 10.1016/j.mtbio.2019.100038.
[133] E. Sacristan *et al.*, «Development of a universal second generation pneumatic ventricular assist device and drive unit», in *Proceedings of the 25th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (IEEE Cat. No.03CH37439)*, 2003, pp. 427-430 Vol.1. doi: 10.1109/IEMBS.2003.1279699.
[134] J. Garcia, L. Kadem, e P. Pibarot, «Silicone rubber trileaflet valve assessment using cardiovascular magnetic resonance imaging.», *Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. IEEE Eng. Med. Biol. Soc. Annu. Int. Conf.*, vol. 2010, pp. 5169–5172, 2010, doi: 10.1109/IEMBS.2010.5626141.
[135] M. Weber *et al.*, «Multiple-Step Injection Molding for Fibrin-Based Tissue-Engineered Heart Valves», *Tissue Eng. Part C Methods*, vol. 21, fasc. 8, pp. 832–840, ago. 2015, doi: 10.1089/ten.tec.2014.0396.
[136] R. Masheane, J. Combrinck, e L. Masheane, «Development of a compression moulding process for the manufacturing of artificial polymer heart valves», *MATEC Web Conf.*, vol. 388, p. 06002, 2023, doi: 10.1051/matecconf/202338806002.
[137] B. B. Roe, J. W. Owsley, e P. C. Boudoures, «EXPERIMENTAL RESULTS WITH A PROSTHETIC AORTIC VALVE», *J. Thorac. Surg.*, vol. 36, fasc. 4, pp. 563–570, ott. 1958, doi: 10.1016/S0096-5588(20)30134-3.
[138] R. L. Li *et al.*, «Mechanical considerations for polymeric heart valve development:

Biomechanics, materials, design and manufacturing», *Biomaterials*, vol. 225, p. 119493, dic. 2019, doi: 10.1016/j.biomaterials.2019.119493.
[139] S. H. Daebritz *et al.*, «New Flexible Polymeric Heart Valve Prostheses for the Mitral and Aortic Positions», *Heart Surg. Forum*, vol. 7, fasc. 5, pp. E525–E532, ott. 2004, doi: 10.1532/HSF98.20041083.
[140] M. Zagho, E. Hussein, e A. Elzatahry, «Recent Overviews in Functional Polymer Composites for Biomedical Applications», *Polymers*, vol. 10, fasc. 7, p. 739, lug. 2018, doi: 10.3390/polym10070739.
[141] A. V. Rane, K. Kanny, V. K. Abitha, e S. Thomas, «Methods for Synthesis of Nanoparticles and Fabrication of Nanocomposites», in *Synthesis of Inorganic Nanomaterials*, Elsevier, 2018, pp. 121–139. doi: 10.1016/B978-0-08-101975-7.00005-1.
[142] H. W. Toh *et al.*, «Polymer blends and polymer composites for cardiovascular implants», *Eur. Polym. J.*, vol. 146, p. 110249, mar. 2021, doi: 10.1016/j.eurpolymj.2020.110249.
[143] G. D. Goh, Y. L. Yap, S. Agarwala, e W. Y. Yeong, «Recent Progress in Additive Manufacturing of Fiber Reinforced Polymer Composite», *Adv. Mater. Technol.*, vol. 4, fasc. 1, p. 1800271, gen. 2019, doi: 10.1002/admt.201800271.
[144] F. P. W. Melchels, J. Feijen, e D. W. Grijpma, «A review on stereolithography and its applications in biomedical engineering», *Biomaterials*, vol. 31, fasc. 24, pp. 6121–6130, ago. 2010, doi: 10.1016/j.biomaterials.2010.04.050.
[145] B. Duan e M. Wang, «Selective laser sintering and its application in biomedical engineering», *MRS Bull.*, vol. 36, fasc. 12, pp. 998–1005, dic. 2011, doi: 10.1557/mrs.2011.270.
[146] M. J. Vernon *et al.*, «3D printing of heart valves», *Trends Biotechnol.*, vol. 42, fasc. 5, pp. 612–630, mag. 2024, doi: 10.1016/j.tibtech.2023.11.001.
