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Recent advancements in polymeric heart valves: From basic research to clinical trials

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ABSTRACT

Valvular heart diseases (VHDs) have become one of the most prevalent heart diseases worldwide, and prosthetic valve replacement is one of the effective treatments. With the fast development of minimal invasive technology, transcatheter valves replacement has been exploring in recent years, such as transcatheter aortic valve replacement (TAVR) technology. In addition, basic research on prosthetic valves has begun to shift from traditional mechanical valves and biological valves to the development of polymeric heart valves. The polymeric heart valves (PHVs) have shown a bright future due to their advantages of longer durability, better biocompatibility and reduced cost. This review gives a brief history of the development of polymeric heart valves, provides a summary of the types of polymer materials suitable for heart leaflets and the emerging processing/preparation methods for polymeric heart valves in the basic research. Besides, we facilitate a deeper understanding of polymeric heart valve products that are currently in preclinical/clinical studies, also summary the limitations of the present researches as well as the future development trends. Hence, this review will provide a holistic understanding for researchers working in the field of prosthetic valves, and will offer ideas for the design and research of valves with better durability and biocompatibility.

1. Introduction

1.1. Epidemiology of valvular heart disease

With an estimated 17.9 million deaths annually, cardiovascular disease (CVD) is currently the leading cause of death worldwide [1,2]. Deaths from cardiovascular diseases have continued to increase worldwide in recent years. In total, the number of deaths due to CVD worldwide increased from 12.4 million in 1990 to 19.8 million in 2022 [3]. Valvular heart disease (VHD) is a category of CVD with a high prevalence in recent years [4], and the epidemiology of VHD varies significantly worldwide. In high-income countries, functional and degenerative diseases are more prevalent, while rheumatic heart disease is more common in low-income and middle-income countries [1,5].

The human heart contains four valves: the aortic valve, the pulmonary valve, the mitral valve and the tricuspid valve. These valves function as one-way valves that prevent the back flow of blood through the heart. Natural heart valves are composed of three layers: the fibrosa layer, the cancellous layer, and the ventricular layer. The leaflets are composed mainly of extracellular matrix (ECM) and a variety of cells, including valve interstitial cells (VICs) and valve endothelial cells (VECs). Degenerative valve diseases are commonly considered to be closely related to endocarditis due to bacterial infections, aging, and lifestyle. These diseases are clinically reflected by two characteristics: valvular regurgitation and valvular stenosis [6]. Valvular regurgitation is primarily attributed to deficiencies in leaflet closure, prolapse, and tearing, all of which collectively result in blood reflux. Conversely, valve stenosis is largely attributed to thickening, calcification, and other related phenomena, which impede the leaflets open and close in a normal cycle. Additionally, congenital heart valve disease predominantly observed in young patients typically presents as aortic stenosis [7], the younger trend of congenital valve disease is gradually

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significant, so valve replacement will be particularly important.

1.2. Development of prosthetic heart valves

1.2.1. Mechanical and biological heart valves

Existing clinical treatments include drug conservative treatment, valve repair, and valve replacement [8]. Among these, heart valve replacement represents the primary mode of treatment for aortic stenosis and regurgitation. The two principal categories of prosthetic valves are mechanical and biological valves, with clinical application ratios of 55 % and 45 %, respectively. In the 1950s, the advent of mechanical valves [9] marked the advent of prosthetic heart valves. Since the introduction of prosthetic mechanical valves, prosthetic heart valves have evolved into a series of products over the decades. The evolution of valves has encompassed three distinct phases, namely mechanical, biological, and polymeric valves (Fig. 1) [10–12]. The use of mechanical valves requires long-term anticoagulant therapy to prevent thrombosis [13,14]. While this approach benefits patients by extending their prolonged survival period, it also has a significant impact on their life quality following surgery. Biological valves exhibit good blood compatibility and require only short-term anticoagulation [15,16]. However, bioprosthetic valves must overcome the immune compatibility issues. Furthermore, bioprosthetic leaflets are highly susceptible to tearing and calcification, as well as degeneration under high-loading mechanical stress *in vivo*, leading to a service life of 10–15 years, which is insufficient to meet the needs of young patients [17].

The leaflet materials of currently commercially available biological valves are still largely derived from animal sources, including porcine pericardium and bovine pericardium, and so forth [18,19]. Nevertheless, the source of materials is limited, and the problems of immunogenicity and biocompatibility must be overcome. The advent of polymer materials has brought a novel approach to the development of cardiac valves, which is anticipated to address the shortcomings of traditional valve materials [20].

1.2.2. Transcatheter aortic valve replacement (TAVR) and polymeric heart valve

The development of interventional cardiovascular devices has popularized the concept of minimally invasive clinical interventions, and with the social structure of population aging, it is forecasted that the clinical demand for interventional valves will grow in the future. Transcatheter aortic valve replacement (TAVR) [18,21,22]is a minimally invasive procedure that utilizes a valve delivery system to deliver a valve to a specific part of the body from an external route, such as the femoral artery, to allow for effective valve replacement. The concept of TAVR was first introduced in 1999 by the start-up companies PVT (NJ, USA) and ARAN R&D (Caesarea, Israel). ARAN R&D subsequently completed the first-in-man (FIM) study in 2002 [23]. TAVR technique has gained considerable popularity in 65 countries and regions across the globe, with approximately 300,000 procedures performed [24]. The TAVR technique is less invasive with a faster postoperative recovery, and can significantly improve life quality of patients. Consequently, this procedure is a preferred option for elderly patients with aortic valve disease.

The current TAVR valves can be categorized into balloon-expandable valves and self-expandable valves according to the type of valve frame. In contrast, balloon-expandable valves are held open in the annular plane by the expansion of the balloon, which makes the release process relatively controllable and causes minimal damage to the cardiac structure. However, they cannot be recovered because the balloon-expandable valves are pre-compressed outside of the body and cannot be withdrawn by the delivery system. Thus, the operator has less chance for error in their actions. Self-expanding valves are typically composed of memory alloys that can be compressed into the delivery sheath at low temperatures and subsequently self-expanded at a body temperature of 37 °C following implantation. The retrievable design of the self-expanding valve's accompanying delivery device allows for repositioning of the valve, as demonstrated in Fig. 2.

As previously mentioned, polymeric valve technology offers several unique advantages in terms of fatigue resistance when compared with

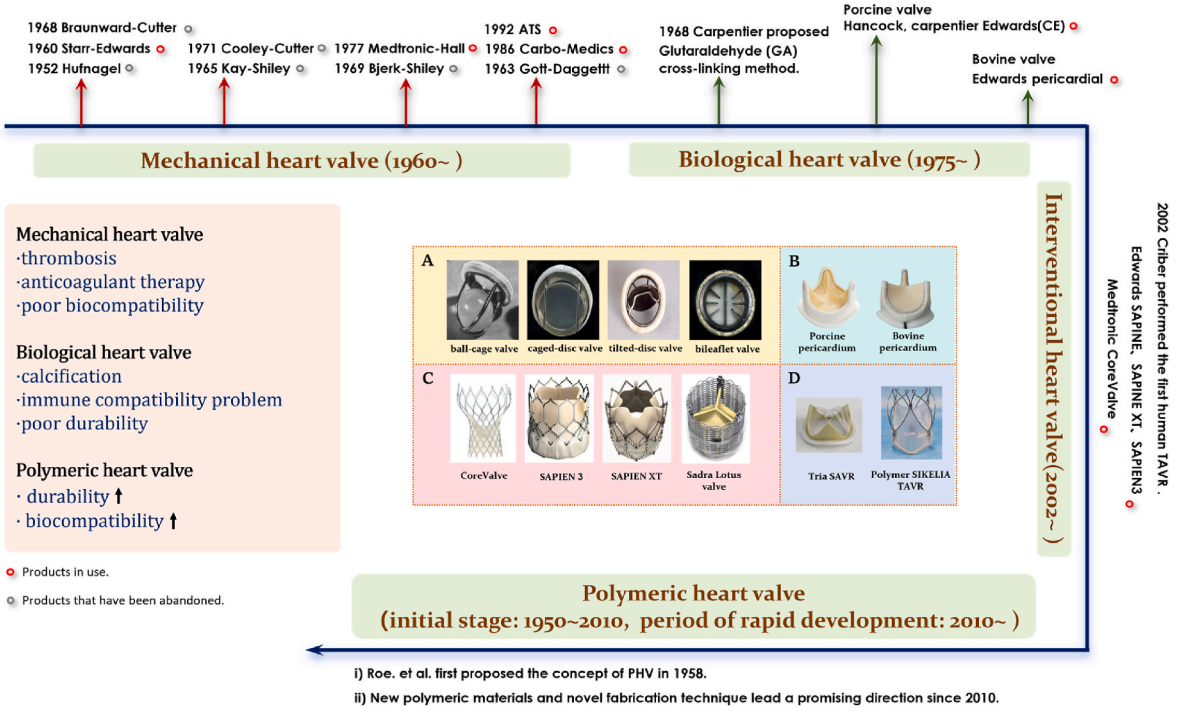

Fig. 1. Summary of development history and representative prosthetic heart valves. (A) Mechanical valves, including ball-cage valve, caged-disc valve, tilted-disc valve and bileaflet valve; (B) Biological valves derived from porcine pericardium and bovine pericardium; (C) Interventional heart valve, bioprosthetic valves are delivered through transcatheter valve replacement; (D) Polymeric valve under development, which is a hot competing spot in recent years.

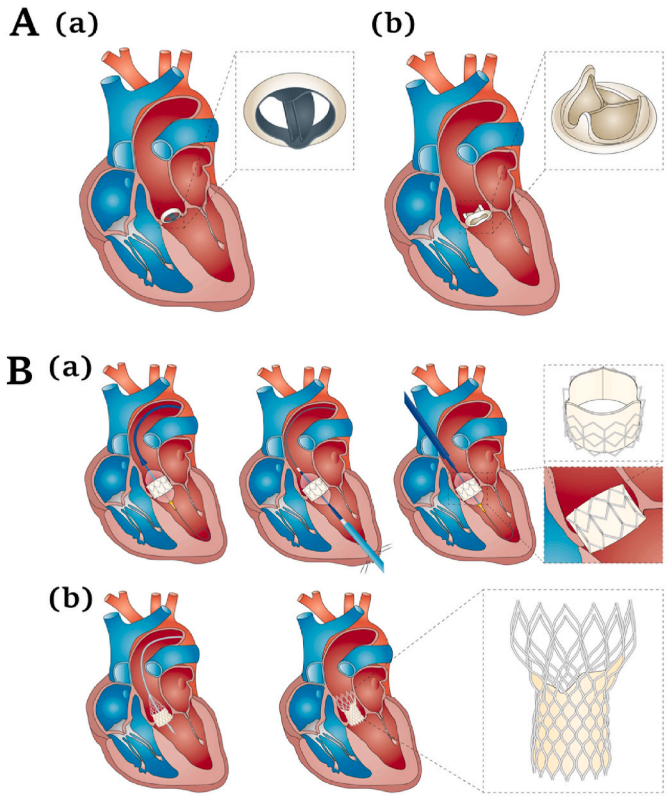

Fig. 2. Prosthetic heart valve categories. (A) Surgical valve replacement. a) Mechanical valves and b) biological valves used in aortic valve replacement. (B) Transcatheter aortic valve replacement. a) balloon-expandable valve replacement via transfemoral, transapical, or transaortic access; b) self-expandable valves via transfemoral access [25].

mechanical and biological valves. It is expected that the lifespan of these valves will be approximately 25 years [26], which is a significant improvement compared to biological valves. Additionally, the use of polymeric valves can address some of the inherent limitations associated with biological valves, including low biocompatibility, easy calcification, and poor mechanical properties of the material. Consequently, polymeric valves [27] have emerged as a promising solution to address the longevity challenges in TAVR development. An increasing number of research teams are now focusing their attention on the use of polymer materials for TAVR valve development and design (Fig. 3). In addition, the polymer TAVR valve leaflet materials can be manufactured with a controllable thickness, and the processing and preparation of the material is relatively simple and minimally affected by the grip-release process.

