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Development of Innovative Biomaterials and Devices for the Treatment of Cardiovascular Diseases

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Cardiovascular diseases have become the leading cause of death worldwide. The increasing burden of cardiovascular diseases has become a major public health problem and how to carry out efficient and reliable treatment of cardiovascular diseases has become an urgent global problem to be solved. Recently, implantable biomaterials and devices, especially minimally invasive interventional ones, such as vascular stents, artificial heart valves, bioprosthetic cardiac occluders, artificial graft cardiac patches, atrial shunts, and injectable hydrogels against heart failure, have become the most effective means in the treatment of cardiovascular diseases. Herein, an overview of the challenges and research frontier of innovative biomaterials and devices for the treatment of cardiovascular diseases is provided, and their future development directions are discussed.

1. Introduction

Cardiovascular diseases have become the leading causes of death worldwide, accounting for 17.7 million deaths per year, and this number is expected to increase to 23.6 million by 2030,[1,2] which is much higher than that of cancer and other diseases. Coronary heart disease (CHD) and structural heart disease (SHD) are the main cardiovascular diseases for the high morbidity and mortality. The increasing burden of cardiovascular diseases has become a major public health problem, and how to carry out active and reliable treatment of cardiovascular diseases has become an urgent global problem to be solved. At present, implantable biomaterials and devices, especially minimally invasive interventional ones, have become the most effective means in the treatment of cardiovascular diseases. As the second largest market in the medical device industry, biomaterials and devices for the treatment of cardiovascular diseases, such as cardiovascular stents and artificial grafts for CHD, and artificial heart valves, cardiac occluders, cardiac patches, atrial shunt, and injectable hydrogels against heart failure for SHD, are essential for human health.[3,4] In this review, the research overviewed falls into the research status, challenges, and research frontier of innovative biomaterials and devices in the treatment of cardiovascular diseases and prospects of their future development direction.

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2. Cardiovascular Stents

A typical feature for CHD is associated with the development of plaque within the vascular wall, mainly due to atherosclerosis, which is also recognized as an ongoing process of chronic inflammatory disease. Without treatment, plaques can easily rupture and lead to acute vascular occlusion, ultimately causing myocardial infarction and potential stroke.[5,6] Mantovani and co-workers illustrated generally how to select proper therapeutic techniques to treat CHD at different stages.[7] Pharmacological-based treatments are effective in the early stages of CHD by control of blood pressure and cholesterol levels, but are usually insufficient once the disease evolved into severe stages.[8] CHD treatment was achieved through coronary artery bypass grafting, especially for patients with multivascular disease.[9] However, in recent decades, it has been surpassed by use of percutaneous coronary intervention (PCI), accompanied with continuous technology development, especially with the wide application of cardiovascular stents, which will be systematically reviewed hereunder.

2.1. Development and Current Status

Before the invention of stents, Andreas Gruentzig, a German physician, tried the first percutaneous transluminal coronary angioplasty in 1970s.[10] The improvement was limited in long-term clinical outcomes until the introduction of coronary stents in PCI.[11] Stenting, first performed in 1986 by Sigwart and Puel, as an innovative invention in PCI, could give mechanical support against vascular wall after the expansion of bare metal stent (BMS), showed definite advantages in reducing restenosis rate compared to balloon angioplasty alone.[12] Since then, within the fast development in stent design and material evolution, stent implantation has made great progress and saved tens of millions of lives during the last two decades, indicating the great contributions of stenting in PCI.[13–16] **Figure 1**A summarized the time point of the development of coronary angioplasty.

For the innovation of PCI, feedback on clinical outcomes is the most direct driving force for the development of interventional materials and devices. For instance, although the reduction of restenosis was achieved by BMS, the excessive healing

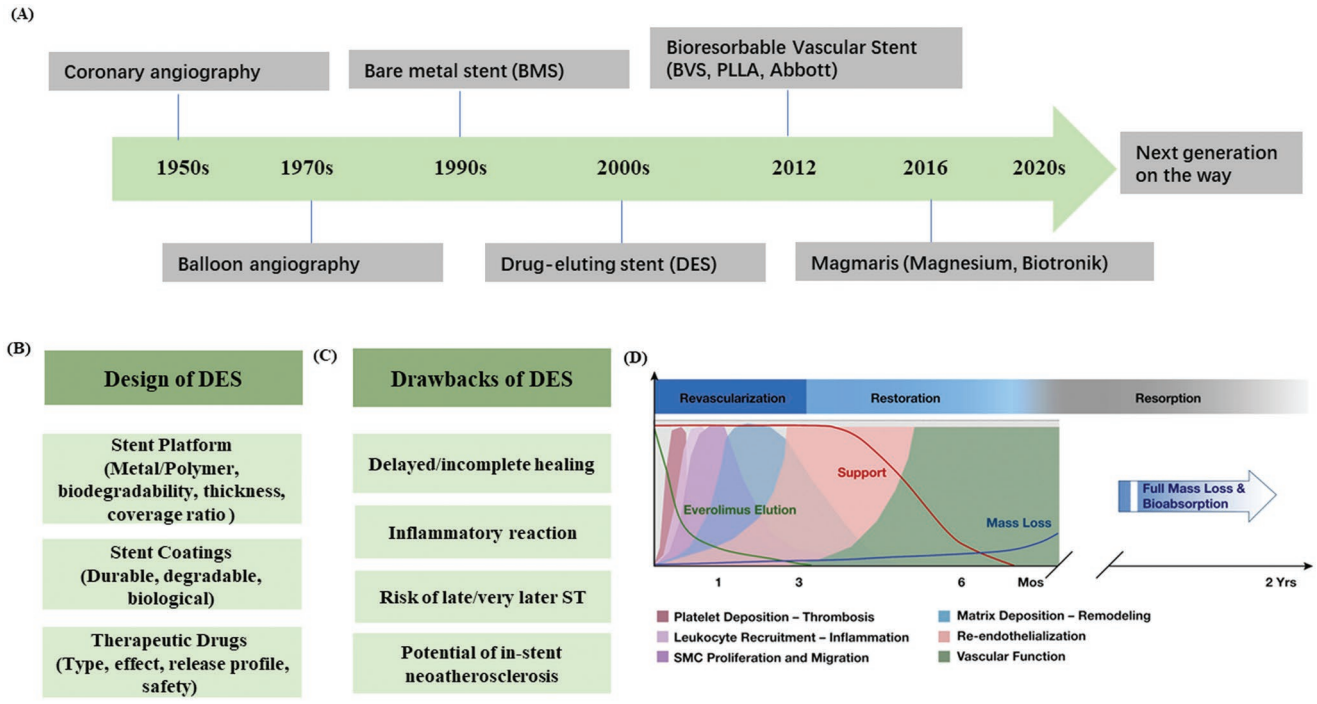

Figure 1. A) The milestones in coronary angioplasty. B) The design principles of DES. C) Some drawbacks existing in DES and D) the representation of three phases of functionality and temporal physiological response for a bioresorbable scaffold. D) Reproduced with permission.[20] Copyright 2014, Elsevier.

of neointimal caused a new pathological state, so called in-stent restenosis (ISR), with an average rate of around 25% or even higher.[15] Then came the successful used of drug-eluting stents (DESs) in the beginning of the 21st century, which was a combination of mechanical support and pharmacological treatment.[16] By localized delivery of antihyperplasia drugs, compared with BMS, a significant reduction in restenosis was demonstrated, and DES has become the most effective treatment for patients with CHD. DES is also constantly innovated in terms of polymeric coatings, stent structs, and types of eluted drugs.[17] After a brief period of high spirits, more clinical data revealed that during drug-eluting process, not only the hyperplasia of smooth muscle cells but also the healing of endothelial cells was inhibited, which then ultimately caused a risk of late/very late thrombosis formation, usually around 2–5%.[18] Besides, a high demand for the recovery of the physiological pulsation function of blood vessels on the stenting site was recommended, which could not be found on nondegradable DES.[19] Upon this, fully bioresorbable stents (BRSs) were designed to solve the problems in metallic DES, which permanently existed, thereby might prevent normal coronary vasomotion, and might long-term foreign-body responses.[20] It is worth noting that though BRS could be considered as an ideal solution, the drug-eluting strategy for BRS does not change, which means the clinical outcomes associated with late/very late thrombosis might also be a challenge that could not be ignored. Thus, besides the bulk stent struct material/structure design, potential functional coatings that can selectively direct the smooth muscle cell/endothelial cell fate are also attractive.[21] More experiment and animal or clinical evidence should be addressed to carefully direct the future design of cardiovascular stents, especially for bioresorbable cardiovascular stents.

2.2. DES

Upon the nature of ISR, it is then clear that biological targets could be addressed to some extent by pharmacological therapy.[16] Given that the systematic drug therapy failed to deliver effective drug on the lesion site, DESs that can reserve and locally release antihyperplasia drugs were invented to decrease the incidence of severe ISR. Currently, implantation of DES is the main treatment strategy in PCI revascularization procedures for the patients with computer-aided design (CAD). A typical DES consists of three parts (Figure 1A): 1) stent platform; 2) stent coatings; and 3) therapeutic drugs.[17,22] The modifications to those three components may therefore be considered as incremental evolution. **Table 1** gives an overview of the characteristics of selected DES, including bioresorbable DES (BRS). In this review, they were classified into three categories: A) DES with both nondegradable backbone and coating; B) DES with nondegradable backbone and degradable coating; and C) DES with both degradable backbone and coating (BRS).

2.2.1. Stent Design of DES

In stent design of DES (including BRS), factors like strut thickness, stent material, vessel-wall coverage, drug type, and release profile all influence the final clinical outcomes of DES. Stent design influences near- and long-term clinical outcomes. The mechanical support is important as the primary role of stenting is to open up the blood vessels and keep blood flowing. It is easy for metallic stent but challenging for polymeric stent, which will further be discussed in the biodegradable stent part.

Table 1. An overview of the characteristics of selected DES (including bioresorbable drug-eluting stents). Note: EES, everolimus-eluting stent; NA, not applicable; PEVA poly(ethylene vinyl acetate); PBMA, poly(*n*-butyl methacrylate); PLGA, poly(lactic-*co*-glycolic acid); PLLA, poly(L-lactic acid); PVDF–HFP, poly(vinylidene fluoride-*co*-hexafluoropropylene); SES, sirolimus-eluting stent; ZES, zotarolimus-eluting stent; PMPC, poly(methylpropylphosphocholine); BVS, bioresorbable vascular scaffold; IBS, iron bioresorbable scaffold; PDLLA, poly(D,L-lactide).

Category of DES	Product/manufacturer	Backbone materials	Coating materials	Strut thickness [μm]	Drug type	Complete resorption [months]	Ref.
A	Xience Sierra (EES)/Abbott	Co–Cr	PBMA–PVDF–HFP	81	Everolimus	–	[23]
A	Resolute Onyx (ZES)/Medtronic	Co–Ni (outer) + Pt–Ir (core)	BioLinx	81	Zotarolimus	–	[23]
A	Cypher (ZES)/Cordis	Stainless steel	PEVA–PBMA	140	Sirolmus	–	[24]
A	Endeavor (ZES)/Medtronic	Co–Cr	PMPC	91	Zotarolimus	–	[24,25]
B	Synergy (EES)/Boston Scientific	Pt–Cr	PLGA	74	Everolimus	–	[26]
B	Orsiro (SES)/Biotronik	Co–Cr	PLLA, silicon carbide	60	Sirolimus	–	[27]
B	Ultimaster (SES)/Terumo	Co–Cr	Poly(D,L-lactide-*co*-caprolactone)	80	Sirolimus	–	[28]
B	MiStent (SES)/Micell Technologies	Co–Cr	PLGA	64	Sirolimus	–	[27]
C	Absorb BVS/Abbott	PLLA	PDLLA	157	Everolimus	36–42	[29]
C	DESolve Nx/Elixir Medical	PLLA	Polylactide-based polymer	150	Novolimus	24	[30]
C	NeoVas/Lepu Medical	PLLA	PDLLA	<170	Sirolimus	<36	[31]
C	XINSORB/HuaAn Biotechnology	PLLA	PDLLA	160	Sirolimus	24–36	[32]
C	Firesorb/MicroPort	PLLA	PDLLA	≈120	Sirolimus	36	[33]
C	Amsorb/Beijing Advanced Medical Technologies	PLLA	PDLLA	150	Sirolimus	<36	[34]
C	Magmaris/Biotronik	Magnesium	PLLA	150	Sirolimus	9–12	[35]
C	IBS/Lifetech Scientific	Iron	PDLLA	70	Sirolimus	>12	[36]