[147] A. Cavallo *et al.*, «Fabrication and in-vitro characterization of a polymeric aortic valve for minimally invasive valve replacement», *J. Mech. Behav. Biomed. Mater.*, vol. 115, p. 104294, mar. 2021, doi: 10.1016/j.jmbbm.2020.104294.
[148] F. Schröter, R.-U. Kühnel, M. Hartrumpf, R. Ostovar, e J. M. Albes, «Progress on a Novel, 3D-Printable Heart Valve Prosthesis», *Polymers*, vol. 15, fasc. 22, p. 4413, nov. 2023, doi: 10.3390/polym15224413.
[149] U. Siemann, «Solvent cast technology – a versatile tool for thin film production», in *Scattering Methods and the Properties of Polymer Materials*, Berlin, Heidelberg: Springer Berlin Heidelberg, 2005, pp. 1–14. doi: 10.1007/b107336.
[150] P. Boloori Zadeh, S. C. Corbett, e H. Nayeb-Hashemi, «In-vitro calcification study of polyurethane heart valves», *Mater. Sci. Eng. C*, vol. 35, pp. 335–340, feb. 2014, doi: 10.1016/j.msec.2013.11.015.
[151] Q. Wang, A. J. McGoron, L. Pinchuk, e R. T. Schoephoerster, «A novel small animal model for biocompatibility assessment of polymeric materials for use in prosthetic heart valves», *J. Biomed. Mater. Res. A*, vol. 93A, fasc. 2, pp. 442–453, mag. 2010, doi: 10.1002/jbm.a.32562.
[152] E. Ovcharenko *et al.*, «Polyisobutylene-Based Thermoplastic Elastomers for Manufacturing Polymeric Heart Valve Leaflets: In Vitro and In Vivo Results», *Appl. Sci.*, vol. 9, fasc. 22, p. 4773, nov. 2019, doi: 10.3390/app9224773.
[153] M. Broadwin *et al.*, «Exploring Electrospun Scaffold Innovations in Cardiovascular Therapy: A Review of Electrospinning in Cardiovascular Disease», *Bioengineering*, vol. 11, fasc. 3, p. 218, feb. 2024, doi: 10.3390/bioengineering11030218.
[154] D. N. Ghista, «Toward an optimum prosthetic trileaflet aortic-valve design», *Med. Biol. Eng.*, vol. 14, fasc. 2, pp. 122–129, mar. 1976, doi: 10.1007/BF02478737.
[155] H. Ghanbari, H. Viatge, A. G. Kidane, G. Burriesci, M. Tavakoli, e A. M. Seifalian, «Polymeric heart valves: new materials, emerging hopes», *Trends Biotechnol.*, vol. 27, fasc. 6, pp. 359–367, giu. 2009, doi: 10.1016/j.tibtech.2009.03.002.
[156] J. S. Sachweh e S. H. Daebritz, «Novel "Biomechanical" Polymeric Valve Prostheses with Special Design for Aortic and Mitral Position: A Future Option for Pediatric Patients?».
[157] D. N. Ghista e H. Reul, «Optimal prosthetic aortic leaflet valve: design parametric and longevity analyses: development of the Avcothane-51 leaflet valve based on the optimum design analysis.», *J. Biomech.*, vol. 10, fasc. 5–6, pp. 313–324, 1977, doi: 10.1016/0021-9290(77)90004-5.
[158] N. H. C. H. Ken P. Chong David W. Wieting e J. H. Kennedy, «Stress Analysis of Normal

Human Aortic Valve Leaflets during Diastole», *Biomater. Med. Devices Artif. Organs*, vol. 1, fasc. 2, pp. 307–321, 1973, doi: 10.3109/10731197309118544.
[159] C. B. Wisman, W. S. Pierce, J. H. Donachy, W. E. Pae, J. L. Myers, e G. A. Prophet, «A POLYURETHANE TRILEAFLET CARDIAC VALVE PROSTHESIS: IN VITRO AND IN VIVO STUDIES», *ASAIO J.*, vol. 28, fasc. 1, 1982, [Online]. Disponibile su: https://journals.lww.com/asaiojournal/fulltext/1982/28000/a_polyurethane_trileaflet_cardiac_valve.33.aspx
[160] K. J. Lockie, M. Butterfield, J. Fisher, N. P. Juster, K. watterson, e G. A. Davies, «Geometry of homograft valve leaflets: Effect of dilation of the aorta and the aortic root», *Ann. Thorac. Surg.*, vol. 56, fasc. 1, pp. 125–130, lug. 1993, doi: 10.1016/0003-4975(93)90415-E.