To date, only Foldax® Tria™ valve has successfully completed preclinical testing and entered formal clinical trials. Furthermore, Eshin Medical has demonstrated the feasibility of implanting the polymer TAVR SIKELIA™ aortic valve in patients over the age of 80, as evidenced by the successful implementation of this procedure in 2022. It is notable that globally, only a few companies are able to achieve mastery of the fundamental technology associated with polymeric valves. Polymeric valves are featured with improved minimally invasive delivery techniques, enhanced durability and biocompatibility. These dominant features represent a promising new avenue for the development of prosthetic valves.

2. History of polymeric heart valves (PHVs) research

The concept of polymeric heart valve was initially introduced by Roe, Owsley and Boudoures in the 1950s [28,29], paving way for their subsequent development and employment. In 1960, the first animal studies and clinical implantation feedback of valves made of polyurethane materials were reported in a study [30]. The research on polymeric valves can be considered to be contemporaneous with the mechanical and biological valves, but during the exploratory phase of the polyurethane materials, it was found that they could not provide sufficient durability.

As a result, mechanical and biological valves outpaced their development for a long period of time, contributing to the slow progress of polymeric valve development in the early 21st century. It is crucial to select the appropriate material for the leaflets in polymeric valves. The

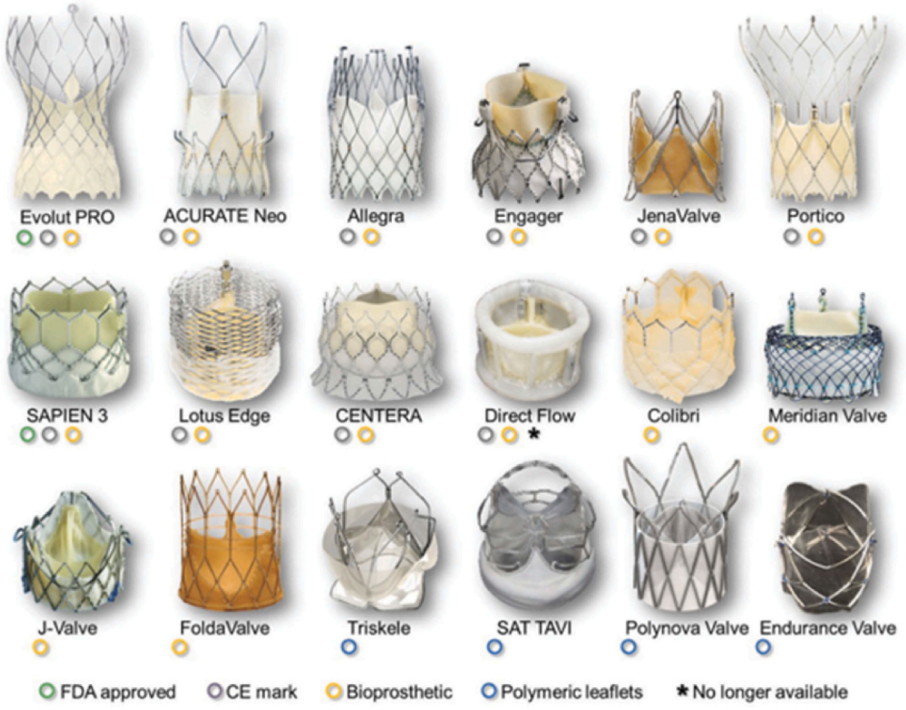

Fig. 3. Representative commercially available TAVR valves and devices under-investigation [22].

materials currently used in polymeric valves include natural, synthetic, and composite polymers [31,32]. The development of polymeric valves has been leaded by advances in materials science research, which have led to the identification of new materials and the optimization of existing materials.

Over the past few decades, national and international researchers have tried different polymer materials [33,34]. The earliest documented uses of polysiloxanes, polytetrafluoroethylene (PTFE), polyurethane (PU), poly (L-lactide-*co*-ε-caprolactone) (PLCL), poly (lactic-*co*-glycolic acid) (PLGA), polycaprolactone (PCL), poly (lactic acid-hydroxyacetic acid) (PLA), and poly (L-lactic acid-hydroxyacetic acid) (PLLA) were in the 1960s and 1970s. However, these polymeric materials were found unsuitable for use in subsequent preclinical tests or clinical trials due to poor biocompatibility, mechanical properties, and high calcification rates [33,35]. At the beginning of the 21st century, novel polymer materials were obtained through surface modification, material compounding, and optimization of the synthesis method, with the help of existing polymer synthesis techniques and nanotechnology. These polymer materials have been improved in terms of stress level, biocompatibility, and degradability properties. Currently, these novel polymer materials include silicone polyurethane (SiPUU), polyhedral oligomeric silsesquioxane polycarbonate polyurethane (POSS-PCU), nanocomposite graphene-polycarbonate polyurethane polymer (FGO-PCU), poly (styrene-*b*-isobutylene-*b*-styrene) (SIBS) and poly (styrene-*b*-4-vinylbenzocyclobutene-*b*-isobutylene-*b*-styrene-*b*-4-vinylbenzocylcobutene) (xSIBS) have been developed through surface modification and optimization of synthesis methods, compared with other examples, which were demonstrated a promising potential for future application [34] (Fig. 4, Fig. 5).

2.1. First-generation polymer materials

Polymeric valve materials must have good biocompatibility, noninflammatory, and good mechanical properties. The first generation of representative polymer materials include PTFE, Polysiloxanes, PU, PET (Polyethylene terephthalate), etc. PTFE was one of the first polymer valve materials studied, with excellent stability and biocompatibility. ePTFE (expanded polytetrafluoroethylene) was obtained by rapidly stretching PTFE at high temperatures, with significant advantages in good tensile strength, which better meets the valve's physiological requirements for long-term fatigue resistance. PET prostheses have been widely used in cardiovascular prosthetic materials since they first appeared in 1957, owing to their good mechanical properties. However, the strategies of composite materials and modification of the material surface are needed to be addressed, as factors such as the limited performance of a single material have led to little success in actual polymeric valve translational research.

2.1.1. Polytetrafluoroethylene

The presence of carbon-carbon bonds and stable carbon-fluorine bonds in the chemical structure of PTFE is very important in determining the inherent stability and low surface energy of the material. The initial development of this material stimulated the design of a heart valve, as described by Braunwald et al. in 1963 [36]. However, severe regurgitation and leaflet tears were observed following implantation in patients, resulting in the termination of further applications in the field of heart valves. Currently, PTFE materials are widely utilized in cardiovascular surgery for the development of PTFE blood vessels [37]. In 1969, Robert et al. [38]applied the technology of producing fluoroplastics to a new method for obtaining a new material with good porosity and permeability, ePTFE. Subsequently, the initial application was in a tricuspid valve model in sheep. However, the use of polymer materials based on ePTFE was limited by the subsequent hardening and calcification of the leaflet.

2.1.2. Polysiloxanes

Polysiloxane has been employed in the development of numerous medical devices on the grounds of its excellent biocompatibility and resilience to fatigue previously [39]. The presence of high bonding energies in the silicone-oxygen bonding greatly enhances the chemical as well as thermal stability of silicone materials. The mechanical properties of polysiloxanes are influenced by chain length, side chain groups, and degree of cross-linking. In the 1960s, both Roe and Hufuagel [40] developed polymeric valves based on polysiloxanes, which were implanted in patients and subsequently failed due to structural valve degradation and thrombosis. In the initial stages of development, polymeric valves were manufactured with organosilicone-based polymers, which were found to exhibit suboptimal long-term durability *in vivo*. These polymers also displayed high load resistance and leaflet failure in large animal studies. Consequently, polysiloxane materials are no longer considered for use in the development of polymeric valves.

2.1.3. Polyurethanes

The advent of polyurethane materials, which were first synthesized

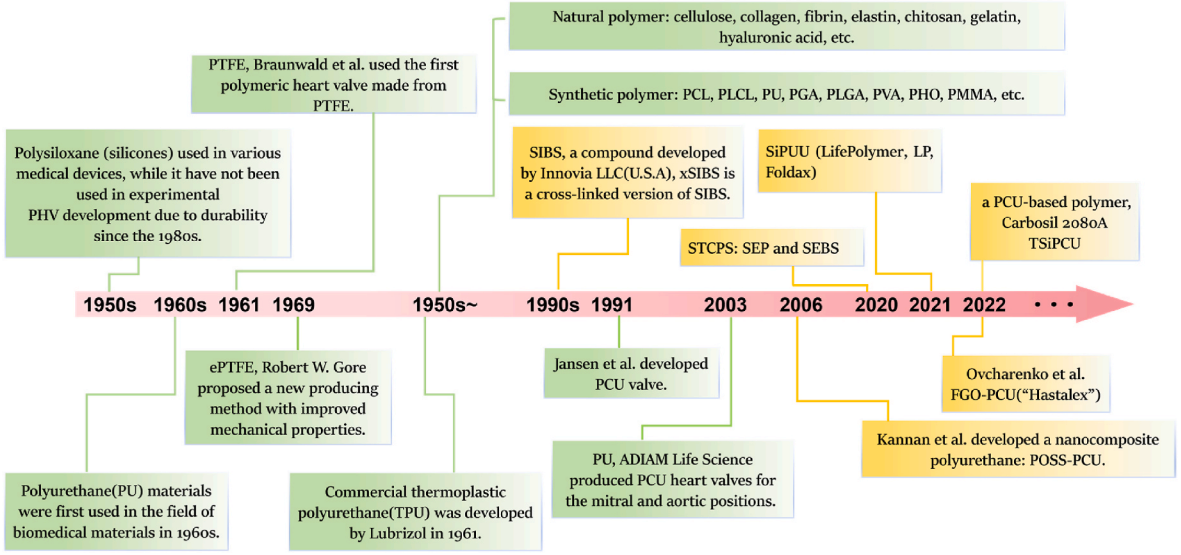

Fig. 4. The development timeline of polymer materials. The green sections represent the first generation of polymer materials and the yellow sections represent the second generation. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

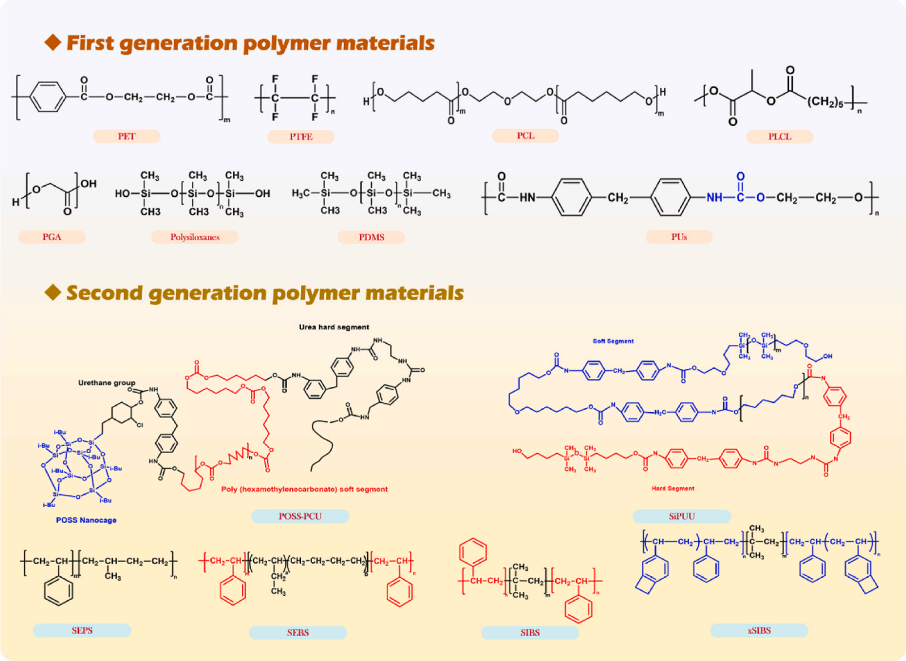

Fig. 5. Various chemical structure formulas of polymer compounds used in PHV construction.

in 1950 [41], marked an important advancement in polymer chemistry, as their distinctive monomer structure contains both dibasic/polyol (soft segments) and diiso/polyisocyanate (hard segments). Urethanes are produced by the reaction between an isocyanate (R–N = C=O) and an alcohol (R–OH). When the alcohol is a diol or macrodiol, and the isocyanate comes from diisocyanates or polyisocyanates, PU polymers can be synthesized [42]. This structural composition allows the ratio of soft to hard segments to be precisely controlled to achieve the desired flexibility of the resulting material. PU, a multiblock polymer, is characterized by its flexible and variable structure, which allows for the design of materials with different properties. This is achieved through the adjustment of the types and ratios of diisocyanates, chain extenders, and low-polymer diols. From a structural standpoint, the presence of soft and hard segments, along with readily degradable chemical bonds, tends to influence the durability of the valve under conditions of high-temperature oxidation, enzymatic conditions, and mechanical stress. A modified polyurethane, polycarbonate polyurethane (PCU), was obtained through a compounding strategy [43]. The hydrolysis resistance of polyurethane elastomers is related to the structure of the hard segment. Regular diisocyanate core structure, more benzene rings, and regular chain extender are conducive to the formation of a compact hard segment to improve the hydrophobicity of the elastomers. Therefore, the hydrolysis resistance of PCU is better than that of polyether polyurethane and polyester polyurethane. Currently, polyurethane has a wide range of applications in biomedical materials, including the fabrication of artificial heart valves, artificial blood vessels, and pacemaker insulating wires. The category of medical polyurethane raw materials is extensive, with thermoplastic polyurethane (TPU) representing the most prevalent and utilized material. The United States Lubrizol and the United Kingdom DSM are the two leading suppliers of polyurethane in the global market.