The stent must have a low crimped profile and must possess a high degree of flexibility to be delivered. The dilated stent should undergo minimum shortening and should be deployed in accordance with the geometry of the vessel, without any unnaturally straightened vessels. In addition, stents should provide optimal vessel coverage and have high radial strength for minimal radial recoiling. Modular or slotted-tube configurations are the most suitable for manufacturing stents. For the metallic stent platform, investigators focused primarily on increased radial strength and improved deliverability and conformability. Radial strength is mainly directed by the type of bulk metals, the structure of the stent strut (including width and thickness), as well as the architecture of the stents.[37] Regarding the different generations of DES, the first-generation DES (e.g., Cypher and Taxus) adopted the 316 L stainless steel with relatively thick structs around 130–140 μm,[23,24] while newer-generation DES (e.g., Driver, Xience Sierra, Resolute Onyx) possessed thinner cobalt–chromium alloy strut around 80 μm.[26,38] Some preclinical studies revealed that thick-strut stents might have greater thrombogenicity than that with thinner-strut stents, because of the possible accumulation of procoagulant and proinflammatory elements, which might in turn increase the risk of restenosis due to neointimal hyperplasia.[39] More importantly, endothelialization rate was also lower on the stents with thicker struts.[40]

The type of drugs and drug efficacy have a great impact the effectiveness of suppressing the excessive hyperplasia of neointima. Some strategies showed promising via the local release of antioxidants[41] or endogenous molecules (e.g., prostacyclin[42] and nitric oxide[43]) to either inhibit the oxidative stress or mimic the endothelium function after stent implantation. However, the real clinical breakthrough came with the use of the antiproliferative drugs, sirolimus and paclitaxel. Papafaklis et al. had systematically summarized the drug types for DES. Challenges to be addressed were mentioned: 1) identification of a biocompatible carrier that can deliver drug for the required therapy, 2) the most appropriate agent, and 3) determination of the proportion of the systemic dose needed locally.[44] Polymers evaluated for coating stents can be roughly classified as three kinds: 1) durable polymers (poly(*n*-butyl methacrylate), poly(ethylene-*co*-vinyl acetate), poly(styrene-*b*-isobutylene-*b*-styrene), polyurethane, silicone, poly(ethylene terepthalate) (PET), etc., usually applied in the first-generation of DES), 2) biodegradable polymers (polyglycolic or poly(lactic acid) or their copolymers, etc., applied in the newer generation of DES), and 3) biological polymers (hyaluronic acid, fibrin, etc.). Diverse polymer coatings may finally affect the stent thrombosis, endothelialization effect, and inflammation. Pathological data from human DES specimens showed that Xience everolimus-eluting stent (EES) was better in healing and inflammatory response compared to the first generation of DES. Xience EES and Resolution zotarolimus-eluting stent (ZES) both also performed better than first-generation DES.[45] There are typically four classes of drugs (anti-inflammatory, immunosuppressive, antithrombogenic, and antiproliferative) that could be applied in DES. These drugs can reduce restenosis by inhibiting one or more biochemical pathways. Paclitaxel, rapamycin (also named as sirolimus), and everolimus are the most famous ones. It

should be noted that the success of DES is strongly associated with effective delivery of antiproliferation drugs to the target site in the form of treatment concentration, sufficient time, and bioactivity.[46]

2.2.2. Drawbacks of DES

Ever since DES demonstrated the superiority compared with BMS, they had considerable drawbacks, including delayed vascular healing, inflammation reactions, and neoatherosclerosis (Figure 1B), leading to an increased risk in major adverse cardiovascular events over time in patients.[47,48] With more evidence collected, it should be specially realized that in-stent neoatherosclerosis might be the major issues that need to be addressed in the future design of DES. In-stent neoatherosclerosis, is defined as the accumulation of foamy macrophages in the new lining after stent implantation, with or without necrotic core formation and/or calcification.[49] Although DES showed better clinical effect than BMS, the neoatherosclerosis sometimes occurred earlier and more frequently in DES in a pathology analysis,[50] which meant neoatherosclerosis might be a potential cause of late adverse events, such as in-stent restenosis and stent thrombosis. The mechanism of atherosclerosis is mainly related to the barrier function of endothelial cell layer.[51] Healthy endothelial cells could prevent lipoproteins from infiltrating the subendothelium from the lumen. The dysfunction of the endothelial barrier is considered to be the initiating event in neoatherosclerosis.[52]

2.3. Biodegradable Stents

Fully BRSs were designed to overcome the limitations in nondegradable metallic stent and perceived as the 4th revolution technology in PCI.[20,52,53] Although many BRSs had been or are in development, the Absorb Bioresorbable Vascular Scaffold (BVS; Abbott Vascular) was the first US food and drug administration (FDA)-approved device and was widely expected to fulfill the dream of interventional cardiologists.[54] Although the Absorb BVS device was withdrawn from the market because of nonideal market and business value, the application of two BRSs were realized in China (NeoVas and XINSORB).[53,55] Finn and co-workers said that by fully understanding the preclinical and clinical data available for BRS, it is helpful to understand the difference between BRS and DES on the vascular biological reactions.[3] More importantly, how these responses translate into clinical outcomes should be specially discussed in future design.

2.3.1. Biodegradable-Polymer-Based Stents

As compared with typical metallic DES, the application of biodegradable polymer stents has some limitations, including insufficient mechanical strength and radiopacity.[3] Poly(L-lactic acid) (PLLA)-based structs are successfully applied in BRS, the commercialized Absorb BVS, NeoVas, and XINSORB stents all use PLLA. Taking Absorb BVS as an example, PLLA (a semicrystalline polymer) degrades upon hydration to lactic acid and, finally, into carbon dioxide and water through the Krebs cycle.[56] Noteworthy that, although all of the final degradation products are safe, during degradation and owing to the implantation of a foreign material, an inflammatory reaction is induced, consisting of early neutrophil infiltration followed by macrophage and lymphocytic infiltrate.[57] Thus, it is essential to address the desired inflammatory reaction by designing the degradable materials, not only for polymers, as well as for degradable metals.

Especially for bioabsorbable polymer scaffolds, it is generally required that the scaffolds have mechanical support properties comparable to metal scaffolds to support and maintain blood vessels during the support period (usually in the first year after implantation). As the scaffold is completely enveloped by the neointima, the scaffold degrades and is absorbed by tissues. This poses an important challenge for polymer scaffolding design. As needed to meet the radial strength of metallic stent, the thickness of the polymeric BRS is greater, which then hinders the vascular healing process and might increase the risk of stent malapposition because of potential risks like fracture or breaks of the stent during the process of stent absorption.[20] Experts suggested that an optimal implantation technique is likely to improve clinical outcomes to some extent, however, more considerations need to be addressed, including the type of polymer, stent design, strut thickness, and vessel-wall coverage.

2.3.2. Biodegradable-Metal-Based Stents

Biodegradable-metal-based stents were developed in parallel to the PLLA polymeric scaffolds.[58] Potential advantages are the good radial strength with negligible early elastic recoil and a better adaptability to vascular anatomy. Currently, Magmaris stent (Biotronik) is made from a refined, slowdegrading proprietary magnesium alloy. It had a strut thickness of 150 μm, coated with PLLA polymer coating with sirolimus at a concentration of 140 μg cm^{-2}.[59] The resorption process of the bulk material has two main phases: an anodic reaction and then conversion to calcium phosphate.[60] The final product mainly consists of amorphous calcium phosphate. Besides the development of Mg-based degradable metallic stent, the iron bioresorbable stent (IBS), led by Lifetech Scientific is now under clinical study. The strut is plasma nitride-iron stent, with the thickness of about 53 μm, following with sequential coating by zinc electroplating (600 nm) and sirolimus (235 μg cm^{-2})-loaded poly(D,L-lactide) (PDLLA) (12 μm) coating. The radial strength of the scaffold is equivalent to that of the CoCr-EES (Xience Prime; Abbott) stent (123 ± 3 vs 116 ± 6 kPa).[61] A recent study disclosed the detailed information of the in vivo degradation process of IBS in a 36 month's implantation in rabbits. At 13 months after implantation in the rabbit model, scaffold struts could not be identified with the use of optical coherence tomography, and the struts appeared dim and small with ongoing corrosion when imaged with micro-CT.[62] Zn-based biodegradable stent is also under investigation, with which most data are collected from in vitro and animal study.[63]

Moving ahead, compared with degradable polymer stents, bioabsorbable metallic stents are still on the way to explore.

It should be aware that, for degradable metallic implants, although sufficient mechanical properties are required, appropriate corrosion rate that can match the evolution of tissue healing should be fully considered. Diverse stent backbones have different degradation behaviors. For Mg-based stents, fast corrosion might lead to insufficient radical support before completing the mission of vessel remodeling. Degradation products such as hydrogen and hydroxide ions may cause damage to the vessels. On the contrary, Fe-based stents with good corrosion resistance might lead to a long-term retention in the artery vessel. Zn-based stents, seemed to be a potential candidate to balance the corrosion rate between Fe- and Mg-based struts.[64] Besides, the metabolism of degradation products also should be further clear up.

2.3.3. Considerations of the Development of BRS

The developing of Absorb BVS has provided important information about strut thickness, vessel-wall coverage, and their influence on clinical outcomes. New generation BRSs are being developed, but most have not been examined in large-scale clinical trials or real-world registries; the technology must be rigorously tested before initiating trials in humans.[65] Although potential longterm benefits such as resuming native coronary vasomotion seem attractive, important lessons about strut thickness, vessel-wall coverage, and their influence on thrombosis induced by shear forces and the timing of degradation must be better understood before this technology can become mainstream.[66] More importantly, the design of currently drug-eluting coatings in BRS is somehow similar to that in DES, indicating that potential risk of late/later thrombosis and potential formation of neoatherosclerosis would also exist. New drugs that can promote the healing of neointima are expected, besides, better stent coatings that can address the desired endothelialization, antithrombosis, and antiexcessive inflammation are also highly demanded and under investigation,[4] some of which will be discussed below.

2.4. Functional Modification of Vascular Stent

Drug-eluting stents have shown to be of great clinical value, but the feedback of clinical outcomes mentioned above has also driven researchers to wonder if there are some other approaches to reduce in-stent restenosis and thrombosis with/without the use of antihyperplasia drugs. The essential function of endothelial cells has led to a potential direction that deserves investigation. The healing of neointima is a complex and systematic engineering. Rapid endothelialization, antithrombogenicity, anti-inflammation, and inhibition of excessive proliferation of smooth muscle cells should be considered.[67–71] **Figure 2**A illustrated the factors needed to be considered to address functional surface coatings on vascular stents. The surface characteristics (surface wettability, potential, energy, stiffness, roughness, etc.) play important roles in directing the hemocompatibility and cell compatibility of stents.[72] Surface functionalization with cell-based tissue engineering or biomolecule-immobilized in situ tissue engineering are also attractive.[73] In recent decade, biomimetic approaches were also done to mainly mimic the endothelium function or the component in the sublayer of endothelial cells. Our group developed a sandwiched-like coating (a chitosan/heparin multilayer coating using epigallocatechin gallate as a stabilizer) that could mimic the endothelium function via the continuous releasing of heparin and nitric oxide.[74] The coating could effectively promote functional endothelialization. Interestingly, a brand-new recombinant human type III collagen (hCOLIII, with the sequence of $_{483}$GERGAPGFRGPAGPNGIPGEKGPAGERGAP$_{512}$) was explored to evade its binding site with platelets, while well retaining the good affinity for the endothelial cell growth. Such coating could dramatically suppress the inflammation response and direct an excellent healing of neointima.[75] Cooperated with Ji and co-workers, we reported on a design of hierarchical capillary coating, which composes a base solid region and a top microporous region for incorporating rapamycin and vascular endothelial growth factor (VEGF), respectively. The top spongy region can guarantee the efficient, safe, and controllable loading of VEGF up to 1 μg cm^{-2} in 1 min. The coeluting of VEGF and rapamycin could help to remarkable endothelium regeneration while maintaining a very low level of in-stent restenosis.[76] In addition to the direct mobilization of endothelial cell proliferation for in situ endothelialization, recently, we developed a thrombin-triggered self-regulating anticoagulant strategy combined with anti-inflammatory capacity.[77] With response to thrombin, the loaded antithrombus drug would release and help to protect the stent against acute thrombus after implantation. Suppressed coagulation and inflammation level provided an excellent microenvironment for endothelialization process in vivo. Lots of studies that aim at promote in situ endothelialization could not be simply summarized here. Most of them demonstrated potential in vitro or in vivo in animal studies. More evidence and systematic evaluation in pathology evaluation in large animal experiment were needed and carefully investigated prior to the next stage.