[161] M. E. Leat e J. Fisher, «A synthetic leaflet heart valve with improved opening characteristics.», *Med. Eng. Phys.*, vol. 16, fasc. 6, pp. 470–476, nov. 1994, doi: 10.1016/1350-4533(94)90071-x.
[162] M. Butterfield, D. J. Wheatley, D. F. Williams, e J. Fisher, «A new design for polyurethane heart valves.», *J. Heart Valve Dis.*, vol. 10, fasc. 1, pp. 105–110, gen. 2001.
[163] H. Mohammadi, D. Boughner, L. E. Millon, e W. K. Wan, «Design and simulation of a poly(vinyl alcohol)—bacterial cellulose nanocomposite mechanical aortic heart valve prosthesis», *Proc. Inst. Mech. Eng. [H]*, vol. 223, fasc. 6, pp. 697–711, ago. 2009, doi: 10.1243/09544119JEIM493.
[164] G. Burriesci, F. C. Marincola, e C. Zervides, «Design of a novel polymeric heart valve.», *J. Med. Eng. Technol.*, vol. 34, fasc. 1, pp. 7–22, gen. 2010, doi: 10.3109/03091900903261241.
[165] K. Li e W. Sun, «Simulated transcatheter aortic valve deformation: A parametric study on the impact of leaflet geometry on valve peak stress», *Int. J. Numer. Methods Biomed. Eng.*, vol. 33, fasc. 3, p. e02814, mar. 2017, doi: 10.1002/cnm.2814.
[166] S. H. Gharaie e Y. Morsi, «A novel design of a polymeric aortic valve.», *Int. J. Artif. Organs*, vol. 38, fasc. 5, pp. 259–270, mag. 2015, doi: 10.5301/ijao.5000413.
[167] R. P. Ghosh *et al.*, «Comparative Fluid–Structure Interaction Analysis of Polymeric Transcatheter and Surgical Aortic Valves' Hemodynamics and Structural Mechanics», *J. Biomech. Eng.*, vol. 140, fasc. 12, p. 121002, dic. 2018, doi: 10.1115/1.4040600.
[168] E. A. Farokhi, H. Niroomand-Oscuii, e K. Yazdanpanah, «Investigation the effect of geometry and position of polymeric heart valves on hemodynamic with fluid-structure interaction numerical method», *Med. Eng. Phys.*, vol. 97, pp. 10–17, nov. 2021, doi: 10.1016/j.medengphy.2021.09.002.
[169] J. Zhou, Y. Li, T. Li, X. Tian, Y. Xiong, e Y. Chen, «Analysis of the Effect of Thickness on the Performance of Polymeric Heart Valves», *J. Funct. Biomater.*, vol. 14, fasc. 6, p. 309, giu. 2023, doi: 10.3390/jfb14060309.
[170] M. Weber *et al.*, «Blood-Contacting Biomaterials: In Vitro Evaluation of the Hemocompatibility», *Front. Bioeng. Biotechnol.*, vol. 6, p. 99, lug. 2018, doi: 10.3389/fbioe.2018.00099.
[171] L. H. Edmunds, «Thrombotic and Bleeding Complications of Prosthetic Heart Valves», *Ann. Thorac. Surg.*, vol. 44, fasc. 4, pp. 430–445, ott. 1987, doi: 10.1016/S0003-4975(10)63816-7.
[172] S. K. Singh *et al.*, «Polymeric prosthetic heart valves: A review of current technologies and future directions», *Front. Cardiovasc. Med.*, vol. 10, p. 1137827, mar. 2023, doi: 10.3389/fcvm.2023.1137827.
[173] S. K. Choudhary, S. Talwar, e B. Airan, «Choice of prosthetic heart valve in a developing country», *Heart Asia*, vol. 8, fasc. 1, pp. 65–72, apr. 2016, doi: 10.1136/heartasia-2015-010650.