In 2003, aortic and mitral valves were developed by ADIAM Life Sciences in Germany using PCU materials, and *in vitro* accelerated fatigue tests demonstrated excellent durability of both the mitral and aortic valves, with 1 billion and 300 million cycles, respectively [44]. Nevertheless, subsequent animal studies revealed the formation of calcification deposits in both valves, which prevented the single PCU material from advancing to the next phase of clinical trials.

Hence, the main factors of limited success of first-generation polymer material research can be summarized as follows [45]: (i). the mechanical strength of human natural valves is almost 2–3 MPa [46], whereas the average stress of the first-generation polymer materials is 1 MPa, which renders the material easy to tear. (ii). thrombosis is predominantly caused by hydrophobic groups on the surface of polymer materials (e.g., aliphatic and aromatic groups) in contact with blood. This interaction results in the adhesion of various blood constituents, namely proteins, red blood cells, and platelets. The subsequent stimulation of platelets to release reactive factors such as adenosine diphosphate and thromboxane A2 activates the release of thrombin, ultimately facilitating the formation of platelet thrombi. It is commonly accepted that hydrophilic and hydrophobic groups exert a significant influence on protein adsorption [47]. (iii). calcification represents a significant cause of failure in valve function, which frequently occurs in surface cracks and joints of valve leaflet materials [48]. Furthermore, *in vivo* experiments with first-generation polymer materials have demonstrated a tendency for adsorption to recruit platelets and accelerate calcification, which may contribute to this process. (iv). the chemical composition affects not only the structure and properties of the materials but also their degradation stability. In the initial generation of polyurethane materials utilized in biomedical applications, polyester polyurethanes linked by ester bonds [49,50] are known to exhibit facile hydrolysis. The advent of PCU [51] has been shown to address the hydrolysis and oxidation issues associated with polyester polyurethanes to a certain extent [52].

2.2. Second generation polymer materials

The limited success of first-generation polymer material research is largely due to inherent material limitations in the mechanical properties, poor degradation properties, serious calcification problems, and biocompatibility. Consequently, second generation polymers have been applied to polymeric valves. Based on the defects of first-generation materials, new polymers have been developed, and strategies such as combining natural polymers with synthetic polymers to achieve complementary functionality have been proposed. Representative second-generation polymer materials are nanocomposite siloxane-polycarbonate-urea-polyurethane (POSS-PCU) [53], silicone polyurethane (SiPUU), nanocomposite polyvinyl alcohol (PVA), polystyrene-*b*-isobutylene-*b*-styrene (SIBS), and nanocomposite

graphene-polycarbonate-polyurethane polymer (FGO-PCU).

2.2.1. Siloxane polycarbonate urethane (POSS-PCU)

It has been demonstrated that the introduction of POSS groups into a single PCU material can protect the soft segment portion of PCU from oxidation or hydrolysis, and the composite polymerization of PCU and POSS yields a novel nanocomposite material POSS-PCU [53], which was further optimized for performance and applied to TRISKELE® TAVR valve design and vascular grafts [43]. This nanocomposite modification strategy was further applied in the FGO-PCU material developed by Ovcharenko et al. [54]. In their Hastalex surgical valve, carbon nanoparticles were introduced into the original polymer structure. Compared to ePTFE, FGO-PCU was found to have good resistance to calcification and biocompatibility, with cells showing good proliferative activity on the surface of the material. The valve has been developed and designed as a first step and relevant *in vivo* kinetic data as well as *in vivo* test results are still required at a later stage in order to prove its efficacy.

2.2.2. Styrene triblock copolymers (STCPs)

STCPs are synthetic thermoplastic elastomers that already have practical applications in drug-eluting coronary stents [55]. Stasiak JR et al. have developed a novel polymeric valve, PoliValve, containing two styrene triblock copolymers, polystyrene-*b*-ethylene/propylene-b-styrene (SEP) and polystyrene-*b*-ethylene/butylene-b-styrene (SEBS). Innovia LLC [56], USA, developed a compound poly (styrene-*b*-isobutylene-*b*-styrene) (SIBS), but calcification and thrombosis problems occurred in early experimental results. Recently, new compounds xSIBS have been obtained by crosslinking for use as SAVR Polynova valve materials, showing good anti-calcification and blood compatibility [57,58].

3. Preparation technology for polymeric heart valves

At present, the mainstream materials preparation techniques for valve leaflets include: electrospinning, 3D printing, melt electrospinning writing (MEW), focused rotary jet spinning (FRJS), and computer-aided design (CAD) of valve conformation (Fig. 6). In recent years, these preparation methods have found many applications not only in the basic research field of cardiovascular biomedical materials, but also in other materials fields: such as the preparation of wound repair materials by electrospinning technology, the construction of human cochlea using 3D printing technology, bone tissue and other applications to promote organ regeneration.

Based on the current preparation technology, there exists advantages and disadvantages as for different methods (Table 1). Meanwhile, the basic study in the field of polymeric valves in recent years is summarized in terms of the selection of materials for polymeric valve leaflets, the preparation techniques, and the construction methods, respectively (Table 2).

3.1. Electrospinning

Electrospinning is a simple and efficient method for obtaining micro- and nanofibers [92]. In 1934, the modern electrospinning technique was born when Formhals first proposed how polymer solutions form jets in the preparation of polymer fibers by electrospinning. In 1996, Reneker [93] reported the first study on the preparation of nanofibers by electrospinning technique, where a high voltage electric field was applied and the electrospun solution formed a polymer jet in the shape of a “Taylor cone", the solvent is rapidly evaporated in the jet process, the polymer fibers are cured and attached to the receiving device, and finally the micro-nanofibers with random orientation or directional arrangement are obtained.

At present, electrospinning is mainly used to produce fiber scaffolds with diameters in the range of tens to hundreds of nanometers that exhibit high porosity and specific surface area with uniform fiber diameter, making them suitable in biomedicine, tissue engineering,

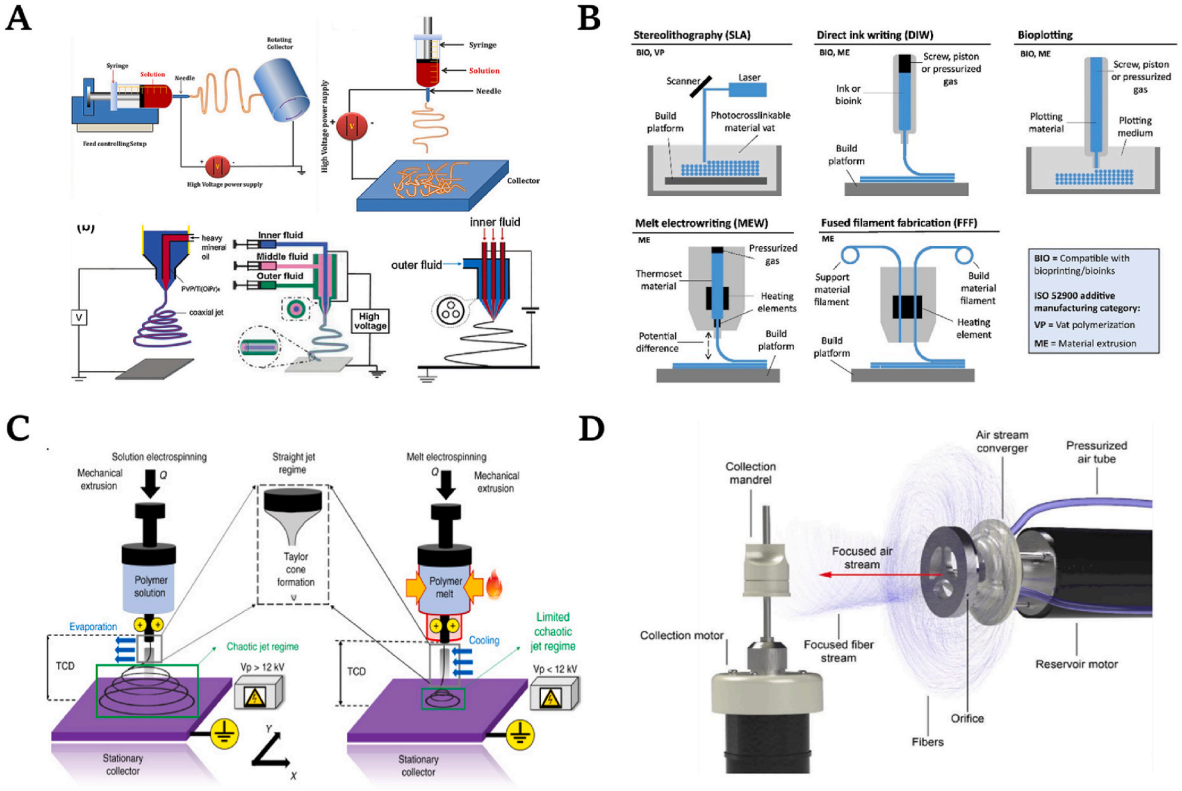

Fig. 6. Common preparation technologies of polymeric valve. (A) Electrospinning (ES) technology [59–61]; (B) 3D bioprinting technology [62,63]; (C) Melt electrospinning writing (MEW) [64]; (D) Focused rotary jet spinning (FRJS) [65,66].

Table 1
The advantages and disadvantages of different preparation techniques for polymeric heart valves.