2.5. Perspectives of Cardiovascular Stents

Since 1990s, cardiovascular stent implantation has become the main tool for the treatment of CHD. Material innovation in both bulk stent structs and surface coatings continuously make contributions in stent evolution. Biodegradable vascular stents are expected to fundamentally provide potential for the healing of native blood vessels. For developing next generation of BRS, current study concentrated on optimizing stent struts to obtain sufficient radial strength with thinner thickness and smaller crossing profiles. More importantly, a special challenge might be overlooked when developing BVSs, that is, they should not apply the standard adopted for drug-coated metal stents, where the lumen loss required is as small as possible. When fully degradable vascular stent is implanted, if the thickness of the neointima is too thin, there is a risk of a small amount of falling off into the blood vessel when the stent is degraded and fragmented, which may cause adverse events like late thrombosis.[21,67] Thus, for developing stent coatings, whether using antiproliferative drug alone or in combination with functional coating, the desired healing of blood vessels that allow a thicker

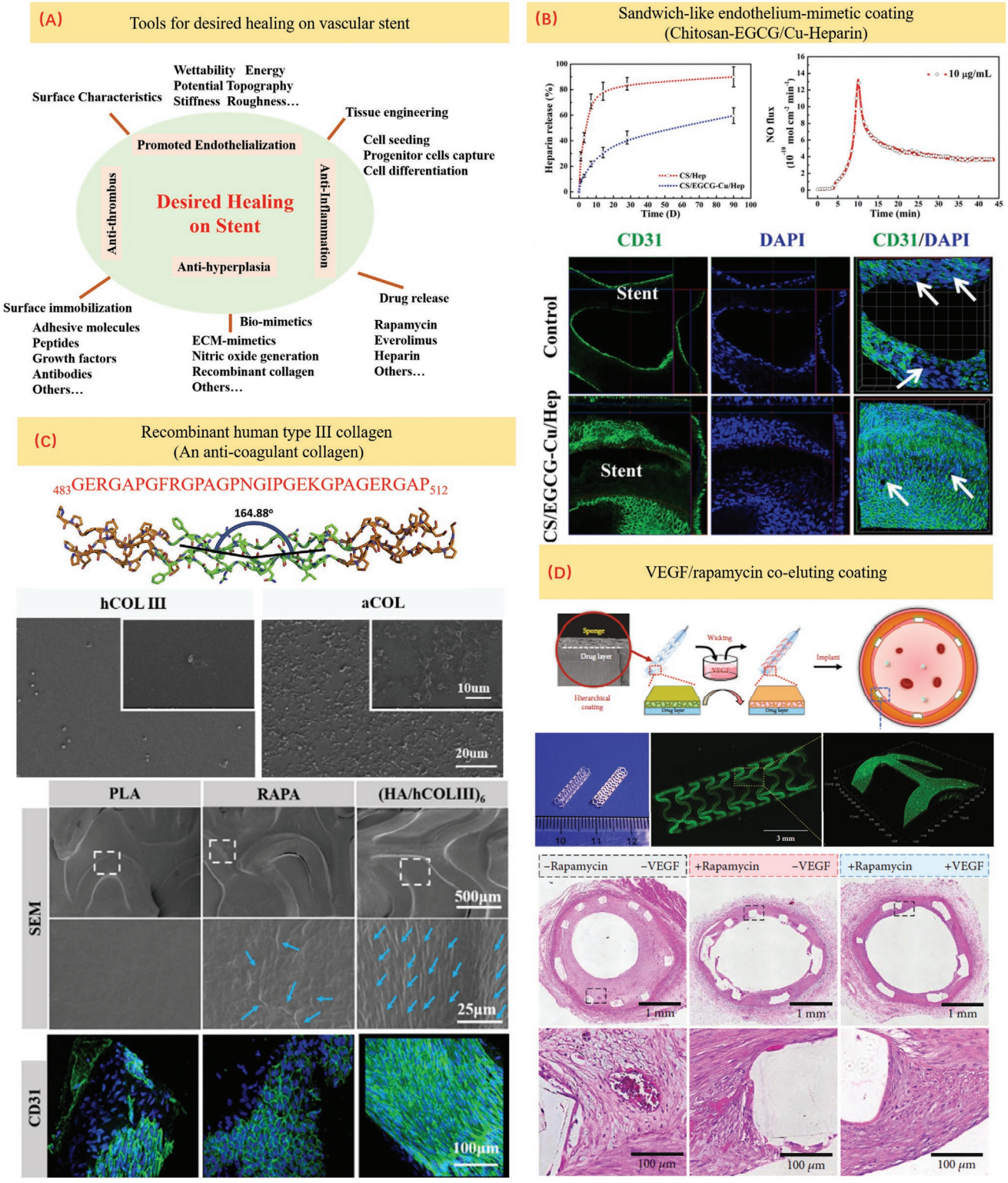

Figure 2. A) The factors need to be considered for the modification of a functional stent coating. B) A sandwiched-like endothelium mimetic coating with in situ continuous release of nitric oxide heparin. B) Reproduced with permission.[74] Copyright 2020, Elsevier. C) A brand-new anticoagulant recombinant human type III collagen and its effect in directing the healing of endothelial cell layer. Reproduced with permission.[75] Copyright 2021, Elsevier. D) A hierarchical capillary coating to biofunctionlize the DES for improving endothelium regeneration by coeluting VEGF and rapamycin. Reproduced under the terms of the CC-BY Creative Commons Attribution 4.0 International license (https://creativecommons.org/licenses/by/4.0).[76] Copyright 2020, The Authors, published by AAAS.

neointima to protect the stent structs during degradation should also be paid attention.

3. Artificial Heart Valves

Heart valve disease, as a common cardiovascular disease, has become one of the important reasons for the high mortality of cardiovascular disease.[78,79] What is more, due to the particular position of the heart valve, there are no effective drugs for treatment of severe heart valve disease in clinic, and the artificial heart valve replacement has been the optimal solution.[80,81] However, traditional surgical valve replacement (SVR) through thoracotomy suffers from the high risk and the long recovery time, and about one-third of patients are not suitable for SVR.[82–84] In recent years, the minimally invasive transcatheter heart valve replacement (THVR) has been developed, which is to deliver the artificial heart valve through catheter and release accurately to the designated position to restore the normal physiological function of the heart valve. With the advantages of no requirement of thoracotomy, lower risk, and shorter recovery time, THVR has become the development trend of heart valve replacement surgery and brought dawn to elderly patients and other patients who are not suitable for thoracotomy.[85–87] Recent studies for artificial heart valve of THVR are mainly focused on the bioprosthetic heart valves (BHVs) and synthetic polymer heart valves based on their characteristics and advantages, and several factors are essential for an ideal artificial heart valve, such as good mechanical properties, good biocompatibility, excellent anticalcification and anticoagulation properties, superior endothelial cell adhesion, great hydrodynamic and fatigue performance, and others. The enhanced material is the key for the development of advanced artificial heart valve and evokes new hopes for the treatment of heart valve disease. The development of materials for bioprosthetic heart valves and synthetic polymeric heart valves are mainly involved in this section.

3.1. Bioprosthetic Heart Valves

BHVs, with superior hemodynamic performance and no need for long-term anticoagulation, are the first choice for THVR in recent years.[88–90] So far, almost all the commercial BHVs are prepared from glutaraldehyde (Glut)-treated xenogenetic tissues, such as animal pericardium. Mechanical properties are important essentials for the performance of BHVs. Good mechanical properties, such as high tensile stress and suture stress, have been proved for Glut-treated BHVs, exhibiting satisfactory performance in the clinical application. However, several deficiencies still cannot be ignored for such valves, from highly toxic, calcification, thrombosis risk, immune rejection reaction to the adhesion difficulty of endothelial cells and others owing to the aldehyde residues in the Glut-treated BHVs, resulting in the limited lifetime of Glut-treated BHVs of only about 10 years.[91–94] The development of new types of BHVs has attracted more and more attentions and different kinds of BHVs with improved properties are achieved through advanced methods including: 1) modification of Glut-treated BHVs through the introduction of anticalcification, antithrombosis, and other functional units; 2) development of novel nonglutaraldehyde crosslinked BHVs to solve the inherent defect of the Glut-treated BHVs; 3) development of novel technology of dry-tissue storage of BHVs to reduce the risk of calcification of BHVs.

3.1.1. Modification of Glut-Treated BHVs

Modification of Glut-treated BHVs through surface modification or functional molecular grafting can efficiently improve the valve performance while maintaining its good mechanical properties. As the calcification, thrombosis, and the adhesion difficulty of endothelial cells are main causes for valve failure, the functionalization of Glut-treated BHVs with anticalcification, antithrombosis, and enhanced endothelial cell adhesion functional units have been developed in recent years.

The coating of polymeric films can be an efficient way to prevent calcification of Glut-treated BHVs. Beppu and co-workers developed a kind of BHV from Glut-treated bovine pericardium with a polymeric coating of silk fibroin film. The study results indicated that Glut-treated BHV coated with chitosan or silk fibroin film showed noncellular cytotoxicity and high affinity to endothelial cells. Furthermore, no obvious calcification was shown for these Glut-treated BHVs with biopolymeric coatings in the in vitro calcification tests.[95] Glut-treated BHV from fabrication of poly(ethylene glycol) (PEG) hydrogels and chicken eggshell membranes was also developed by Zhang and co-workers by mimicking native heart valves to obtain the equivalent mechanical and biological functions for these artificial heart valve leaflets. This fabricated Glut-treated BHV showed mechanical properties similar to human heart valve leaflets with elastic moduli of 3.3–5.0 MPa and elongation percentages of 47–56%. Less calcification and enzyme degradation could be observed for this fabricated Glut-treated BHV attributed to the PEG hydrogels by preventing the penetration of ions and other molecules.[96]

Construction of zwitterionic hydrogel coating on BHVs can prevent the transportation of Ca^{2+} ions and other biomolecules by the electrostatic repulsion and efficiently improve the of performance of BHVs, such as anticalcification and anticoagulation properties and reduced inflammatory reaction. A new type of functional BHV has been developed by Wang and co-workers through the modification of Glut-treated pericardium with a designed aminated zwitterionic copolymer via a simple dip-coating approach to improve anticoagulation and anticalcification properties of Glut-treated BHV.[97] Along with the good mechanical properties similar to the Glut-treated BHV, this functional BHV exhibited long-term anticoagulation in vitro and ex vivo investigation. Meanwhile, improved anticalcification and reduced inflammation could also be demonstrated through the subcutaneous implantation of animal. Furthermore, the long-term anticoagulation and anticalcification properties could be retained for this functional BHV after the storage in glutaraldehyde solution, indicating great potential in the clinical application. A kind of balanced charged networks was developed by Zhang and co-workers using poly(ethylene glycol) diacrylate (PEGDA) and zwitterion (2-[methacryloyloxy]ethyl) dimethyl-(3-sulfopropyl)ammonium hydroxide/sulfobetaine

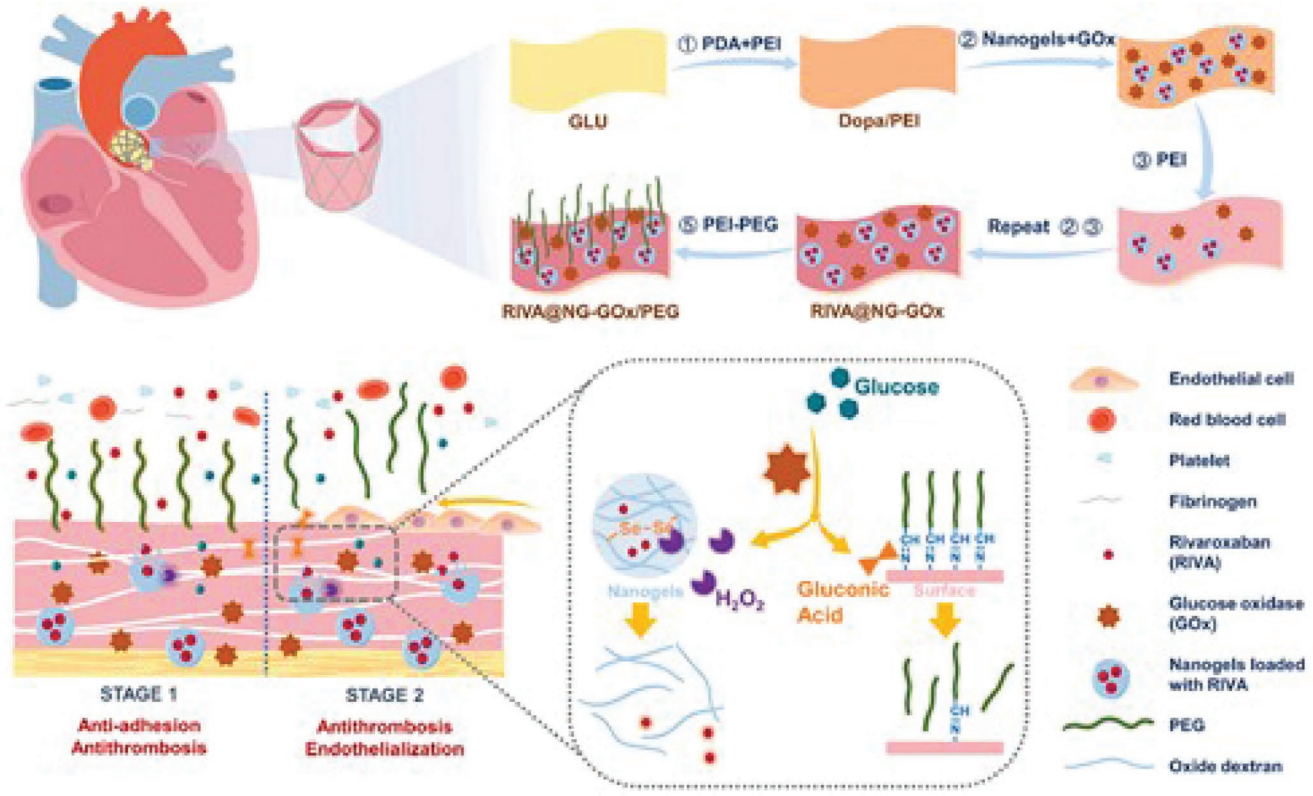

Figure 3. Illustration of the multi-in-one coating with glucose-triggered long-term antithrombogenicity and sequentially enhanced endothelialization. Reproduced with permission.[100] Copyright 2021, Elsevier.

methacrylate (SBMA). Modification of this balanced charged networks to Glut-treated decellularized heart valves exhibited no obvious calcification in the in vitro calcification study. The inflammatory reaction of the zwitterionic-hydrogel-coated BHVs could also be mitigated due to the less biosorption of the zwitterionic hydrogel.[98]

A healthy endothelium plays an important role in the delay of the valve deterioration by preventing the inflammatory cell recruitment, calcification, and other valve damages for the native heart valves. A type of BHV of Glut-treated porcine pericardium with the optimization of biodegradable methacrylated chondroitin sulfate hydrogel has been obtained by Melgar-Lesmes and co-workers with the functional hydrogel to mimic the physiological environment of the inherent biological systems to reconstitute the endothelium by the host endothelial cells.[99] With the functional hydrogel modification, the Glut-treated BHV showed reduced cytotoxicity, increased endothelial cell adhesion and proliferation, and high thromboresistance.