[174] J. M. Vesey e C. M. Otto, «Complications of prosthetic heart valves», *Curr. Cardiol. Rep.*, vol. 6, fasc. 2, pp. 106–111, mar. 2004, doi: 10.1007/s11886-004-0007-x.
[175] R. F. Siddiqui, J. R. Abraham, e J. Butany, «Bioprosthetic heart valves: modes of failure», *Histopathology*, vol. 55, fasc. 2, pp. 135–144, ago. 2009, doi: 10.1111/j.1365-2559.2008.03190.x.
[176] S. Jana, «Endothelialization of cardiovascular devices», *Acta Biomater.*, vol. 99, pp. 53–71, nov. 2019, doi: 10.1016/j.actbio.2019.08.042.
[177] D. E. Heath, «Promoting Endothelialization of Polymeric Cardiovascular Biomaterials», *Macromol. Chem. Phys.*, vol. 218, fasc. 8, p. 1600574, apr. 2017, doi: 10.1002/macp.201600574.
[178] G. M. Bernacca e D. J. Wheatley, «Surface modification of polyurethane heart valves: effects on fatigue life and calcification.», *Int. J. Artif. Organs*, vol. 21, fasc. 12, pp. 814–819, dic. 1998.

[179] M. Douglass, M. Garren, R. Devine, A. Mondal, e H. Handa, «Bio-inspired hemocompatible surface modifications for biomedical applications», *Prog. Mater. Sci.*, vol. 130, p. 100997, ott. 2022, doi: 10.1016/j.pmatsci.2022.100997.
[180] C. Mao *et al.*, «Various approaches to modify biomaterial surfaces for improving hemocompatibility», *Adv. Colloid Interface Sci.*, vol. 110, fasc. 1–2, pp. 5–17, giu. 2004, doi: 10.1016/j.cis.2004.02.001.
[181] P. Alves, R. Cardoso, T. R. Correia, B. P. Antunes, I. J. Correia, e P. Ferreira, «Surface modification of polyurethane films by plasma and ultraviolet light to improve haemocompatibility for artificial heart valves», *Colloids Surf. B Biointerfaces*, vol. 113, pp. 25–32, gen. 2014, doi: 10.1016/j.colsurfb.2013.08.039.
[182] A. M. Benson *et al.*, «Synthesis of a low thrombogenic heart valve coating with horseradish peroxidase», *Polym. Adv. Technol.*, vol. 16, fasc. 2–3, pp. 117–122, gen. 2005, doi: 10.1002/pat.561.
[183] P. Lancellotti *et al.*, «Bioactive surface coating for preventing mechanical heart valve thrombosis», *J. Thromb. Haemost.*, vol. 21, fasc. 9, pp. 2485–2498, set. 2023, doi: 10.1016/j.jtha.2023.05.004.
[184] Y. Chen *et al.*, «Comparison study of surface-initiated hydrogel coatings with distinct side-chains for improving biocompatibility of polymeric heart valves», *Biomater. Sci.*, vol. 12, fasc. 10, pp. 2717–2729, 2024, doi: 10.1039/D4BM00158C.
[185] T. Boggs, R. Carroll, R. Tran-Son-Tay, H. Yamaguchi, F. Al-Mousily, e C. DeGroff, «Blood Cell Adhesion on a Polymeric Heart Valve Leaflet Processed Using Magnetic Abrasive Finishing», *J. Med. Devices*, vol. 8, fasc. 1, p. 011005, mar. 2014, doi: 10.1115/1.4025853.
[186] X. Ye, Y. Shao, M. Zhou, J. Li, e L. Cai, «Research on micro-structure and hemo-compatibility of the artificial heart valve surface», *Appl. Surf. Sci.*, vol. 255, fasc. 13–14, pp. 6686–6690, apr. 2009, doi: 10.1016/j.apsusc.2009.02.068.
[187] G. Vigano *et al.*, «Laser texturing of a St. Jude Medical RegentTM mechanical heart valve prosthesis: the proof of concept», *Interact. Cardiovasc. Thorac. Surg.*, vol. 33, fasc. 6, pp. 986–991, nov. 2021, doi: 10.1093/icvts/ivab185.