Methods	Advantages	Disadvantages	Ref.
Electrospinning	- Simple operation and low costs - Capable of fabricating randomly oriented/ aligned micro and nanofibers - The design of the receiver end allows direct access to geometrically shaped scaffolds	-The preparation process requires careful consideration of environmental factors (e.g. ambient temperature and humidity) - The concentration of the polymer electrospinning liquid must be within a specific range to ensure the optimal production of fibers -Pore size, diameter and thickness of the nanofiber scaffolds are precisely regulated to meet the desired specifications	[60, 61]
3D printing	- Preparation of scaffolds with different structural levels and specific morphology -Accessible to multi-material bioprinting -The implementation of both the printing process to produce the scaffolds and the cell-seeding process	-Bioink development that simultaneously meets printability, mechanical properties and biocompatibility still needs to be explored -The uniformity and reproducibility of 3D printing technology needs to be improved -Large-size complex structures are printed at a slower speed and with lower precision than natural tissues and organs	[62, 63]
MEW	-Capable of fabricating randomly oriented/ aligned micro and nanofibers -Fast scaffold production	-Limited to flat or cylindrical collectors -Only been applied to thermoplastic elastomers such as PCL	[64]
CAD	-High degree of design freedom to realize more advanced geometric configurations -Advance assessment of *in vivo* stress distribution in polymer valves - Pre-screening predicts durability	-Only focuses on the analysis of the mechanics and durability of materials -Difficult to predict the biocompatibility of materials	[67, 68]
FRJS	-More efficient electrostatic spinning design for faster speeds -Low preparation cost-porous -Mesh nanofibers can enable cell penetration and proliferation	-Mechanical properties of the scaffolds are unknown	[66, 68, 69]

textile, etc [94]. Stadelmann K. et al. [95] developed a cryo-electrostatically spun bilayer scaffold with a well-defined morphology prepared using cryo-electrostatic spinning technology. The scaffold supported the growth of VECs and VICs adherent to the scaffold (Fig. 7A) and was a multifibrous tissue structure with a natural fiber structure and mechanical properties similar to those of aortic valves. Electrospinning technology enables the regulation of fiber orientation, and studies have shown that nanofibers with both regular and random orientations can be obtained by adjusting the rotational speed of the receiver device. Ghomi. et al. [96] found that the fiber orientation tended to be regularly distributed by setting a series of gradients such as the receiver speed of 500–2000 rpm in electrostatically spun PCL/GEL composite scaffolds. Snyder, Y. et al. [97] in their study found that fiber orientation and anisotropic properties affect the properties of cells and ECM in the structure by preparing bionic three-layer valve structures (Fig. 7C). Mingze et al. [98]used a novel techniques to fabricate bionic multilayer materials combined with solution casting, electrospinning and lyophilization. The BMM (a biomimetic, multilayered material) showed good anisotropic behavior and was closer to the mechanical properties of the aortic valve than the commercially available materials (Gore-Tex®, CorMatrix®, CardioCel®) (Fig. 7D).

The applicability of the electrospinning technique can be extended to many polymeric materials, and the simplicity of the spinning solution preparation process has facilitated the application of this technique in cardiovascular tissue engineering [99–101].

3.2. 3D printing

3D printing is a new type of additive manufacturing technology that enables the production and fabrication of 2D and 3D materials using computer-aided design. In brief, 3D printing achieves the process of transforming a digital model into a solid body through the steps of digital construction, slicing, layered stacking, layered bonding, and repeated stacking. 3D printing technology first appeared in the 1990s, and Sodian R. et al. [102] used stereolithography models to fabricate biocompatible and biodegradable tissue-engineered heart valves in 2002. It was not until 2019 that Coulter, F.B. et al. [103] used silicone resin feedstock (silicones), which has excellent biocompatibility and mechanical properties, in conjunction with additive manufacturing processes of spray and extrusion and digital fabrication design to develop polymer aortic valves similar to natural tissue, marking the first application of 3D printing technology in the field of polymeric heart valves [87,103–105]. The data from the *in vitro* pulse test showed a good hemodynamic performance (Fig. 8C and D).

Nachlas ALY et al. [88] studied recent years devoted to a valve that can accompany growth and remodeling *in vivo*, using 3D printing and molding to recreate a native leaflet structure consisting of PCL and cell-loaded gelatin methacrylate/poly (ethylene glycol) diacrylate (GelMA/PEGDA) hydrogel, and then evaluated the multilayer scaffolds for their ability to produce collagen under physiological shear stress conditions (Fig. 8A). A. Jafari et al. [88]developed a bioink combining polyvinyl alcohol (PVA), gelatin (Gel), and **κ**-carrageenan (CG) for the 3D printing of tissue-engineered heart valves (TEHV). The use of freeze-thaw cycling, a physical cross-linking method, avoids the use of chemical cross-linking agents, and the CAD-designed valves show good potential for application under *in vitro* pulsatile flow conditions (Fig. 8B).

3D printing technologies are generally categorized according to material properties and different application scenarios into stereolithography (SLA), bio-plotting, direct ink writing (DIW), MEW, fused filament fabrication (FFF), etc. [63], which are constantly being improved to meet a wider range of needs. In clinical application, where different patients have individual characteristics, the use of 3D printing to achieve the production of customized medical devices has become a new development direction. At present, this technique can realize the construction of three-dimensional models of living tissue and organs, such as heart tissue, bone, and so on, and can realize the substrate with adjustable uniform pore size, porosity, and geometry.

However, there are still many factors that limit the pace of development of 3D printing technology [62], and the current limitation is to create tissues with mechanical properties similar to those of natural tissues, particularly the problem of material sources and printability that limit the development of the technology. It is expected that improved materials will lead to breakthroughs in performance and stability. Furthermore, it is possible to improve printing process by increasing printing precision and speed [63], and incorporate intelligent manufacturing ideas that will further lower costs, realize large-scale manufacturing, and further develop 3D printing technologies.

Table 2
Recent study on fabrication method and scaffolds design of polymeric heart valve.

Method	Polymer	Fabrication Strategy	Innovation	Year	Ref.
Electrospinning	PGS/PCL	-Random or aligned fibers were fabricated	-A directional electrospinning technique -Change the ratio (PGS: PCL) to improve mechanical properties	2014	[70–73]
	PLLA/TPU (γ-Fe_2O_3) (1:1)	-Mixed electrospun solutions, electrospinning	-Biological/mechanical properties of maghemite was confirmed -Nanofiber based scaffold fabrication shows a potential choice for TEHV	2017	[74]
	PLA	-Bi-layered cryogenic electrospun scaffold (BCES) design -Infiltration layer (IL) and non-infiltration layer (n-IL)	-Cryogenic Coat Electrospinning with low tissue temperature drum -A novel 3D bilayer *in vitro* assay system -Co-cultured aortic heart valve model	2022	[75]
	PCL	-Electrospinning, tri-layered structure with a circular orientation layer (2000 rpm), a random orientation layer (125 rpm) and a radiation orientation layer (2000 rpm)	-Leaflet scaffolds have native tri-layered structure and orientations	2023	[76,77]
	PLCL/GEL, PLCL/SF,PLCL/HA	-Electrospinning -Biomimetic tri-layer TEHV	-Natural polymer and synthetic polymer composite strategy -PLCL/GEL-fibrosa layer, PLCL/HA-sponge layer, PLCL/SF-ventricular layer -The ability tissue regeneration of HA layer	2023	[78,79]
MEW	PCL	-Fibers with consistent wavy -Architecture-collagen fibers orientation	-Each 5 stracked layers increase 0.1 kV to keep flight path -J-shaped stress/strain curves	2019	[80–84]
	PLA	Al–Ti and Al-PLA collectors	-Manufacture 3D geometry scaffold via MEW -Fabricate biomimetic tri-layered scaffolds	2020	[84,85]
3D printing	PCL and GelMA/PEGDA	-PCL-fibrosa layer -GelMA/PEGDA-spongiosa/ventricularis layer	-PCL-circuferential direction (similar to collagen alignment) -GelMA/PEGDA improve biocompatibility	2020	[86]
	PU (CarboSil 55D)	-Fused deposition model 3D printer -Leaflets thickness 300 μm	-Minimally invasive techniques -Fabricated combining 3D printing and spray technology	2021	[87]
	PVA/Gelatin/CG	-P10/G2.5/C2.5 ink, tri-leaflets valve	-Physical crosslinking of PVA by freeze/thawing cycles	2024	[88]
	flexible silicone	–	–	2022	[89]
FRJS	P4HB/Gelatin (60/40) 4 % (w/v)	-Two-step collection process: i). collection of force-extruded fibers, ii). automation of the rotary jet spinning system (aRJS)	-Jet Spinning Method for Rapid and Automatic Fabrication of Fibrous Heart Valve Scaffolds -Rotary jet spinning (first take up)	2017	[90]
	PLCL	-Similar to previous RJS platform -Focused air jet valve-shaped collection mandrel	-Manufactured MFs & NFs in minutes, -A viable method for manufacturing heart valves	2023	[65,91]

Abbreviations: PGS: poly (glycerol sebacate); PCL: polycaprolactone; PLLA: L-polylactic acid; TPU: thermoplastic polyurethane; PLA: polylactic acid; PLCL: poly(L-lactide-*co*-ε-caprolactone); SF: silk fibroin; GEL: gelatin; HA: hyaluronic acid; GelMA: gelatin methacrylate; PEGDA: poly (ethylene glycol) diacrylate; PU: polyurethane; PVA: polyvinyl alcohol; CG: carrageenan; P4HB: poly(4-hydroxybutyrate).

3.3. Melt electrospinning writing (MEW)

MEW technology [106] combines the principles of electrospinning and bioprinting to create a fiber substrate with micro-scale accuracy by melting synthetic polymeric materials and ejecting them through a filament ejector, creating a polymer jet, similar to that of electrospinning. MEW generally refers to the extrusion of molten polymers by applying a voltage between a nozzle and a computer-controlled moving electrode, which produces high-precision electrohydrodynamic fiber deposition, with the resulting fibers having the potential to be submicron fibers [107]. PCL materials are widely used in the field of tissue engineering and in the development of polymeric valves due to their good biocompatibility and desirable degradation rate. Based on the principle of biomimicry, Saidy NT et al. [86,108]simulated the wavy orientation of collagen fibers to design the scaffold and set the aluminum plate receptor to move at 280 mm/min to obtain multilayer valve leaflet material (Fig. 9A).

On the basis of the MEW technology, the subsequent team combined the MEW technology with 3D printing in the hope of overcoming the limitations of the electro-writing technology to fabricate scaffolds with specific microstructures and complex anatomical structures [64]. Furthermore, the proximity of the collector to the nozzle and the absence of an electrospinning solvent provides stabilization of the polymer beam and allow extensive control of the deposition of fibers [109].

3.4. Focused rotary jet spinning (FRJS)

While traditional solution casting results in materials with structural homogeneity that fails to meet quantitative criteria, the development of electrospinning and 3D printing technologies allows for parameter tuning [110], resulting in controllability in terms of thickness and porosity. Parker's team at Harvard Medical School [65,111] developed a FRJS method combining rotary jet discharge (RJS) and focused airflow in 2023, where biodegradable polymer fibers produced by focused rotary jet spinning can be made into heart valve 3D printed structures in minutes, creating revolutionary pediatric heart valves.

The team designed the Jet valve heart valve back in 2017 [112], and continued to optimize the design of the valve leaf shape to reduce valve regurgitation. The preparation of the Jet valve can be summed up as a two-stage process, with releasing of the fibers by external compression of the spinning solution at the first stage, and establishing an automated rotary jet spinning system (aRJS) at the receiving end at the second stage (Fig. 10B), while adding a focused airflow vortex device at the receiver end to achieve more efficient fiber deposition. The introduction of the air jet and the improvement of the focused spinning design allow the