A functional Glut-treated BHV with long-term antithrombogenicity and enhanced endothelialization properties has been developed by Wang and co-workers through the modification of hydrogen peroxide responsive rivaroxaban (RIVA)- and glucose-oxidase (GOx)-loaded nanogels and the further grafting with PEG through detachable pH-sensitive bonds (**Figure 3**).[100] The long-term antithrombogenicity and enhanced endothelialization could be realized through a hierarchical response to the local environment. The glucose could be oxidated by the catalyzation of GOx, providing hydrogen peroxide and a local acidic environment. Along with the hydrogen peroxide response, long-term antithrombogenicity was realized through the continuous of RIVA and the antifouling property of the PEG grafts. Meanwhile, the endothelialization could also be enhanced along with the gradual dissociation of PEG group in the local acidic environment. Meanwhile, no impact on the initial mechanical properties of the Glut-treated BHV was observed after the functional modification, showing broad application potential in the functionalization of Glut-treated BHVs. Besides, our recently reported thrombin-triggered self-regulating anticoagulant strategy was also applied to enhance the ability of antithrombus and anticalcification of BHVs.[69] The modified coating worked as a precise strategy to resist coagulation and inflammation, provided a new perspective for designing endothelium-like functional coatings.

The crosslinking mechanism of Glut-treated BHVs is mainly through the reaction of glutaraldehyde with amino groups on collagen, and a large number of carboxyl groups remain on the Glut-treated BHVs. Taking advantage of the remained carboxyl groups, Wang and co-workers developed a kind of novel biomimetic BHV by further crosslinking of erythrocyte membrane along with anti-inflammatory drugs to Glut-treated BHV to improve the comprehensive performance of BHV with enhanced properties of anticoagulation, anti-inflammation, anticalcification, and endothelialization.[101] Good blood and cell biocompatibility, anticoagulation, and enhanced endothelialization properties were shown for this biomimetic BHV. The inflammatory response can be efficiently reduced after

implantation in rats with the release of anti-inflammatory drug, and no obvious calcification was observed for this biomimetic BHV after implantation for 120 days, supplying a new approach to designing the therapeutic biomimetic BHVs.

3.1.2. Nonglutaraldehyde Crosslinked BHVs

The toxicity of glutaraldehyde and the remaining aldehyde residues in the Glut-treated BHVs are considered the inherent defect for calcification, coagulation, inflammation reaction, endothelialization difficulty, and others in the clinical application, resulting in the short lifetime of the Glut-treated BHVs. In recent years, different types of novel nonglutaraldehyde-crosslinked BHVs with superior performance have been developed to avoid the problems of Glut-treated BHVs.

A type of nonglutaraldehyde-crosslinked BHV was developed from the procyanidin-treated porcine aortic heart valve. Compared to glutaraldehyde-crosslinked heart valve, the procyanidin-treated porcine aortic heart valve showed a lower cytotoxicity and enhanced valve interstitial cell proliferation along with a higher tensile strength and similar enzymatic degradation resistance. However, the release of procyanidin from the crosslinked BHVs was found when stored in D-Hank's solution, which might affect their further clinical applications.[102]

Quercetin is a polyphenolic compound with a similar structure to the procyanidin monomer, and often used as antioxidant, free-radical scavenger, and cardiovascular protector. The crosslinked porcine aortic heart valve by quercetin has been prepared with high tensile strength, noncytotoxic, anticalcification in vitro, and no inhibition on vascular endothelial cell proliferation.[103] Similar to procyanidin-crosslinked heart valve, the release of the crosslinker of quercetin still existed during the storage in D-Hank's solution.

A kind of nonglutaraldehyde-crosslinked porcine aortic heart valve has been developed by a multiple fixation using three crosslinkers of carbodiimide, neomycin trisulfate, and pentagalloyl glucose to realize the stability of different components of the extracellular matrix (ECM), such as collagen, elastin, and glycosaminoglycan.[104] With the multiple ECM stability, this nonglutaraldehyde-crosslinked BHV exhibited better enzymatic degradation resistance in vitro and better tearing toughness after enzymatic degradation compared to the Glut-treated porcine aortic heart valve. Meanwhile, less calcification and superior stability of ECM component could be demonstrated after subcutaneous implantation in rats for 90 days.

Ployepoxy compounds are also used for crosslinking of ECM to enhance the properties of biocompatibility, immunogenicity, and anticalcification for BHVs. A kind of nonglutaraldehyde-crosslinked bovine pericardium has been developed by the treatment of a quaternary ammonium salt of epoxy chitosan (epoxy-group-modified 3-chlorine-2-hydroxypropyl trimethyl chitosan).[105] Compared to the Glut-treated bovine pericardium, improved anticalcification property along with better biocompatibility and blood compatibility were demonstrated for the epoxy-chitosan-crosslinked bovine pericardium. However, relatively lower mechanical properties and enzymatic degradation resistance attributed to the relatively lower fixation of amine group on bovine pericardium might limit its further application in clinic.

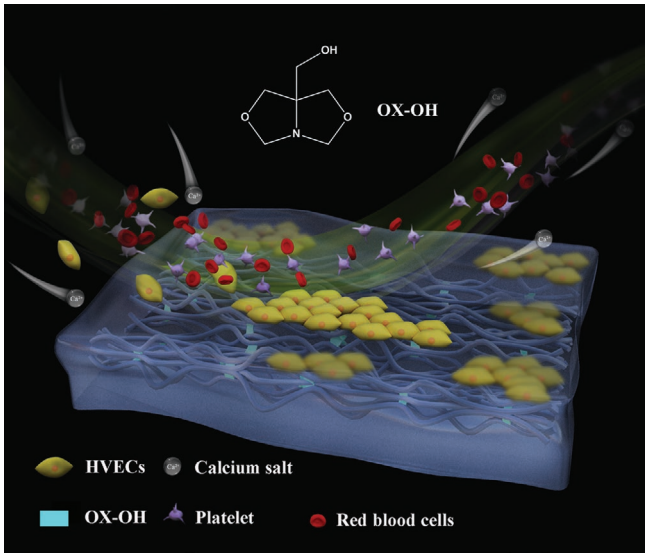

Figure 4. Illustration of nonglutaraldehyde crosslinker OX-OH for bioprosthetic heart valve preparation with better biocompatibility, improved anticoagulation, reduced calcification, and enhanced endothelial cell adhesion properties. Reproduced with permission.[108] Copyright 2021, Elsevier.

3,4-Dihydroxybenzaldehyde, a polyphenol substance with an aldehyde group, was used as a crosslinker to treat porcine pericardium through the reaction of amine and aldehyde and the subsequent polymerization under the oxidation condition.[106] Along with the satisfactory mechanical property, improved hemocompatibility with less platelet absorption and longer activated partial thromboplastin time could be observed for the 3,4-dihydroxybenzaldehyde fixed porcine pericardium compared to the Glut-treated porcine pericardium. Moreover, the cytocompatibility and anticalcification properties were also effectively improved, showing good prospects for the 3,4-dihydroxybenzaldehyde fixed porcine pericardium in the clinical application of BHVs. Sodium lignosulfonate (SLS) was also used as a new crosslinker for BHVs.[107] Compared to the Glut-treated porcine pericardium, SLS fixed porcine pericardium showed enhanced endothelial cells proliferation up to 13.3-fold in 5 days along with an obviously reduced calcification.

Oxazolidine is a kind of heterocyclic derivatives with multifunctional structures, and has great potential in the fixation of ECM. A kind of nonglutaraldehyde-treated porcine pericardium treated with a bicyclic oxazolidine (OX—OH) for the application of BHVs has been developed for the first time by Wang and co-workers (**Figure 4**).[108,109] Compared to the Glut-treated porcine pericardium, great biocompatibility, reduced anticalcification, improved anticoagulation, and proliferation of endothelial cells along with the similar satisfactory mechanical properties were proved for the OX—OH-crosslinked porcine pericardium. Furthermore, the transcatheter aortic valve from OX—OH-crosslinked porcine pericardium has also been manufactured, exhibiting desirable hydrodynamic and fatigue performance and great potential in the clinical application for BHVs.

Different from the conventional crosslinking method, a novel fixation approach of double bond crosslinking totally different from the conventional crosslinking method has been

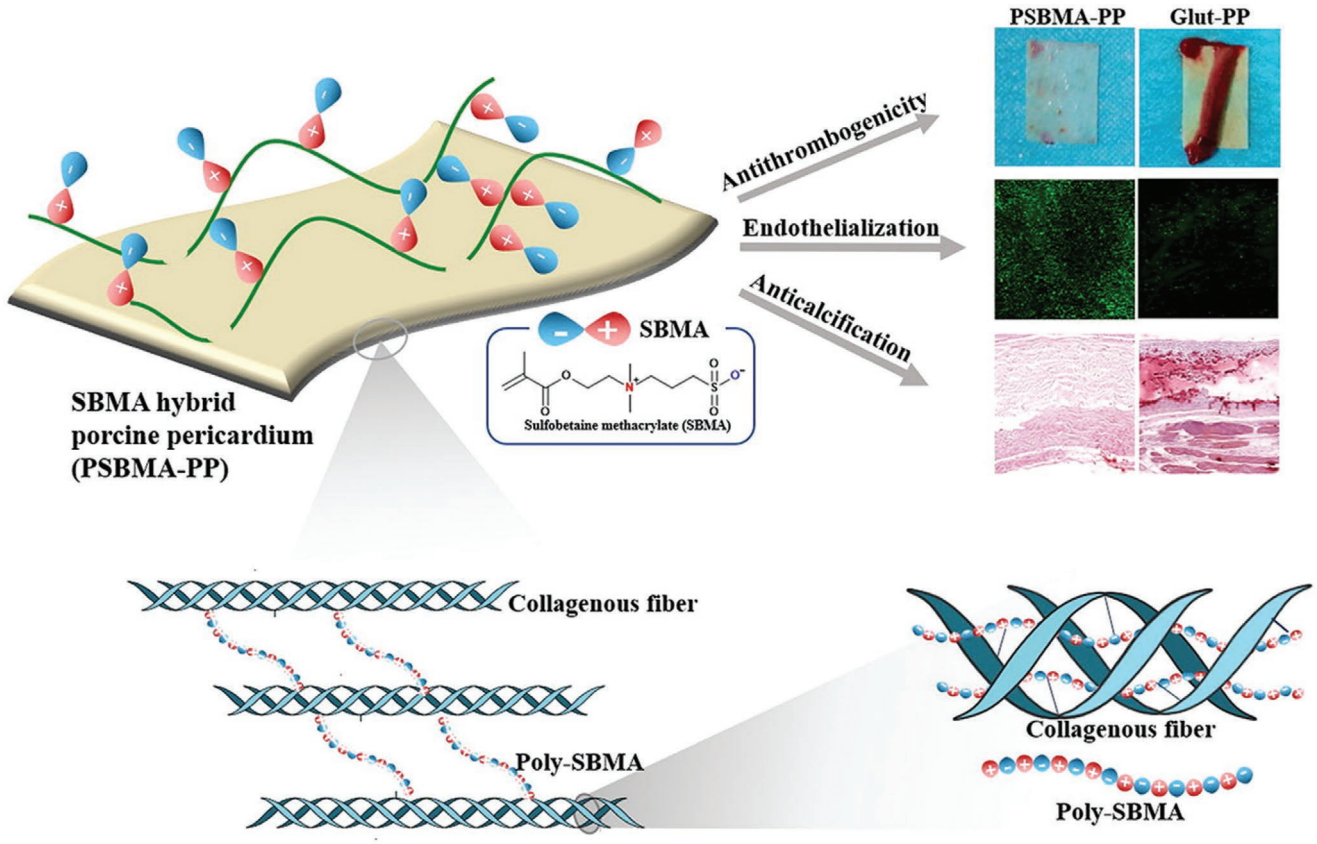

Figure 5. Illustration of polyzwitterion-crosslinked hybrid tissue with antithrombogenicity, endothelialization, and anticalcification properties. Reproduced with permission.[113] Copyright 2020, Elsevier.

developed by Wang and co-workers to reduce calcification and inflammatory response and enhance endothelialization of BHVs, and a series of double bond crosslinked BHVs with good comprehensive performance are developed.[110–115] With the functional modification of methacryloyl groups and the subsequent double bond crosslinking, the stability of collagen and elastin of the porcine pericardium could be remarkably improved. Meanwhile, the enhanced endothelialization potential, reduced inflammatory response, and in vivo anticalcification were shown for the radical polymerization crosslinking (RPC)-treated porcine pericardium.[110,111] Furthermore, through the introduction of different functional monomers, a series of functional BHVs from RPC-treated porcine pericardium were further developed to tailor the biophysical properties of BHVs. With the in situ polymerization of sulfonic monomers, the crosslinking and functionalization of the porcine pericardium were achieved simultaneously to obtain the functional hybrid porcine pericardium, showing less adsorption of albumin, fibrinogen, and platelets, the promoted proliferation and migration of endothelial cells, and reduced immune response and calcification compared with the nonhybrid counterpart without the introduction of sulfonic monomers.[112] Another functional hybrid porcine pericardium with the introduction of zwitterionic monomer SBMA was also developed,[113] and significantly lower thrombogenicity than the nonhybrid RPC-treated porcine pericardium was proved through the ex vivo arteriovenous shunt assay (**Figure 5**). What is more, the introduction of the zwitterionic monomer SBMA could increase the resistance to the adsorption of nonspecific proteins without the inhibition of adhesion and proliferation of endothelial cells, showing great potential of the long-term hemocompatibility. The transcatheter aortic valve from SBMA hybrid porcine pericardium was also prepared and exhibits good antifatigue performance, showing great potential in the clinical application.

3.1.3. Dry-Tissue Storage of BHVs

The commercial BHVs are stored in a glutaraldehyde solution as a wet tissue and should be washed repeatedly before operation to remove the glutaraldehyde. However, the glutaraldehyde cannot be completely cleaned and the residue of glutaraldehyde on the BHVs would increase the toxicity and the risk of calcification. Moreover, the longtime washing before operation may also delay the implantation of the BHVs and increase the surgical risks. The dry-tissue storage of BHVs can resolve these problems of glutaraldehyde solution storage of BHVs. However, the dry-tissue BHVs prepared from the conventional treatment would dramatically destroy the mechanical properties and lose the normal function of BHVs, unsatisfying the requirements of BHVs in clinical use. The novel strategies of the BHV modification should be developed for the dry-tissue storage of BHVs to reach the use standard in clinic.

A series of pioneer studies of dry-tissue storage of BHVs have been investigated by Wang and co-workers.[114,116–125] To realize the dry-tissue storage of the conventional Glut-treated BHVs, a hydrogel hybrid Glut-treated porcine pericardium was developed.[116] Through the in situ polymerization of monomers of sodium acrylate, 2-methacryloyloxyethyl phosphorylcholine, or acryloyloxyethyltrimethyl ammonium chloride in the Glut-treated porcine pericardium, three types of hydrogel hybrid Glut-treated porcine pericardium were prepared. All the hydrogel hybrid Glut-treated porcine pericardium in dry storage could be recovered to their normal wet tissue form in phosphate-buffered saline (PBS) solution without the obvious damage of mechanical properties. Furthermore, compared to the conventional Glut-treated porcine pericardium, these hydrogel hybrid materials exhibited better biocompatibility, promoted endothelial cell growth and proliferation, and reduced immune response.

Another arginine–glutamate–aspartic acid–valine (REDV)-loaded hydrogel hybrid Glut-treated porcine pericardium in dry-tissue storage was developed.[120] Through the soak of Glut-treated porcine pericardium in the solution of poly(ethylene glycol) methacrylate and REDV, and the following in situ polymerization, the hydrogel hybrid material for BHVs was prepared. Along with the rapid recover to normal wet tissue in PBS solution from its dry tissue, this REDV-loaded hydrogel hybrid Glut-treated porcine pericardium exhibited great potential to efficiently promote endothelialization. Meanwhile, reduced calcification and immune response was also proved for this REDV-loaded hydrogel hybrid material through the in vivo rat subdermal implantation.

Beside the dry tissue Glut-treated BHV material, a non-glutaraldehyde-crosslinked dry tissue BHV material has also been developed from the multiple crosslinked porcine pericardium by ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and curcumin.[119] Compared to the Glut-treated porcine pericardium, this EDC-/curcumin-crosslinked BHV material exhibited superior comprehensive properties, such as better biocompatibility and mechanical properties, efficiently improved anticalcification and anticoagulant properties, and enhanced enzyme degradation resistance. What is more, the dry tissue of the EDC-/curcumin-crosslinked BHV material can recover to the normal wet tissue without creases or damage.

3.2. Synthetic Polymeric Heart Valves

Synthetic polymer is one of the earliest and most widely studied heart valve materials. Compared to the BHVs, synthetic polymeric heart valves (PHVs) exhibit many advantages, such as easy engineering design, potential of the long-term durability, good product uniformity, and others. The selection of the polymeric material is the key for the performance of the PHVs. Due to the limitation of polymer material property, the development of PHVs in early stage is relatively slow. In recent years, different types of polymer materials with superior properties have been developed, which brings new hope for the development of PHVs with excellent performance and inspires a new wave of research for PHVs. PHVs based on different types of polymeric materials are introduced in this section.[125–129]

3.2.1. Polysiloxane Heart Valves

Polysiloxane is one of the earliest polymeric materials studied for heart valves. Polysiloxane heart valves exhibit high durability in accelerated in vitro tests. However, high mortality rate due to the thromboembolism, clinical complications, and other causes in the clinical trial limits their further clinical application.[125,127]

3.2.2. Polyurethane Heart Valves

Polyurethanes (PUs) have good blood compatibility, hemodynamics, and mechanical properties, which make them very attractive materials in the development of cardiovascular materials. Through their tunable two phase of hard and soft segments, their stiffness and elasticity can be adjusted. However, the degradation of the polyurethane materials is a basic concern owing to their degradable chemical bonds, which may result in the failure for the polyurethane heart valves. Different types of PUs have been developed in recent years to improve their biocompatibility and biostability, such as polycarbonate urethane (PCU) with a polycarbonate soft segment, polysiloxane urethane (PSU) with polysiloxane soft segment, polyhedral-oligomeric-silsesquioxanes (POSS)-composited PUs, and others.

A trileaflet PU valve developed by Wheatley et al. was implanted in the mitral position of growing sheep with ATS bileaflet mechanical and Carpentier–Edwards (CE) porcine valves as control groups.[130] Platelet aggregates without thromboembolism or functional change could be observed for the mechanical valve group and fewer aggregates and calcification were shown for bioprosthetic valve group at 6 months. Meanwhile, low level of platelet aggregates along with small degree of fibrin attachment was present for the PU valve.

A type of flexible trileaflet-heart-valve-based PSU has been developed by Bernacca and co-workers.[131,132] After implantation in young adult sheep for 6 months, no obvious degradation of the PSU heart valve along with a slight surface enrichment of siloxane soft segment was shown. Little amounts of calcified fibrin were found attached to the leaflet surfaces, exhibiting a good hydrodynamic behavior after implantation.

A nanocomposite polymer (POSS–PCU) has been developed by Seifalian and co-workers with POSS nanoparticles covalently bonded to the hard segment of PCU.[133,134] Compared to PCU, better mechanical strength, such as higher tensile strength, tear strength, and Young's modulus were shown for POSS–PCU, which might be beneficial to the valve durability. Meanwhile, resistance to the platelet adhesion and calcification were shown for POSS–PCU after exposure to platelet-rich plasma and calcium solution, respectively.

3.2.3. Poly(tetrafluoroethylene) and Expanded Poly(tetrafluoroethylene) Heart Valves

Owing to its inertness, low surface energy, and good biocompatibility, poly(tetrafluoroethylene) (PTFE) and expanded poly(tetrafluoroethylene) (ePTFE) with special porous structures have been widely used in the field of medical devices. Compared to PTFE, apart from the improvement in mechanical

properties for ePTFE, the porosity might also impact the properties of heart valves, such as calcification and mobility of valve leaflets. Early clinical studies of nonporous PTFE heart valves in by Braunwald and Morrow showed that several drawbacks such as stiff, calcification, and tear emerged after implantation in 23 patients.[135] Pulmonary valves based on ePTFE have been developed by Quintessenza et al. and implanted in the right ventricular outflow tract of 126 patients, and 84 patients implanted heart valves with 0.6 mm thickness ePTFE, while 42 patients with 0.1 mm thickness ePTFE.[136] The replacement of PTFE pulmonary valve for six patients was required due to the immobile and calcified leaflets, which might be attributed to the use of 0.6 mm ePTFE. After using the 0.1 mm ePTFE, it could last longer, which might meet the long-term function. Another type of ePTFE-valved conduit has been reported by Ootaki et al.[137] The ePTFE-valved conduits with 0.1 mm ePTFE as the tricuspid leaflets were implanted in 26 patients for the right ventricular outflow tract reconstruction, and pulmonary insufficiency and significant valve dysfunction were mild for most of the patients (92%).

3.2.4. Other Polymeric Heart Valves

In recent years, other types of polymeric materials and synthetic polymeric heart valves have also been reported. A type of material of poly(styrene-*block*-isobutylene-*block*-styrene) (SIBS) and a trileaflet polymeric heart valve based on SIBS have been developed and implanted in sheep.[138] After 20 weeks, material failure and calcification could be observed, which indicated that the material SIBS needed to be further improved for the long-term use as a heart valve. Through the modification of the SIBS with ECM coating via chemical binding, the biocompatibility, anticalcification, anticoagulant, and promoting endothelial cell growth of the valve material could be further improved, which might meet the requirement for the use of heart valve.[139] xSIBS, a crosslinked version of SIBS, has been reported, showing good hemocompatibility and resistance to calcific deposition. Heart valve based on xSIBS has also been developed, showing a good valve hemodynamic performance.[140] A type of tricuspid heart valve based on polyvinyl alcohol (PVA) cryogel has also been developed by Campbell and co-workers. The PVA heart valve can be manufactured through the PVA solution in the mold by freezing and thawing. The biostablity of the PVA heart valve was not investigated yet.[141]

3.3. Outlook of Artificial Heart Valves

In recent years, the development trend of heart valve replacement has changed from surgical valve replacement to minimally invasive interventional implantation. The current commercial transcatheter interventional valve products are bioprosthetic heart valves made from pericardial materials, which still suffer some drawbacks such as calcification, limited lifetime, individual differences, immunogenicity, the need for manual sewing in valve preparation, and others. The development of new type of bioprosthetic heart valve with long-term lifetime is still highly demanded. Compared with bioprosthetic heart valves, synthetic polymeric valves have the advantages of easy large-scale preparation and low cost, showing broad prospects in the development of transcatheter interventional valves. However, challenges still exist for the current polymeric materials such as limited durability, calcification, hardening and tearing of valve leaflet, and others. How to further improve the biocompatibility, biosafety, and durability of synthetic polymeric materials and polymeric valves will be the key to get the satisfied polymeric valves for the application in clinic. In addition, tissue-engineered heart valves based on biodegradable materials with expectation of function reconstruction and valve regeneration of heart valve is also an important direction for the treatment of heart valve disease.

4. Heart Failure Therapy

Cardiac function is propagated through the rhythmic contractions of the myocardium, which comprises cardiomyocytes, ECM, and capillary microcirculation. The incidence of myocardial infarction (MI) results in the irreversible loss of cardiomyocytes (CMs), myocardial ischemic necrosis, and the formation of a noncontractile scar.[142] During the subsequent adverse remodeling process, damaged myocytes are replaced by noncontractile scar tissue and expand over time.[143] The maturing scar restricts proper contraction biomechanics, leading to myocardial hypertrophy, left ventricular dilation, heart failure (HF), and even death. It should be noted that ≈50% of patients with HF will die within 5 years after diagnosis, indicating that it is a serious threat to patients' health and quality of life.[144] However, most of the current drug therapies only target symptoms or slow the progression of the disease. Moreover, heart transplants and left ventricular assist devices are limited by supply shortages and related complications caused by infection, bleeding, stroke, and right ventricular failure, respectively.[145] Therefore, during the past 40 years, many efforts have been invested in the study of the prospects of stem cells for HF treatment. Unfortunately, the body of evidence accumulated so far has shown that stem cell therapy does not produce clinically meaningful therapeutic effects for HF owing to poor control, poor retention in the infarct area, and the low survival rate of the cells injected into the patient.[143] Recently, biomaterials designed to slow down ventricular remodeling, reverse ventricular wall thinning, and to promote the regeneration of myocardial tissue and the restoration of cardiac function have attracted increasing attention. Cardiac patches, injectable hydrogels, and atrial shunts are the three emerging directions of HF treatment.