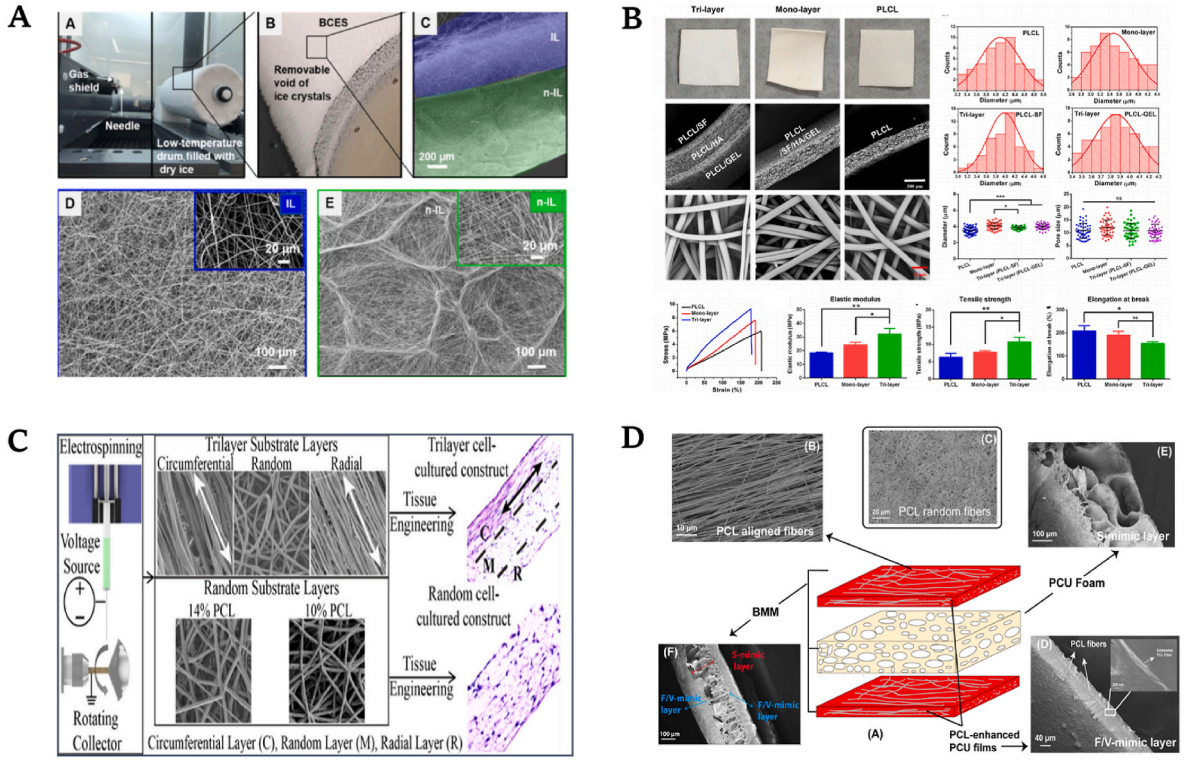

Fig. 7. (A) Electrospinning in polymeric valve fabrication. The device of cryogenic electrospinning process; Bi-layered cryogenic electrospun scaffold (BCES) structure consists of the IL layer with large pores with randomly-oriented and loosely-packed fibers, and the n-IL layer with small pores with honeycomb structure after lyophilization [95]. (B) Fabrication of biomimetic three-layer polymeric heart valves (PLCL/GEL, PLCL/HA, PLCL/SF) by electrospinning technology [78,79]. (C) Three layers of polymeric heart valve with anisotropic and randomly oriented fibers were constructed by electrospinning technique [97]. (D) Schematic drawing for the design of biomimetic, multilayered material, and its tri-layer structure is 'Film-Foam-Film' via the cross-section view [98].

FRJS technique to obtain nanoscale fibers compared to 3D printing techniques, and such porous mesh nanofibers can enable cell penetration and proliferation. This FibraValve manufacturing process allows for minimal manufacturing steps: mandrel design, fiber scaffold collection, leaflet embossing, and trimming and suturing into a final shape. Parker's team and Hoerstrup's team at the Institute for Regenerative Medicine in Zurich designed the FibraValve pulmonary valve with a customized PLCL polymer material that mimics the physical properties of natural valves and resorbable PLCL that can be replaced by tissue to form a regenerative heart valve (Fig. 10A). In addition, the FibraValve has been evaluated *in vivo* in sheep, and deposition of fibrin etc. and cellular infiltration on the valve surface were found within 1 h [113]. The long-term efficacy and regenerative capacity of the FibraValve needs to be further evaluated in long-term animal studies.

Compared to previously reported Jet valve, (i). FRJS allows multi-scale resolution, which means modulation from micro- and nanofibers to complex geometries at the centimeter level. Parameters such as height (H), leaflet length (LL), diameter (D), and radius of curvature (R) were used to fabricate FibraValve shapes [91]. In addition, the longer LLs of the FibraValve created larger coaptation areas than the Jet valve, helping to limit regurgitation during diastole. (ii)The Jet valve uses an automatic syringe pump to rotate the reservoir at 30,000 rpm, extruding a jet of solution through two 360 mm diameter orifices in the reservoir, creating a horizontal "fiber extrusion plane". FRJS custom machined aluminum reservoir is perforated with three cylindrical orifices (diameter = 400 mm) and the internal hollow reservoir is designed to allow air to pass through its openings. It's mounted on a horizontal brushless motor shaft with speeds ranging from 10,000 to 35,000 rpm. As a result, the improvements in reservoir orifice diameter and rotational speed have enabled the FRJS fiber flap to be produced at speeds up to 0.2 g/min, which is 50 orders of magnitude faster than electrospinning systems (0.000167 and 0.0167 g/min), making it promising for the field of tissue scaffold preparation.

3.5. Computer-aided design (CAD)

Computer-aided design is a new idea in the design of polymeric heart valves. By designing various parameters (polymer material, leaflet thickness, size, shape, etc.), the performance of the valve, such as hemodynamics, durability, and stress distribution *in vivo*, can be predicted using computer data processing. Therefore, computer-aided design as a viable tool greatly improves the efficiency and helps us to optimize the design of polymeric valves with better performance. From the design of the first generation of surgical valves to the second generation of polymer TAVR devices, Rotman et al. [115] found that the early SIBS materials, although they showed good blood compatibility, they were prone to calcification, the leading to the failure of early animal experiments in the long term due to the shape of the valve leaflets. Therefore, a new polymer xSIBS was developed and optimized for leaflet optimization using computer simulated thrombosis to reduce the risk of thrombosis. Based on the first generation TAVR device, they further improved the radial force distribution by resizing the valve to reduce the stress during the leaflet opening and closing cycles (Fig. 11).

Emmert et al. [68] designed polymer scaffold tissue-engineered heart valves loaded with vascular cells using computational modeling. After 4 weeks of culture in a bioreactor, the grafts were decellularized and implanted via transcatheter route in 11 sheep for pulmonary valve replacement. Results showed similar *in vivo* performance 1-year post-surgery as predicted. The significance of this work is that it applies the concept of computer modeling to the design and development of tissue-engineered valves, and *in vitro* predictive screening can better guide development and design. The durability analysis and improvement of polymeric valves can be achieved with the help of computer parametric studies and calculations (Fig. 12). Hieu T et al. [67] used

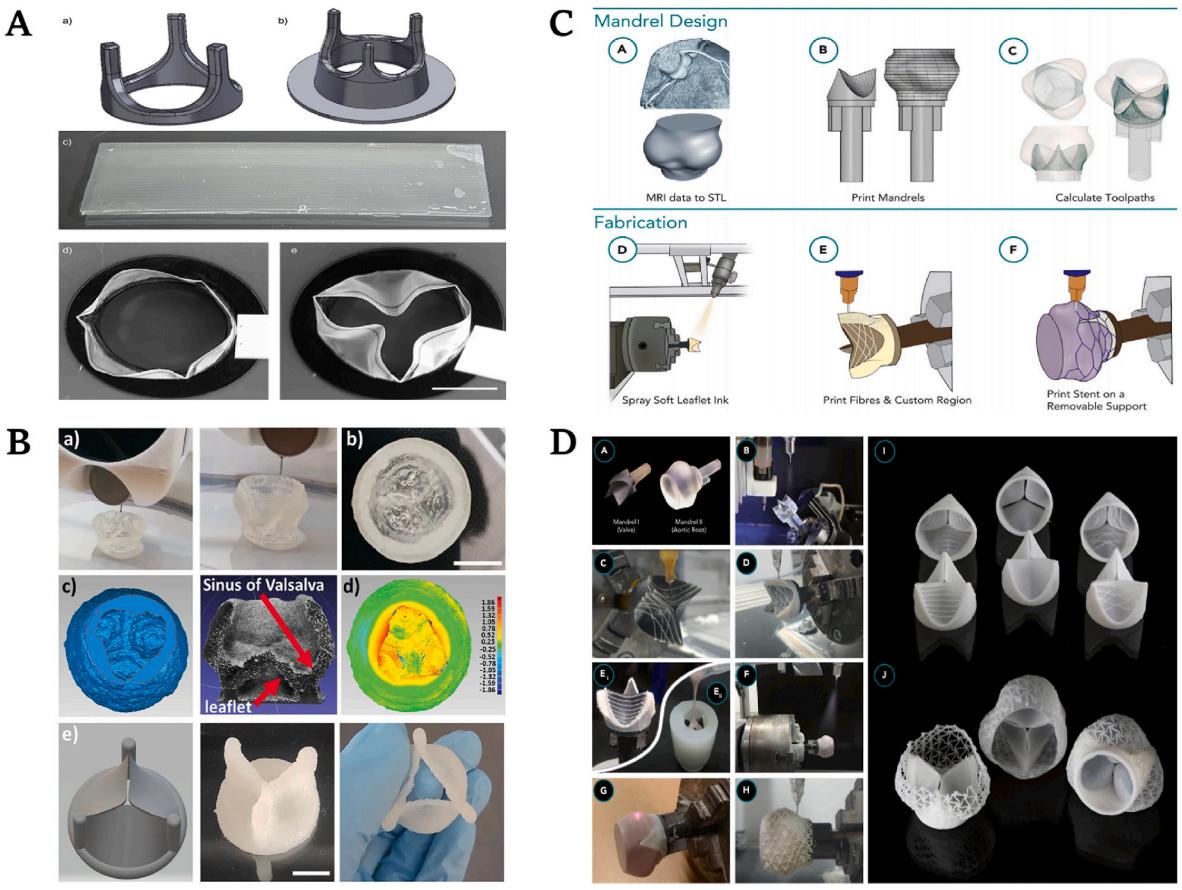

Fig. 8. (A) 3D printing in polymeric valve fabrication. (A) Valve structure composed of PCL and cell-loaded GelMA/PEGDA hydrogel was reconstructed by 3D printing and molding. (B) PVA/gelatin/carrageenan ink (P10/G2.5/C2.5) was used for the 3D printing heart valves, which were designed by CAD [88]. (C) Bionic synthetic valve fabrication process. Aortic root configuration using CT imaging, fabrication of two mandrels (one for valve inner surface and one for root geometry), fabrication of leaflets using silicone ink, and design of a temporary cover for aortic geometry. (D) A multi-material additive manufacturing process used to produce custom silicone heart valves.

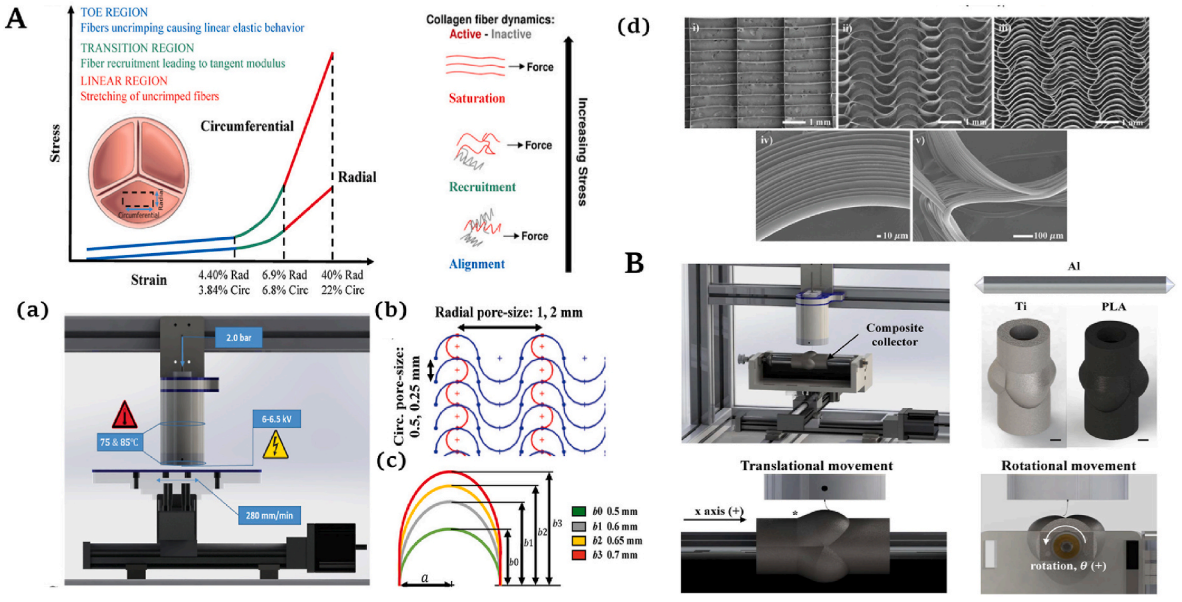

Fig. 9. Melt electrospinning writing (MEW) in polymeric valve fabrication. (A) Deformation behavior of collagen fibers of the aortic valve, showing the J-shaped strain hardening response. a) MEW device to fabricate medical PCL frameworks. b) Support structures with different opening sizes are designed. c) The degree of curvature is varied to control the strain under maximum stress. d) SEM images of novel PCL frameworks [86,108]. (B) Front (left) and side (right) planes of MEW settings using pure aluminum (Al-only), aluminum-titanium (Al–Ti), and aluminum-polylactic acid (Al-PLA) mandrel models for electric field simulation (scale bar = 5 mm) [64].