4.1. Cardiac Patches

Cardiac patches are polymeric porous scaffolds or hydrogels that are attached to the damaged myocardium via spontaneous adhesion or suture fixation after thoracotomy. They provide physical support for failing hearts and increase the left ventricular wall tension to limit ventricular expansion.[146] Cardiac patches have been fabricated using natural materials (such as proteins, decellularized tissues, hyaluronic acid, and alginate) and synthetic biocompatible polymers (such as poly(glycerol-sebacate)

(PGS), PEGDA, PU, and polycaprolactone (PCL)) by a variety of techniques, including molding, evaporation method, electrospinning, electrowetting, and 3D printing.[147,148] In addition, cardiac patches can serve as carriers to deliver therapeutic loads (e.g., induced pluripotent stem cells,[149] human cardiac progenitor cells,[150] CMs,[151] bioactive growth factors,[152,153] and nanozymes[154] with improved retention rates that achieve considerable treatment effects.

In most cases, the biochemical, mechanical, and topographical properties of cardiac patches should be similar to those of native myocardial tissue. Although decellularized-tissue-based patches can meet most of these requirements, the resulting immune response has greatly limited their clinical application. Electrospinning, a cost-effective fabrication technique, has emerged as a prominent method for the fabrication of fibers (with diameters ranging from nanometers to micrometers) that mimic the highly branched nature of the cardiac ECM using a plethora of polymeric materials.[153] Zhu et al. fabricated a nitrate-functionalized cardiac patch through electrospinning using a composite material of high-molecular-weight PCL and PCL oligomers with both ends capped with nitrates ($PCL{-}ONO_2$) and implanted the patch to cover the infarcted myocardium.[155] The site-specific delivery of NO provided effective cardioprotection, markedly ameliorating heart function and attenuating adverse remodeling. In addition, 3D printing technology is considered a promising approach for engineering whole organs. Noor et al. utilized a biopsy of fatty tissue taken from patients and separated the cellular and acellular materials. The cells were reprogrammed to become pluripotent stem cells, further differentiated to cardiomyocytes and endothelial cells, and the ECM was processed into a personalized hydrogel. Subsequently, they combined cells with the hydrogel to print thick, vascularized, and perfusable cardiac patches that could completely match the immunological, biochemical, and anatomical properties of the patients' myocardial tissue.[149]

Some researchers have proposed that the propagation of electrical impulses in nonconductive fibrous scar tissue is severely hampered, resulting in abnormalities in heart pumping function and electrical signaling propagation.[156,157] In addition, they believe that the reconstruction of the internal cardiac electrical connections by transplanting electroconductive cardiac patches is crucial for restoring the normal function of the infarcted heart. A series of electroconductive cardiac patches has been explored by the incorporation of conductive materials such as gold nanoparticles,[158] metal ions,[159] carbon-based nanomaterials,[160,161] and electroconductive polymers.[151,162] Liang et al. prepared a conductive hydrogel patch constructed with a dopamine-doped and pyrrole-group-end-capped hyperbranched polymer that could be crosslinked with Fe^{3+}.[163] As shown in **Figure 6**A, they synthesized hyperbranched poly(amino ester) (HPAE) using dopamine hydrochloride, pentaerythritol triacrylate, and PEGDA through stepwise polymerization. Then, excess pyrrole monomer was added to react with the acrylate groups of HPAE for complete end-capping. Finally, gelatin and Fe^{3+} were added to prepare a conductive patch. The HPAE-Py/Geln hydrogel could be evenly painted on the infarct area, adhered strongly to the surface of the tissue, and was mostly degraded within 4 weeks (Figure 6B). As shown in Figure 6C, fibrous tissue was formed in all infarcted hearts, with the most severe degree of fibrosis presented in the MI group. In comparison, the HPAE/Geln and HPAE-Py/Geln groups displayed decreased fibrosis. Notably, the optimal effect was found in the HPAE-Py/Geln group, where the myocardium was analogous to the normal myocardium. However, the problem with this work is that the patch with weak mechanical properties cannot provide sufficient mechanical support for the damaged heart machine. In addition, compared with isotropic conductive patches, it has been reported that anisotropic conductive patches are more effective in promoting myocardial function after infarction through the bionic restoration of the myocardial electrical microenvironment.[161]

Moreover, several studies have shown patches with properties that mimic the anisotropy, electrical propagation, and mechanical strength of native myocardium that can significantly enhance the cell–cell interaction, maturation, and synchronous calcium transients of neonatal rat primary cardiomyocytes.[164,165] Guo and co-workers developed a series of biocompatible elastomeric films with a surface micropattern composed of PGS and graphene (Gr). The mechanical strength of the micropatterned elastomer film was 0.6–3.2 MPa, while simulating the transverse and longitudinal anisotropy of natural myocardium. In addition, the film had good electrical conductivity (up to 5.80×10^{-7} S m^{-1}), which facilitated electrical signaling between cardiac tissue and cardiomyocytes. The in vivo results showed that the film with 1 wt% Gr content (PGS–Gr1) effectively reduced the infarct size and myocardial fibrosis degree, and significantly promoted the recovery of myocardial function in rats after MI.[166]

During the past few years, there have been some impressive results associated with the use of electrically conductive biomaterials for regeneration of the injured myocardium.[156,157] However, conductive cardiac patches still experience reduced conductivity after long-term implantation. And the electrical conductivity of human myocardial tissue is still unclear. In addition, there are few reports about myocardial patches whose conductivity perfectly match the conductivity of native myocardial tissue (both longitudinal and transverse). More importantly, although there have been few reports of side effects such as arrhythmia or asynchronous heart paces caused by conductive patch implantation, the long-term physiological toxicity (including blood compatibility) of the implantation of conductive materials, especially for inorganic nanomaterials and metal ions, requires further study.

One major challenge for the clinical application of patches is the slow integration between the cells or bioactive-substance-loaded transplanted cardiac patch construct and the host myocardium.[147] To solve this problem, researchers introduced microneedles (MNs) to create channels for communication between the patch and the host myocardium, allowing the transplanted patch to obtain nutrients from the heart while releasing the therapeutic substance for repair of the heart.[167–170] Shi et al. fabricated phase-transition poly(vinyl alcohol) MNs coated with adeno-associated virus (AAV). Compared with local intramyocardial injection (after which the agents were confined to the site of injection), transepicardial permeation using AAV–MNs resulted in the homogeneous distribution of agents. In a rat model of MI, AAV–VEGF-loaded MNs could improve heart function, reduce scar size, and ameliorate adverse remodeling

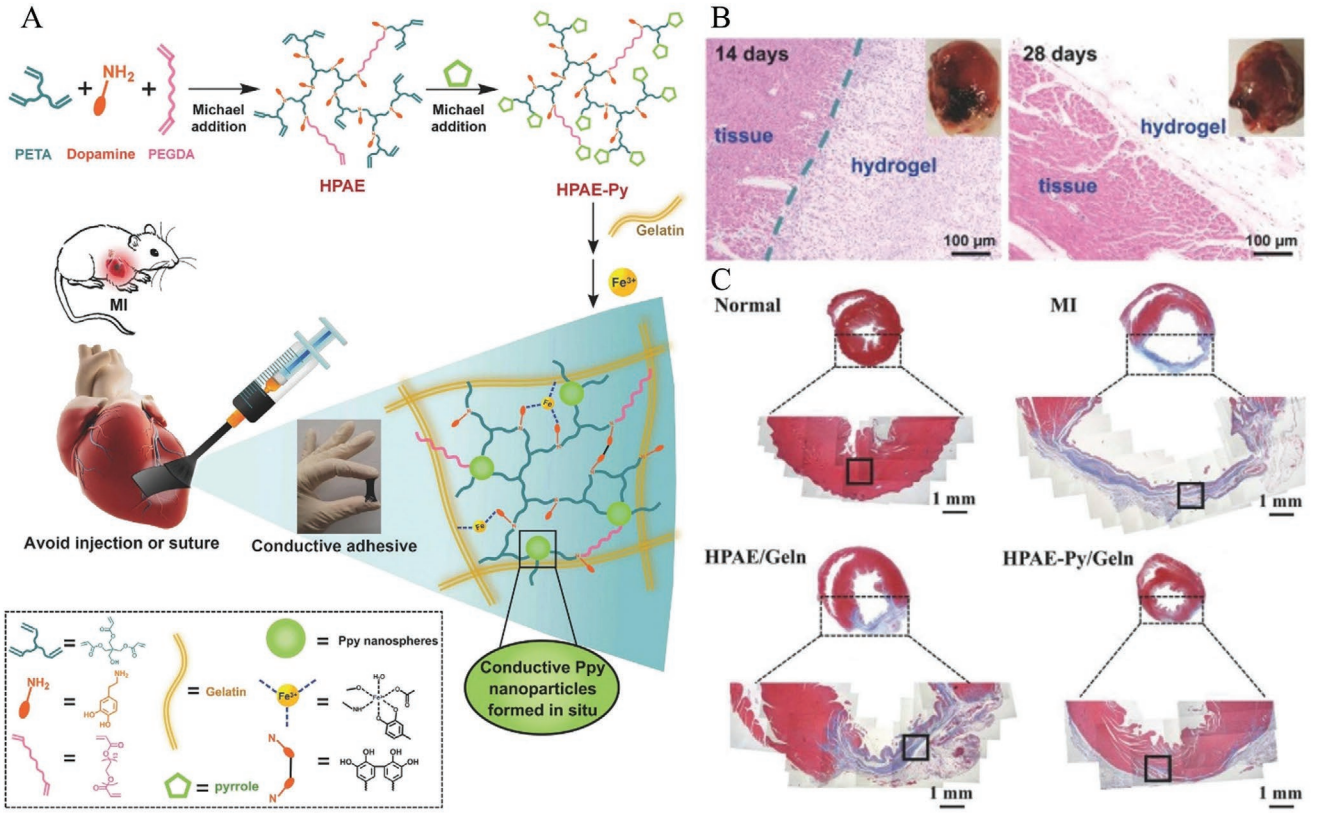

Figure 6. A) Schematic illustration of the preparation of a conductive and adhesive hydrogel and its application by painting directly on the surface of the MI heart in SD rats. B) Hematoxylin–Eosin staining (at 14 and 28 days) of HPAEPy/Geln hydrogel painted on the surface of the infarcted myocardium. C) Cardiac structures in the normal, MI, HPAE/Geln, and HPAE-Py/Geln groups as revealed by Masson's trichrome staining for collagen (blue) and muscle (red). Black boxes indicate the location of immunofluorescence staining. A–C) Reproduced with permission.[163] Copyright 2018, Wiley-VCH.

by enhancing VEGF expression, promoting functional angiogenesis, and activating the Akt signaling pathway.[168] Consequently, MNs may emerge as a promising technology for cardiac patches, offering great versatility for the delivery of various agents to treat ischemic myocardial disease.

Another challenge in the development of cardiac patches is that their implantation normally requires open-chest surgery, which may cause innate surgical damage, increase the patients' risk of death during surgery, induce inflammation after surgery, and subject the patient to a long recovery period, and therefore hampering their application in patients with mild-to-moderate HF after MI. Shape-memory patches that can support multiple stretching cycles without deforming[171,172] and sprayable patches[163] have been successfully transplanted to the heart through minimally invasive surgery. Huang et al. designed a preferable, multifunctional epicardial device (PerMed) consisting of a PGS/PCL (9:1) biodegradable elastic patch (BEP), PCL/gelatin (3:1) permeable hierarchical microchannel networks, and a system to enable the delivery of therapeutic agents from a subcutaneously implanted pump.[172] The PGS/PCL (9:1) BEP had a moderate tensile and compression modulus of 1.61 ± 0.26 and 5.73 ± 0.16 MPa, respectively. These values were similar to those of the normal heart tissue. They also designed a claw-shaped fixator, composed of a middle ring and stretched arms with several barbed needles, to fix the PerMed onto the epicardial surface after minimally invasive surgical implantation. In a rat model of MI, implantation of the PerMed improved ventricular function. When connected to a pump, the PerMed enabled the targeted, sustained, and stable release of platelet-derived growth factor-BB, amplifying the efficacy of cardiac repair as compared with the device without a pump. However, it is still difficult to solve the formation of pericardial adhesion after the implantation of cardiac patches that may cause dysfunction of the heart or even increase morbidity and mortality.[142]

4.2. Injectable Hydrogels

The complications presented in cell therapy and cardiac patches have led research groups to start to pay attention to minimally invasive implant technology.[142] Recent studies indicate that the direct injection of biomaterials into the myocardium has benefit in preventing cardiac maladaptive repair and reducing cardiac dysfunction.[173] In comparison with cardiac patches, injectable hydrogels are regarded as a minimally invasive technology, which confers various advantages: simpler surgical operation, smaller trauma, and better restorative effects on cardiac function.[174] At present, injectable hydrogels can be delivered intramyocardially, transendocardially, intravenously, or intrapericardially (**Figure 7**).[148]

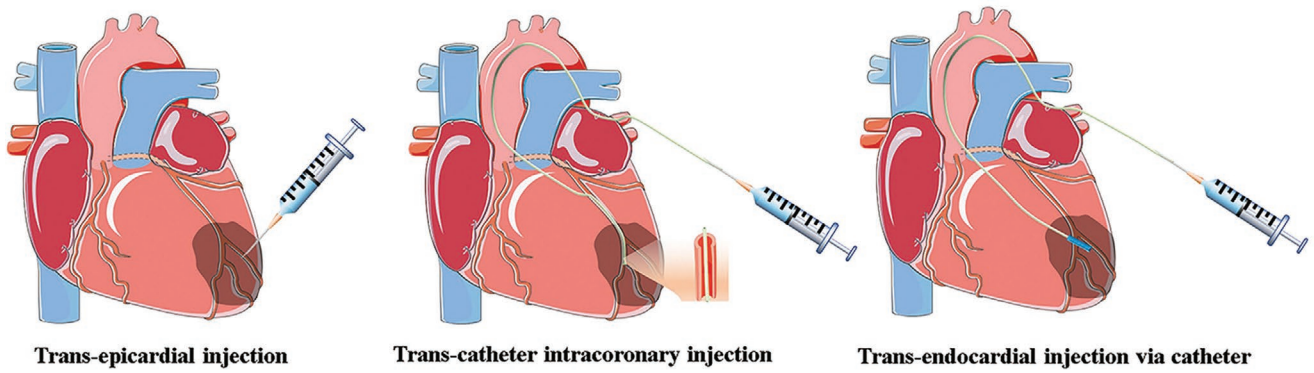

Figure 7. Therapeutic-substance-loaded hydrogel delivery modalities adopted in preclinical studies. Reproduced with permission.[174] Copyright 2021, Elsevier.

According to Laplace's law, the wall stress within a spherical wall at a given pressure is inversely proportional to the wall thickness.[175,176] After MI, the left ventricle expands and the ventricular wall becomes thinner or even ruptures, resulting in increased ventricular wall tension.[176] The injected hydrogel can thicken the ventricular wall and thereby restrains wall stress, which is inversely proportional to wall thickness.[177] Additionally, once being injected into myocardium, these hydrogels are able to improve heart function by providing a unique 3D structure with appropriate biochemical and structural cues for cellular activities and a new construct to integrate with the host.[148] Thus far, injectable acellular hydrogels based on alginate (Algisyl) or the porcine extracellular matrix (Ventrigel) have entered clinical trials. Currently, Algisyl is included in a planned phase II trial to compare this hydrogel with standard medical therapy in an estimated cohort of 240 patients (AUGMENT-HFII, NCT03082508).[178] The new generation of alginate hydrogels, developed by our group and Hangzhou Deke Medical Technology Co., Ltd., has completed early clinical evaluation (10 cases). After transendocardial implantation of the hydrogel, the patients' left ventricular volume was reduced, and the ejection fraction and the patients' 30 day peak oxygen consumption were significantly improved. In conclusion, there is a need to guarantee the complete absence of any immunogenic residue derived from the biomaterial of choice (alginate, decellularized matrix), to ensure both scaled-up production and clinical-grade batch-to-batch reproducibility of the hydrogel and to provide the healthcare institutions with affordable products for patients affected by this disease.[178,179]

Injectable hydrogels may serve as a platform to encapsulate cells or certain biomolecules to promote cardiomyocyte regeneration, regulate inflammation, enhance angiogenesis, or inhibit fibrosis in the diseased myocardium.[178] In addition, injectable hydrogels can overcome the shortcomings of traditional direct injection, including low bioavailability, nonspecific molecular delivery, limited cell proliferation, poor gene retention, and low transfection efficiency, by a modulated sol–gel transition and the localized transport of a variety of encapsulated cargos.[174,175]

Researchers have attempted to treat HF by physically doping cells or active substances in alginate-based hydrogels. For example, lyophilized platelet-rich fibrin that can release a large number of growth factors for promoting vascular regeneration,[180] stem-cell-derived small extracellular vesicles that can protect cardiomyocytes against apoptosis, promote angiogenesis, and reduce infarct size,[181] dendritic-cell-derived exosomes that can improve cardiac function after MI,[182] and melanin nanoparticles for reactive oxygen species (ROS) scavenging.[183] In addition, new series of natural polymers, synthetic polymers, and their composite materials have been applied for the development of multifunctional injectable hydrogels for HF treatment with adjustable gelation rate, degradation rate, mechanical properties, and electrical conductivity, among other properties. Chen et al. fabricated an elastin-mimic hydrogel constructed from a novel peptide sequence (Fmoc-FFVPGVGQGK) for the local delivery of salvianolic-acid-B-loaded polydopamine nanoparticles.[184] The prepared hydrogel could inhibit ventricular remodeling and promote angiogenesis for MI treatment with the long-term release of salvianolic acid B. However, most of these hydrogels have a single function; therefore, they cannot fully meet the requirements for treating the complex clinical syndrome of HF. In addition, the great majority of the previous studies has been performed on rodents and there has been a notable lack of valuable investigations on large animal models.[185] The pathophysiology of MI is complex and contains several sequential phases, including blockage of the coronary artery, necrosis of myocardial cells, inflammation, and myocardial fibrosis.[186] From our point of view, multifunctional hydrogels loaded with multiple active substances, polypeptides and recombinant protein hydrogels with biological activity, and smart hydrogels that respond to the microenvironment of the MI area may be the four main research directions in the future.

By focusing treatment on the different stages of MI, injectable hydrogels can be developed containing two or more active substances with different therapeutic targets to achieve better treatment effects.[173,187] Hao et al. introduced fullerene nanoparticles with antioxidant activity into alginate hydrogels to fabricate a multifunctional injectable hydrogel for the delivery of brown-adipose-derived stem cells (BADSCs). When injected in the MI area in rats, the fullerene/alginate hydrogel caused an effective decrease in ROS level in the MI zone, improving the retention and survival of implanted BADSCs, and inducing angiogenesis, which in turn promoted cardiac functional recovery.[188] Based on the different stages of MI healing, the corresponding therapeutic substances should be released systematically to achieve

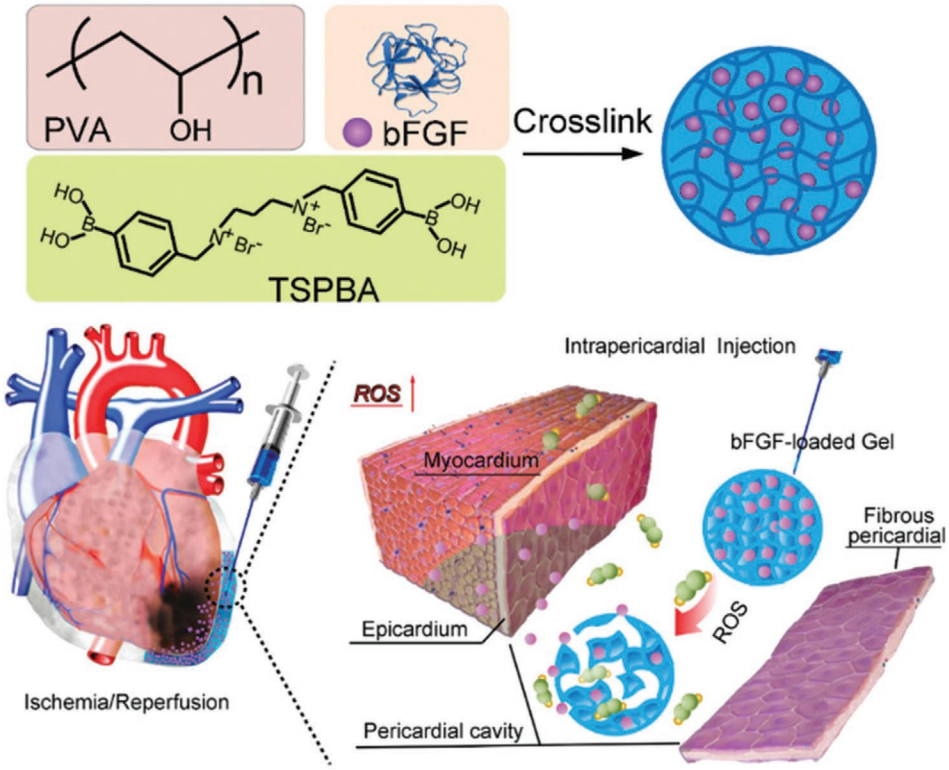

Figure 8. Concept of Gel–bFGF and screening for the optimal FGF for heart repair and the schematic illustration of Gel–bFGF fabrication and overall strategy. Reproduced with permission.[193] Copyright 2021, Wiley-VCH.

the synergistic therapeutic effect. Wu et al. fabricated an injectable alginate hydrogel to load vascular endothelial active factor and silk fibroin microspheres containing bone morphogenetic protein 9 (BMP9) for the release of VEGF and BMP9.[186] The in vitro results indicated a rapid initial release of VEGF during the first few days and a relatively slow and sustained release of BMP9 for days, facilitating the formation of blood vessels in the early stage and inhibiting myocardial fibrosis over the longer term. When injected into the infarct border zone of the mice MI model, this multifunctional hydrogel could promote angiogenesis and reduce the infarction size.

Although numerous biomaterials can provide physical stability to the infarcted myocardium, this somewhat passive structural reinforcement alone may be insufficient to sustain cardiac function in the long term. Therefore, the injectable hydrogels can be designed as a biomimetic matrix with biological activity to restore the disrupted cell–ECM interactions required for cell signaling, function, and survival, thereby supporting cells and stimulating infarction repair. To imitate the healthy cardiac ECM, Li et al. reported the first injectable hydrogels made from recombinant human collagens type I and type III, which were crosslinked by *N*-ethyl-*N*-(3-dimethylaminopropyl) carbodiimide and *N*-hydroxysuccinimide. They demonstrated that an injectable hydrogel made from clinical-grade human collagen was able to prevent adverse cardiac remodeling and to improve cardiac function in the MI heart when applied during the late proliferative phase.[191]

MI results in a series of pathophysiological changes, including activated oxidative stress, aberrant ECM, overloaded intracellular calcium, and activated immune system.[190] Consequently, smart hydrogels show great potential for the treatment of HF in response to the key physiological changes, such as the increased expression of matrix metalloproteinases, decreased pH value, and increased ROS concentration, caused by HF.[191,192] As shown in **Figure 8**, Li et al. synthesized a ROS-responsive hydrogel constructed with PVA and *N*1-(4-boronobenzyl)-*N*3-(4-boronophenyl)-*N*1,*N*1,*N*3,*N*3-tetramethylpropane-1,3-diaminium for the controlled delivery of basic fibroblast growth factor (bFGF).[193] In a rat model of ischemia–reperfusion (I/R) injury, the injected hydrogel could protect cardiac function, enhance angiomyogenesis, and reduce fibrosis in the post-I/R heart by releasing bFGF into the myocardium in an "on-demand" model. Furthermore, they demonstrated the safety and feasibility of minimally invasive injection and access into the pericardial cavity in pigs and human patients. However, long-term maintenance of the functions of hydrogels to promote cardiomyocyte proliferation and angiogenesis while avoiding myocardial fibrosis is an issue that must be considered when designing hydrogel products with clinical translation prospects.

Injectable hydrogels for HF therapy have yielded some promising advances in both scientific research and clinical trials. However, the selection of injection parameters, including injection site, injection volume, injection speed, and injection method, still requires further theoretical research and clinical verification. Finally, for patients with different degrees of HF or different ages, the optimal properties of the hydrogels required (including modulus, degradation rate, injectability,

and self-healing properties) still lack scientific evidence and clear regulations.