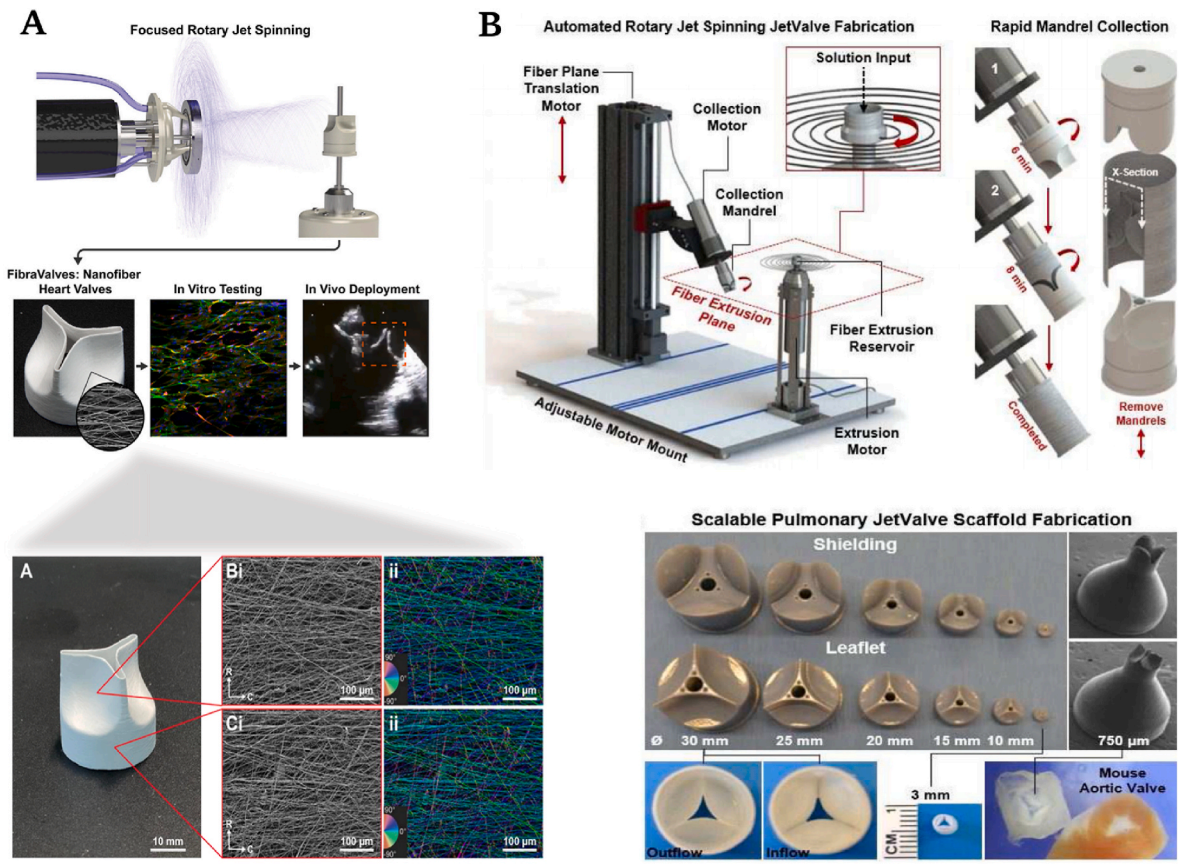

Fig. 10. Focused rotary jet spinning (FRJS) in polymeric valve fabrication. (A) On the basis of rotary jet spinning, the polymer volume is discharged through the nozzle by high-speed centrifugal force, and the fiber deposition is obtained on the custom mold. SEM images show the fiber orientation of the pulmonary FibraValve in different regions on the mold [112]. (B) Schematic diagram of the JetValve device prepared by rotary jet spinning technology. A two-step mandrel collection system was used consisting of a leaflet mandrel and shielding mandrel [114].

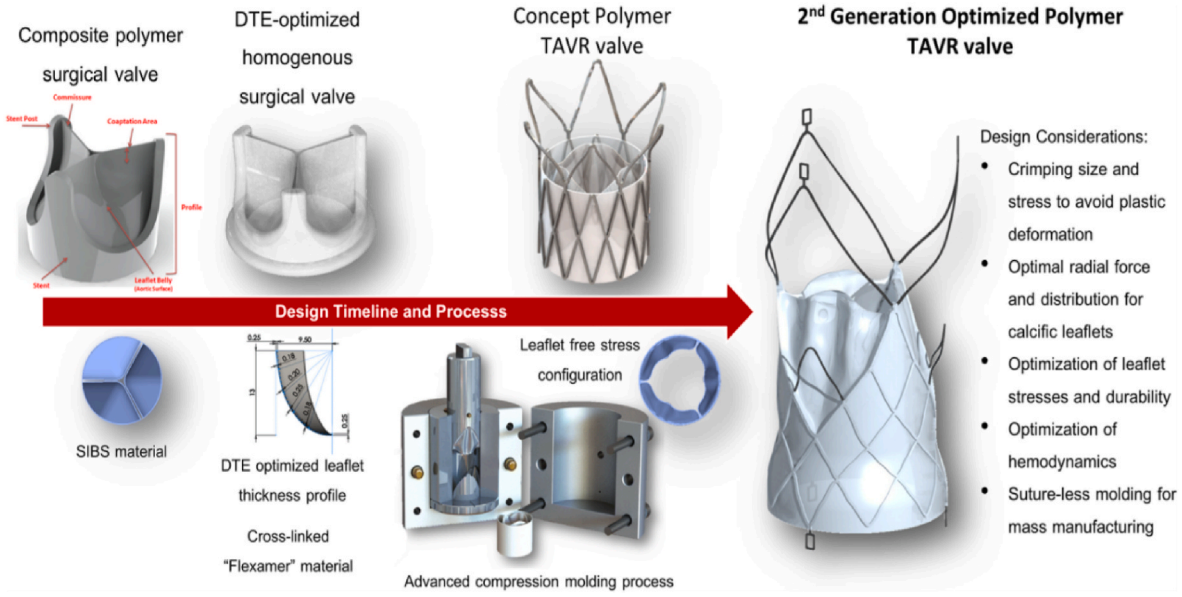

Fig. 11. Graphic illustration of the first-generation Polynova polymer SAVR valve and the second-generation polymer TAVR valve from the initial polymer surgical concept design to the optimized Polynova-2 polymer TAVR device [69].

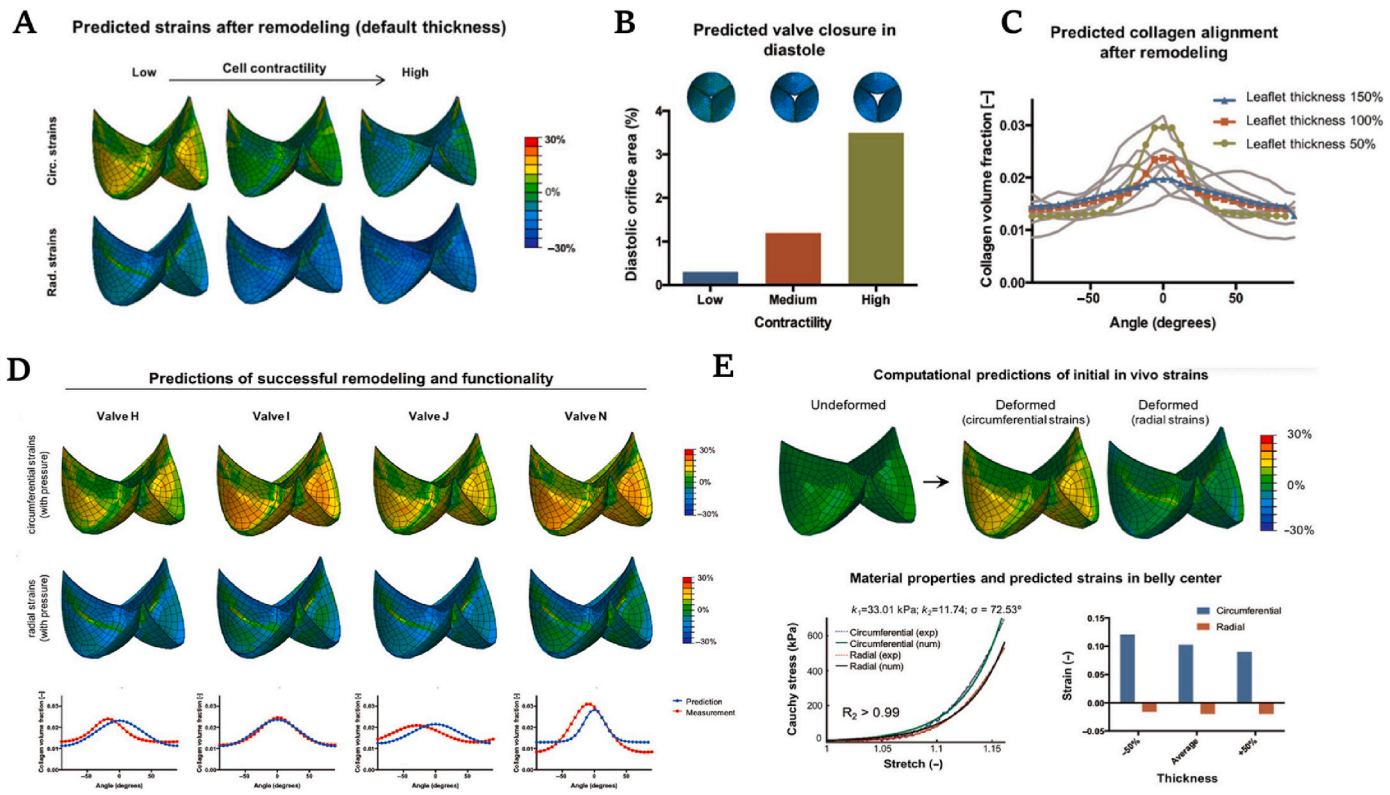

Fig. 12. Computer-aided design (CAD) in polymeric valve fabrication. (A) Predicting circumferential and radial strain conditions with cell contraction force. (B) The predicted valve closure in diastole. (C) Predictions of collagen alignment changes in leaflet thickness. (D) Predicted circumferential and radial strains during hemodynamic loading, measured (red) and predicted (blue) collagen orientation of valves. (E) Stress changes *in vivo* predicted by the computational model (circumferential and radial layers), and average biaxial tensile experimental results (n = 4) [68]. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

linear low-density polyethylene (LLDPE) as a leaflet material for the design of transcatheter heart valves, and the stress distribution of the leaflets in diastole was obtained from computer simulations of the parametric studies and the design of the leaflet's stent was carried out (Fig. 13).

4. Advances in polymeric valve product research

In recent years, with the emergence of novel polymer synthesis strategies, several polymeric valves with practical clinical applications have been developed and designed (Table 3). The clinical trial of Foldax® Tria™ valve in the U.S. began in 2019, with a total of more than 100 implanted cases, making it the polymeric valve with the most implantation present. The clinical trial of Tria™ mitral valve has also been conducted in India in 2023, with a surgical volume of 30 cases. China's polymer SIKELIA ™ TAVR valve, which will be implanted for the first time in 2022 by the team led by Junbo et al., has completed more than 10 clinical trials, with long-term safety and efficacy data awaiting the release of clinical follow-up data [116]. Other polymeric valves (both surgical and interventional) have also shown promising early *in vitro* results (Fig. 14).

4.1. Tria ™ (Foldax®, USA)

Foldax® Corporation (USA) is currently a pioneer in the field of polymeric valve research and development worldwide, and the Tria™ heart valve platform is the world's first polymeric heart valve platform that can be applied to aortic, mitral and tricuspid valve replacement. Its polymeric aortic valve, the Tria™ Heart Valve, is made from a revolutionary new material—LifePolymer [117], and the polymer material of choice is silicone-based polyurethane urea (SiPUU), which is synthesizable as a modified elastic polyurethane by a two-step solution polymerization process. The leaflet thickness is 1/3 that of biological valves, and the Foldax® Tria™ surgical aortic valve consists of a self-expanding nickel-titanium alloy with a 10 mm sealing sleeve. The Tria™ valve is the only heart valve manufactured by robots, and the mechanized manufacturing achieves high precision, quality and repeatability, reducing the uncontrollable factors associated with manual manufacturing of traditional valves, which greatly improves the economics of heart valve manufacturing.

The test results of LifePolymer material demonstrated a high degree of biocompatibility and durability close to that of the human body, providing a solid basis for further research. Under accelerated *in vitro* fatigue testing conditions, it has demonstrated an effective opening area and transvalvular differential pressure similar to that of the Edward Perimount valve, and the Foldax® surgical mitral valve and transcatheter aortic valve replacement devices are moving into the clinical phase. According to a recent report, Foldax® has entered the human clinical trial phase in India in 2023, with the first 30 patients having received the Tria™ surgical mitral heart valve [136]. One year after implantation, patient feedback on transvalvular pressure difference (TPD), effective opening area (EOA) and cardiac function data showed significant improvement.

4.2. TRISKELE® (UCL Cardiovasular engineering Laboratory)

As early as 2005, the Cardiovascular Engineering Laboratory at the University of London (UCL) developed and designed a novel Si_8O_{12} nanocomposite polymer for surgical tricuspid valves and a POSS-PCU-based transcatheter tri-leaflet valve, Polymer TAVR TRISKELE®, which consists of a nitinol wire stent, leaflet material, sealing cuffs, and a skirt [53], and an automated dip-coating process yields a valve with an

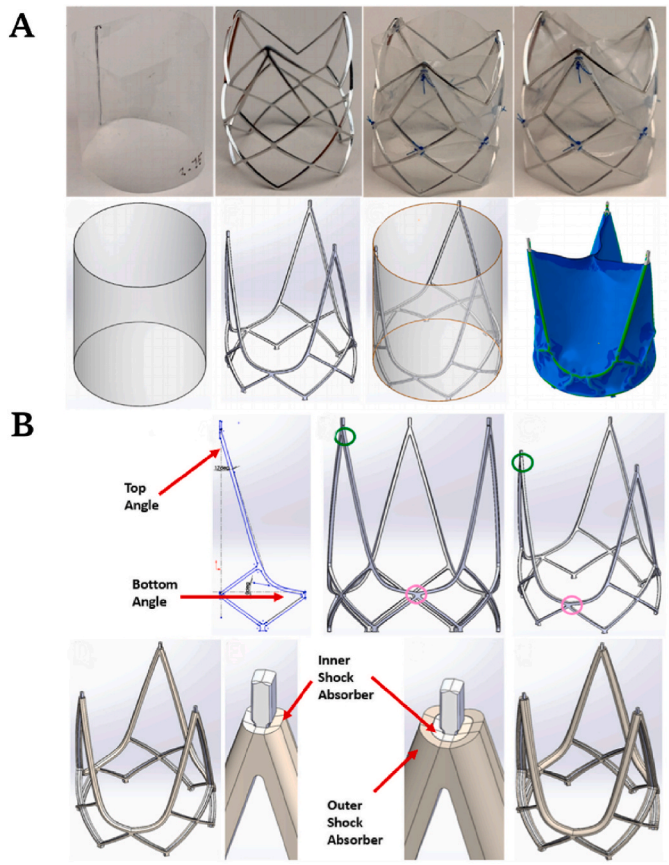

Fig. 13. (A) The assembly steps of LLDPE-TAV. (B) Design view of the CAD carrier. It shows a 2D CAD model of a 1/6 bracket that covers half of a leaflet, where the green circle represents the upper corner and the pink circle represents the lower corner [67]. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

average thickness of 130 ± 10 μm [137]. In comparisons with two currently commercially available TAVR devices, the Edwards SAPIEN XT and the Medtronic Corevalve, it showed that the hemodynamic parameters of the TRISKELE® valve were approximately equivalent [138]. The lower regurgitation rate of the TRISKELE® valve found in the aortic root is thought to be due to the design of the sealing cuff that surrounds the valve, effectively reducing the gap with the natural tissue and reducing the risk of perivalvular leakage.

Based on the same strategy, nanocomposites of functionalized graphene oxide and polycarbonate-polyurethane (FGO-PCU) (trade name "Hastalex") were compared to GORE-TEX, a commercially available polymer for cardiovascular medical devices, with Hastalex showing superior performance in terms of mechanical properties, hemocompatibility, and resistance to calcification, which is still in preclinical testing.

4.3. SAT (Straight Access Technologies Inc.)

Straight Access Technologies (SAT) is a spin-off company from the University of Cape Town, South Africa. SAT has developed a novel balloon-expanded polymer aortic valve for patients with rheumatic and degenerative diseases. Due to the better biostability of the siloxane chain segments and the better mechanical strength of the carbonate chain segments, a PCU-based polymer material, CarboSil thermoplastic silicone-polycarbonate-urethane (CarboSil 2080A TSPCU), was obtained from DSM, Netherlands [139]. The SAT polymeric valve places the prosthetic valve in a hollow balloon, allows free blood flow without the need for rapid pacing, including a transapical and transfemoral approach, allows physicians to confirm ideal valve positioning through haptic feedback, and can be manufactured in batch automatically. The product has been endorsed by the World Heart Federation and clinical trials will commence following regulatory approval.

4.4. STEALTH and MASA valves (PECA Labs)

The STEALTH transcatheter polymer aortic valve and the MASA polymer pulmonary valve are the two polymeric valves currently under development by PECA Labs. The STEALTH valve is designed with fully polymerized leaflets to achieve an ultrathin delivery system that reduces the incidence of vascular injury. The MASA valve is a pulmonary valve suitable for use up to the age of 22 years that effectively reconstructs the right ventricular outflow tract. The world's first implantation of the MASA valve was completed at the Children's Hospital of Philadelphia in June 2023 in a 21-month-old infant. This will also serve as part of an early feasibility clinical study of the MASA valve, and it is believed that the development of the MASA valve will allow for significant improvements in the treatment of pediatric cardiovascular congenital heart disease.

4.5. Polymer TAVR SIKELIA™ (Yixin medical)

Shanghai Yixin Med's self-developed polymer TAVR SIKELIA™ valve has taken the lead in China's polymeric valve research & development (R&D). In July 2022, Junbo et al. successfully implanted the world's first polymer transcatheter aortic valve in an 80-year-old patient, bringing China's valve therapy R&D into the polymer era and demonstrating that China has begun to lead the world in innovation in some areas of cardiovascular medical devices. In 2023, the 1-year postoperative follow-up results of the world's first transcatheter polymer TAVR patient has been announced [116].

The polymer SIKELIA™ TAVR valve is a self-expanding valve composed of a nickel-titanium alloy with synthetic polyurethane (PU) nanocomposites [116]. The leaflet material is only 1/3 of the thickness of biological valves and exhibits good biocompatibility, and the polymer surface has been designed and optimized to effectively reduce irritation and rejection, which improves the durability of the valve *in vivo* and reduces the risk of some complications. In terms of processing, the wire-riveted valve frame and leaflets do not require suturing, which allows for automated production and standardized quality control, and significantly reduces the cost of production. The innovation lies in the large mesh design and memory alloy wire riveted structure, which increases the flexibility and adaptability of the valve frame to a certain extent. In actual surgical procedures, for some complex anatomy and severely diseased aortic valves, such a design can make the valve better adapt and achieve an effective fit, improving the success rate of the surgery. Besides, the design of polymer SIKELIA™ allows for easy retrieval and secondary positioning.

4.6. PoliaValve (Heart Ridge Med)

PoliaValve, Heart Ridge Med's independently developed polymer aortic surgical valve, has completed the first formal animal study of a domestically manufactured polymer surgical valve and is in a leadership position. The polymer surgical valve demonstrates good fatigue resistance and anti-calcification properties compared to biological valves. In addition, Heart Ridge Med is the first company in China to pioneer automated robotized valve manufacturing. The processes of impregnating and forming the leaflet material, drying and thickness measurement can all be replaced by robots, which ensures the stability of the product to a certain extent and enables an intelligent, high-precision production model, which in turn lowers the costs.

4.7. TaurusApex® (Peika medical)

TaurusApex® polymeric valves are the fourth generation of

Table 3
The characteristics and development stages of polymeric heart valve products (PHVs).

	Devices	Polymer	Characteristics	Development stages	Ref.
Foldax®	Tria™ TAVR	SiPUU (LifePolymer)	-1/3 thickness of bioprosthetic valve (controllable thickness), -Manufactured by robot -NiTinol frame	-The first clinical trials in India in 2022 -Mitral polymeric valve implantation in India in 2023	[117, 118–120]
	Tria™ SAVR	SiPUU (LifePolymer)	-Valve structure: polymer leaflets, polyether ether ketone scaffold (PEEK), PTFE suture ring	/	[117, 118–120]
SAT (Strait Access Technology)	TSPCU TAVR	TSiPCU	-Scaffolds, one-piece leaflet, skirt design	-Under preclinical tests	[121–124]
UCL (cardiovascular engineering lab)	TRISKELE® TAVR	POSS-PCU	-Valve can be recovered and repositioned after release	-Complete trial in sheep, FIM study in 2023	[125]
PECA Labs	MASA (pulmonary valve)	ePTFE	-Double leaflet structure -It is suitable for young patients (<22 years), accompanying with growth	-The world's first implant in a child at Children's Hospital of Philadelphia in 2023 -Clinical follow-up data	[126]
	STEALTH TAVR (aortic valve)	/	/	/	/
University of Cambridge, Bristol	Polivalve SAVR	SEPS/SEBS copolymer	/	/	[127]
	Polynova SAVR	x SIBS	-NiTinol frame, -Excellent hemocompatibility and resistance to calcific deposition	-Under preclinical tests	[128–130]
Innovia LLC (USA)	Innovia SAVR	SIBS	-Calcification and thrombosis occurred	/	[131,132]
	Hastalex SAVR	FGO-PCU	-Two unique sides: shiny and opaque, mechanical, hemocompatibility and calcific resistance properties	-Under preclinical study	[130,133]
InFlow (CardValve Consortium, Poland)	Inflow ATHV	PU-PUS copolymer	-Balloon-expandable PTHV	-Under preclinical study	[134]
Xinling Maid	PoliaValve SAVR	/	-First manufactured by robots in China	-Animal tests completed in 2023 -Calcification results show that the number of crystals is one-third of that of biological valves	[34,135]
Yixin Medical	SIKELIA™ TAVR	BioDura® polymer composites	-Thickness 130 ± 10 μm, Ni-Tinol frame (stent design), dry pre-assembly factory -The stent can still be completely recovered after full deployment. -Automatic production (craft) -Skirt structure effectively prevents perivalvular leakage	-Complete the FIM SIKELIA™ Polymer TAVR implantation in 2022 -Clinical follow-up	[34,116, 135]
Peika Medical	TaurusApex® (VI) TAVR	/	-Five layers of hydrophobic biomimetic structure, -Manufacturing process (laser fusion cutting) replaces manual sewing of valves	-Animal test data released in 2022 -Clinical trials await in 2023	[34,135]

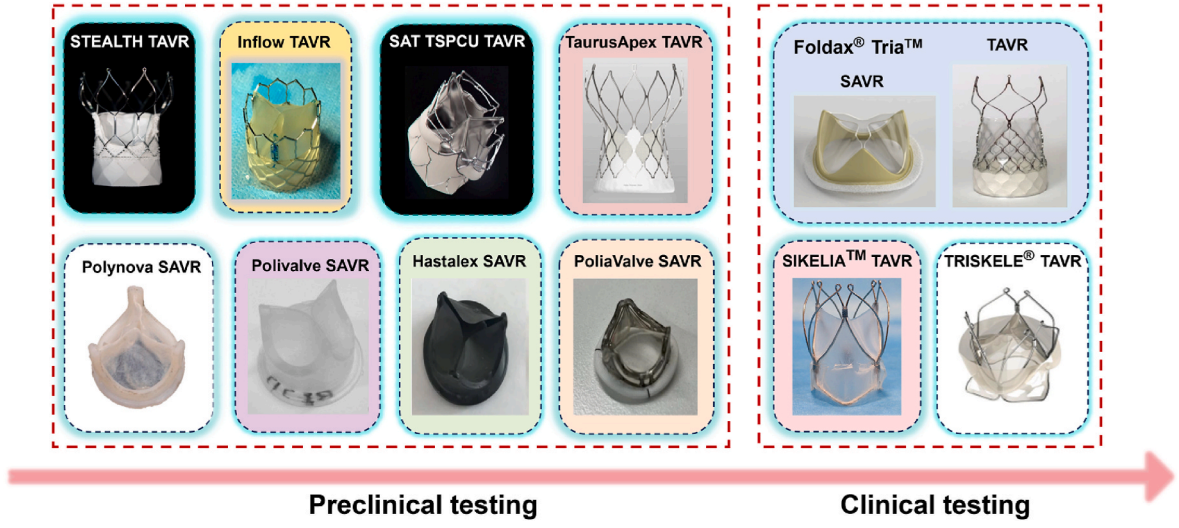

Fig. 14. Summary of current research on polymeric heart valves product (including both TAVR and SAVR) and schedule status.

independently developed interventional valves. TaurusApex® polymeric valves utilize a five-layer bionic polymer fiber braid as the leaflet material, and a sponge and ventricular layer with varying ratios of elastomers to provide improved mechanical stress while maintaining anisotropy similar to natural leaflets. TaurusApex® polymer leaflets are laser cut and sealed, reducing the need for manual suturing and improving yield. TaurusApex® focused on addressing the lack of durability of bioprosthetic valves, and at this stage the valve maintains stable

hemodynamics after 200 million accelerated fatigue tests with no significant leaflet damage, demonstrating excellent durability. The valve has completed animal studies and is poised to enter clinical trials.

5. Challenges and opportunities

However, although research and development of polymeric valves have been carried out by various research teams for decades, most of them are at the preclinical stage and most of them have failed to proceed to the next stage due to biocompatibility, durability and calcification issues. This can be summarized by the following factors.

5.1. Factors that determine the development of PHV

(i). Durable polymeric leaflet material is the initial requirement for prosthetic valve performance. We can consider the following factors that affect the durability of polymeric heart valves: First, under sustained and turbulent hemodynamic conditions, prolonged periods of high *in vivo* blood flow often result in significant leaflet deterioration, such as perforation and delamination, which is manifested by a decrease in EOA and an increase in TPD. Reduced EOA leads to reduced local blood flow, which in turn affects local blood supply and requires more energy compensation to regulate valve opening and closing, thereby accelerating leaflet deterioration. Additionally, the high velocity blood flow environment in the body creates localized stresses around the leaflets, and overly concentrated stress distribution can also affect valve life. This can have a direct impact on the late life durability of valves.

Besides, it is generally accepted that interventional bioprosthetic heart valves with crosslinked acellular matrix are at risk of fibrin rupture after compression, as the fibrin fractures are easily caused by the compression process and these fibrin fractures form calcium deposit site. Above fibrin rupture phenomenon is caused by the less flexible toughness and poor mechanical strength nature of the natural physical property of acellular matrix materials. However, the performance advantages of the well-designed polymer elastomers themselves are not easy to form fibrin rupture and generate such calcification sites. As a result, this is where the potential for the development and design of polymeric valves lies.

Therefore, current research has addressed the durability issue by focusing on parameters such as height, thickness, leaflet length, and leaflet curvature in the design of polymeric valves, as well as improving the overall radial stiffness of polymer valves to increase durability. We have found that the size of the leaflets has a significant impact on the durability of the valve, with too small a leaflet size leading to greater leaflet curvature and significantly reduced hemodynamic performance. And these folds can also affect the mechanical properties locally.

Finally, the nature of the polymer material itself is also an important factor. We can try to explore the novel polymers by synthesizing new materials or compositing/blending several materials, with better mechanical properties, biocompatibility and other properties. Finally, individual differences between patients are also a concern, and their own physical condition may also have an impact on valve survival *in vivo*, such as the risk of developing structural complications of the valve.

(ii). The geometric configuration design of polymeric valves is critical to improve valve function. By using advanced manufacturing processes such as electrospinning technology, 3D printing technology, the microstructure (fiber arrangement, pore size regulation) can generally be modulated. The use of geometric configuration for the design of valve leaflet dimensions now enables the transition from 2D planar design to 3D design. Computer-aided design can help us to pre-screen an *in vivo* hydrodynamic or stress distribution situation with predetermined parameters, thus saving on the cost of labor.

(iii). A suitable validation method is an important tool for the development of prosthetic valves and an important node to increase the success rate of research and development. Aside from the basic physical and chemical properties of biomedical materials to meet the needs of the valve, hydrodynamic testing and durability testing are the basic testing needs to verify the viability of the valve. Pulsatile flow testing is a test device that can simulate the pulsatile flow state after *in vitro* implantation, and the results of pulsatile flow tests are generally concerned with parameters such as TDP, EOA and regurgitant fraction (RF). The steady flow test evaluates the forward flow resistance of the valve, and the durability test predicts the durability of the valve by using accelerated *in vitro* fatigue testing (according to ISO 5840-3 standard: the number of cycles is not less than 200 million for aortic valves) to evaluate a predicted time of failure. Therefore, *in vitro* hydrodynamic indicators are important guides for the development of prosthetic heart valves as medical devices.

5.2. Future directions

5.2.1. Optimal designing of PHVs

There are still many challenges in the optimization of valve design at this stage. For synthetic valve scaffolds, pore size and porosity, thrombosis, calcification, and convolutional retraction of the valve leaflets will be the focus of future research.

(i). Pore size and porosity have important implications in tissue-engineered heart valve applications, affecting cellular behavior, tissue growth, and mechanical properties of the scaffold. It is generally believed that pore sizes in the range of 50–300 μm are suitable for cell infiltration, and the nanometer scale is more conducive to tissue regeneration. (ii). Polymeric valves can be designed as both interventional (TAVR) and surgical (SAVR) valves. In general, the leaflets thickness of TAVR is thinner than that of SAVR, which facilitates smooth placement of the valve through the delivery system, whereas there is mechanical damage to the leaflets during valve compression, so attention should be paid to the degree of leaflet curvature.

5.2.2. Regenerative valves for congenital pediatric patients

Regeneration of prosthetic valves in children with congenital heart disease remains a challenging issue. There is an urgent clinical need for pediatric heart valve implants that can grow with children, as current valve implants cannot accommodate the somatic growth of young patients. The FibraValve, developed by the Parker research team at Harvard University using FRJS technology, is a valve that is designed to attract living cells to regenerate and form new tissue in young patients with pediatric valve disease caused by rheumatic fever. Similarly, Nianguo 's team at Union Hospital, Tongji Medical College of Huazhong University of Science and Technology developed a decellularized porcine aortic valve and performed clinical trial by placing in the pulmonary valve position, which has now been implanted in seven cases, significantly improving the valve needs of pediatric patients with congenital heart disease. After implantation of the new decellularized valve, autologous cells grow inside the valve material, which can remodel and repair tissue and is less prone to calcification and decay. The growable valve breaks the traditional design concept of prosthetic biological valves and expands the development of regenerative medicine, which has already shown some clinical potential. However, there exists a key issue that needs to be addressed in the future is the imbalance between tissue regeneration and material degradation, leading to leaflet shortening and thickening after implantation.

5.2.3. Tissue-engineered heart valve design

Seeded cells, scaffold material, and cell implantation are the three main factors involved in the construction of tissue-engineered heart valves (TEHV). They could grow, repair, and remodel like normal human heart valves. Over the past decades, several in situ tissue engineering strategies have been established to create TEHV using a variety of scaffolds, including natural scaffolds (collagen scaffolds, decellularized scaffolds, etc.) and synthetic scaffolds (typically polymer-derived materials, etc.). Human and animal valve tissues are immunogenic and require decellularization (Triton X-100, SDS, etc.) for homografts and xenografts. The ideal scaffold material can maintain a three-dimensional porous structure, which is important for cell growth and nutrient metabolism, and polymeric valves can be prepared to provide a better material-cell interface to facilitate seed cell attachment and growth. In the case of synthetic materials, we can also achieve a state of equilibrium between the neoplastic tissue and the degradation process through a controlled rate of biodegradation. Furthermore, continuous modification of polymer material properties is expected to provide better scaffold mechanical properties to support nascent tissue mechanically.

It is clinically accepted that autologous cells are the best choice in combination with normal human valve-specific valve endothelial cells and valve mesenchymal stromal cells. In addition, seed cells for tissue-engineered valves have been constructed based on the role of vascular endothelial cells in antithrombotic formation, inhibition of platelet aggregation, and secretion of vasoactive factors. Endothelial progenitor cells and stem cells have also been investigated as sources of seed cells. Co-culture of seed cells and scaffold materials in an *in vitro* bioreactor is essential for tissue-engineered valve construction. The construction of tissue-engineered valves is expected to achieve the advantages of low immunogenicity, better biomimetic properties, excellent biocompatibility, and self-growing function. Polymeric valves can be considered in the current research to create synthetic scaffolds with excellent performance through advanced fabrication techniques, which can provide a better survival environment for seed cells as well as degradation ability. Thus, ideal tissue-engineered valves can be constructed, which can promote the generation of extracellular matrix micro-environment as well as tissue regeneration.

6. Summary and outlook

The current global valve market, the utilization rate of mechanical valves is 70 % and bioprosthetic valves is 30 %. Global TAVR market shows an oligopoly situation, companies such as United States Edward, Medtronic and St. Jude occupy the vast majority of global market share. The life expectancy of polymeric valves has been significantly improved as compared to the biological valves and they are expected to function properly up to 25 years. Durability, good biocompatibility, and low risk of calcification are potential advantages of polymeric valves. Overall, the advantages of polymeric valves over both mechanical and bioprosthetic valves are as follows.

(i). Increased durability. Biological valves have an average lifespan of 8–10 years post-implantation, and their durability is limited by many factors such as leaflet degradation and thrombosis, whereas young patients may face repeated valve replacements throughout their lives, and at this stage, young patients' clinic is still dominated by the idea of "valve-in-valve", the development of polymeric valves is expected to address the needs of the young patient population and realize a longer lifespan of valves. The development of polymeric valves is expected to address the needs of the younger patients and achieve longer service life. Further clinical follow-up data are required to demonstrate this prediction.

(ii). Improved biocompatibility. The choice of polymer materials also reduces the immune rejection and inflammatory reactions caused by animal-derived materials to some extent. Inflammatory factors and endothelial damage lead to inflammatory responses. Studies have shown that α-Gal is a carbohydrate present on the surface of cell membranes in mammals (except humans) and that xenograft implantation of bioprosthetic valves induces an immune response specific for the α-Gal antigen in the human body.

(iii). Reduced cost and improved product stability. Polymeric valve manufacturing can be automated in conjunction with artificial intelligence. For example, the laser cutting technology and integrated molding technology currently used improve the valve sewing process, which significantly reduce labor costs and also ensure product consistency and stability from batch to batch.

However, there is not a single polymeric valve commercially available worldwide until now. Most polymeric valves in development are still in preclinical testing. New advances in materials science should be incorporated to guide the selection of appropriate raw materials. Preparation techniques should be developed toward precision and engineering, using computer-aided modeling to simulate leaflet structure and create customized valves. Researchers should focus more on the potential complications of polymeric materials, and clinical data are needed to further support their efficacy and safety. Although polymeric valves have now demonstrated some advantages over mechanical and biological valves, clinical follow-up data published should be used to guide the optimization of valve design.

CRediT authorship contribution statement

Yuanchi Wang: Writing – original draft, Conceptualization. **Yulong Fu:** Resources. **Qingyu Wang:** Investigation. **Deling Kong:** Writing – review & editing, Supervision, Conceptualization. **Zhihong Wang:** Writing – review & editing, Project administration, Methodology, Conceptualization. **Jing Liu:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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