4.3. Atrial Shunts

The atrial shunt has become an emerging technology for the treatment of HF throughout the world. The atrial shunt is mainly implanted in the atrial septum through minimally invasive percutaneous intervention to create a left-to-right blood shunt, which reduces left atrial pressure and relieves pulmonary congestion and breathing difficulties. At the same time, it does not significantly increase the burden on the right heart, reduce the blood output of the left heart, nor cause abnormal embolism. In particular, for patients with HF with preserved ejection fraction (HFpEF), it can effectively relieve the left atrium overload, thereby improving the clinical symptoms, exercise tolerance, and prognosis of the patients.[194,195]

At present, the atrial shunt has reached the clinical research stage worldwide, and three products (interatrial shunt device (IASD), V-Wave, atrial flow regulator (AFR)) have obtained CE certification. The IASD (Corvia Medical, Tewksbury, MA, USA) is composed of NiTi memory alloy cutting stents with the left and right atrium disks forming the internal buckle structure, and this is the first permanently inserted atrial shunt device. The V-Wave (V-Wave Ltd., Caesarea, Israel) is similar to the IASD, except that its target patients include patients with HF and reduced ejection fraction. The first-generation V-Wave is an hourglass-shaped NiTi frame in which the left atrium is partially covered with a Teflon (PTFE) skirt to improve blood flow and restrict new tissue growth on the device.[196,197] However, the clinical results showed that 13.9% of patients had a blockage in the V-Wave valve and 36.1% had stenosis when the first-generation V-Wave was implanted for 12 months. Consequently, in the second-generation V-Wave, the lumbar valve was removed, and the coverage of the hourglass frame was increased, changing the PTFE skirt to give full coverage. At present, the preliminary clinical results have been announced, with further studies still in progress.[198,199] The AFR (Occlutech, Istanbul, Turkey) is self-expanding NiTi alloy mesh device consisting of two flat disks and one connecting neck with a central opening (size 4, 6, 8, or 10 mm), which has a rivet structure for recycling. Clinical studies have provided preliminary confirmation of the effectiveness and safety of the AFR in the treatment of HF.[200–203]

In addition, some new atrial shunt products have entered clinical use. For example, the Root Device (Edwards Lifesciences, Irvine, CA, USA) has completed a small number of first-in-man studies, but the results have not yet been announced. The NoYA System (DiNovA Medtech, Hangzhou, China) and the D-Shant atrial shunt (Vickor Medtech, Wuhan, China) have also entered the stage of the early clinical feasibility study.[204] Notably, as shown in **Figure 9**, the D-Shant atrial shunt is a shape-memory metal device braided by a NiTi alloy, and can be specified to 4, 6, 8, or 10 mm. This shunt device can be recycled and intervened twice. In addition, its delivery sheath is the smallest of similar products, which effectively improves the safety of surgical operations. The first-in-man study (6 months) of the D-shant atrial shunt has showed positive results.

The NiTi alloy currently used in the atrial shunts is a non-degradable material, the security risks, such as material compression, rebound, and fracture may be inevitable, and possibly cause chronic inflammation, late stenosis, and thrombosis, the long-term use of anticoagulant drugs, atrial arrhythmia. Studies have reported the application of biodegradable PLLA cardiac occluders in clinical cases,[204] which provides ideas for the future development of biodegradable atrial shunts with potential advantages to overcome the above problems. Furthermore, the surface modification of existing atrial shunts to confer rapid endothelialization ability and improve their biocompatibility is also one of the future development directions of atrial shunts.

For patients with severe end-stage HF, the atrial shunt can significantly improve the symptoms of HF, improve the quality of life, and prolong the life of patients. With the continuous release of clinical research results in the field of atrial shunt technology, this is expected to become a landmark technology in the treatment of HF, especially HFpEF, and then alter the survival status of many patients with HF around the world.

4.4. Outlook of Heart Failure Therapy

HF is the end-stage manifestation of various heart diseases such as coronary heart disease, dilated cardiomyopathy, rheumatic heart disease, and myocarditis. Despite advances in the management of HF patients over the past few decades, mortality and hospitalization rates in patients with HF are still high. Therefore, new HF treatment strategies including injectable hydrogels, myocardial patches, and atrial shunts with improved performance are still to be developed to further reduce mortality and morbidity in HF patients and improve patients' quality of life. It is worth mentioning that functional hydrogels and patches should be designed for different causes of HF disease, thereby reversing ventricular remodeling and promoting myocardial tissue repair. In short, for dilated HF, the mechanical strength and structural stability of injectable hydrogels and myocardial patches are required to be high; In ischemic HF, how to restore myocardial blood supply seems to be the primary consideration. We expect that injectable hydrogels, myocardial patches, or atrial shunts based on biomaterials can bring the dawn of cure for HF patients.

5. Vascular Grafts

5.1. Small Diameter Artificial Vascular Grafts

In autologous or allogeneic vascular transplantation, a usual and available method to treat cardiovascular disease, the great saphenous vein and the intrathoracic artery as autologous vessels are the gold standard chosen by surgeons.[206] The use of autologous vascular grafts is limited by the patient's preexisting medical conditions, and associated additional surgery may lead to morbidity and high failure rates at the donor site. After decades of research and development, the artificial vascular grafts in large diameter (>6 mm diameter) are now out of the laboratory and have a number of proven clinical products, while vascular grafts in small diameter (<6 mm diameter) with

Figure 9. Schematic diagram of D-shant structure. Top: structures of D-shant atrium shunt device from top view plane, squint plane, and side view plane. Down: the photos of D-shant atrium shunt device. Reproduced with permission.[205] Copyright 2022, The Authors, published by John Wiley and Sons on behalf of European Society of Cardiology.

small caliber, slow flow rate, are easy to produce anastomotic thrombus and intimal hyperplasia.[207] In addition, they are at risk of chronic foreign body reaction, infection, inflammation, and calcification. The unsatisfactory performance of synthetic vascular grafts is also due to discordance of combining ability with biological components. Over the past 20 years, various techniques for making tissue-engineered vascular grafts have been explored (**Figure 10**).[208] Moreover, various surface modification strategies also improve the surface blood and biocompatibility of small vessels (**Figure 11**). Here, we will briefly discuss the current fabrication technology of small vascular grafts and the emerging trends in surface functional modification.

5.2. Fabrication Techniques for Vascular Grafts

5.2.1. Engineering-Based Techniques

Electrospinning: Electrospinning is a technique that produces polymer fibers at nano- and microscale by applying an electric field to the polymer solution.[209,210] Electrospinning can produce the fibrous scaffold that mimics the ECM of a native blood vessel (BV) in structure and conformation, making it possible for cells to attach and proliferate.[211] In terms of device design, electrospinning strategies typically include single or mixed solution electrospinning, co-electrospinning, simultaneous electrospinning and electrospraying, and coaxial electrospinning.

Natural polymers, such as elastin,[212] silk fibroin,[213] collagen,[214,215] gelation,[216] and chitosan,[217] have been used to fabricate electrospinning vascular grafts (ESVGs). The advantage of natural polymers is the sufficient biocompatibility. They are able to support endothelialization in vivo and in vitro, as well as infiltration of smooth muscle cells; however, their mechanical properties are less than desirable. By contrast, electrospun vascular grafts prepared from synthetic polymers tend to exhibit mechanical strength comparable to that of native BV. The limitation of synthetic polymers such as poly(*ε*-caprolactone),[218] PLLA,[219] poly(glycolic acid),[220] poly(lactide-*co*-*ε*-caprolactone) (PLCL),[221] is low biocompatibility. Wang and co-workers fabricated a bilayer electrospun vascular grafts with PEGlated chitosan as the inner layer and PLCL as the outer layer, mimicking the bilayer structure of native tissue, which exhibited excellent hemocompatibility and strong mechanical properties both in vivo and in vitro.[222,223] Therefore, the rational combination of natural and synthetic materials and the choice of preparation strategy are crucial for the preparation of artificial small blood vessels by electrostatic spinning.

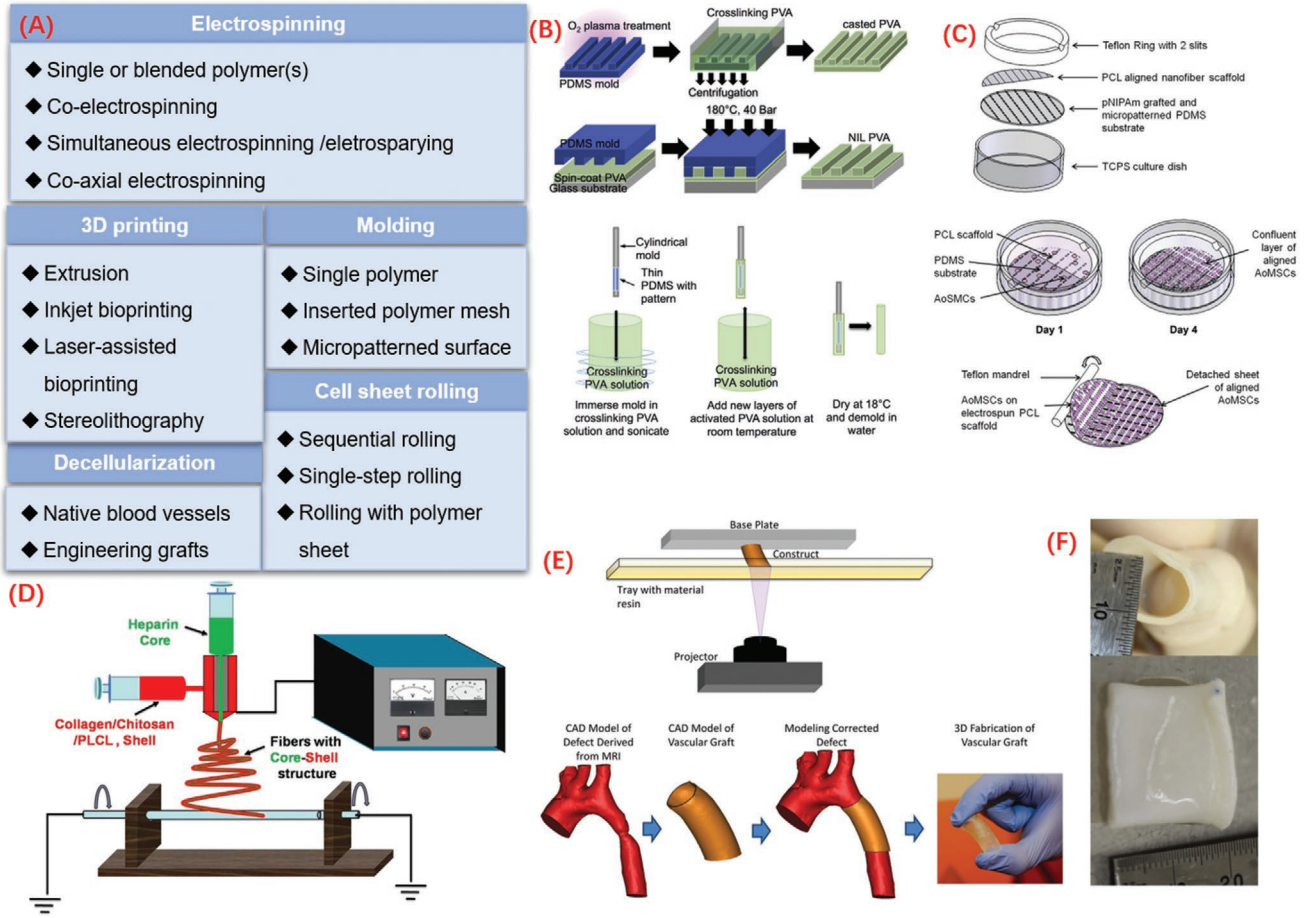

Figure 10. A) Fabrication techniques for vascular grafts. B) Planar and tubular patterning of micro- and nanotopographies on poly(vinyl alcohol) hydrogel for improved endothelial cell responses. B) Reproduced with permission.[227] Copyright 2016, Elsevier. C) Combining cell sheet technology and electrospun scaffolding for engineered tubular, aligned, and contractile blood vessels. Reproduced with permission.[230] Copyright 2013, Elsevier. D) Coaxial electrospinning multicomponent functional heparin controlled-release vascular graft. Reproduced with permission.[238] Copyright 2017, Elsevier. E) 3D-printed biodegradable polymeric vascular grafts. Reproduced with permission.[239] Copyright 2015, Wiley-VCH. F) Decellularized grafts for pulmonary artery replacement in young lambs. Reproduced under the terms of the CC-BY Creative Commons Attribution 4.0 International license (https://creativecommons.org/licenses/by/4.0).[234] Copyright 2016, The Authors, published by Springer Nature.

Molding: Molding allows the manufacture of polymer-based scaffolds in custom shapes. It usually involves pouring the polymer solution into a mold with the desirable geometry and then taking it out of the mold after it has solidified. The advantage of molding is that the geometry of the mold can be designed in any desired shape.[224] Molding is applicable to the preparation of tubular vascular grafts and complex branched vessels. Injection molding is a relatively easy-to-use device, which is usually operated to manufacture molded vascular grafts (MVGs). The annular mold is used to solidify the polymer solution, in which the inner diameter is fixed with an internal rod and the outer tube controls the thickness of the vascular graft. The preparation method provides the conditions for the MVGs with high porosity as well and thus better cell penetration by using techniques that produce small pores, including salt leaching, gas foaming, and phase separation. The multiple selectivity of the mold allows this molding method to obtain a wide range of structures of vascular materials. The mesh can be inserted into two different layers of the molded MVG to provide integral structure and improved mechanical strength, just like microporous mesh produced by polymer.[225,226] Electrospinning fibrous films, which have much higher tensile strength than molded bulk materials, can be applied as MVG coatings to give additional strength and resist breakage.[209] In addition, a thin patterned polydimethylsiloxane (PDMS) can be attached to the inner or outer wall of the mold to achieve surface patterning.[227]

3D Printing: 3D printing is an additive manufacturing method that constructs objects by depositing materials layer by layer, with the guidance from CAD models.[228] Cells are added to the deposited materials to form a substance called bioink. Direct printing of engineered tissues using bioink enables direct spatial alignment of cells without additional cell seeding.[229]

3D printing makes it possible to fabricate precise vascular grafts with predefined pore size and porosity. The model is first reconstructed in 3D from high-resolution magentic resonance imaging or computed tomography images of the native

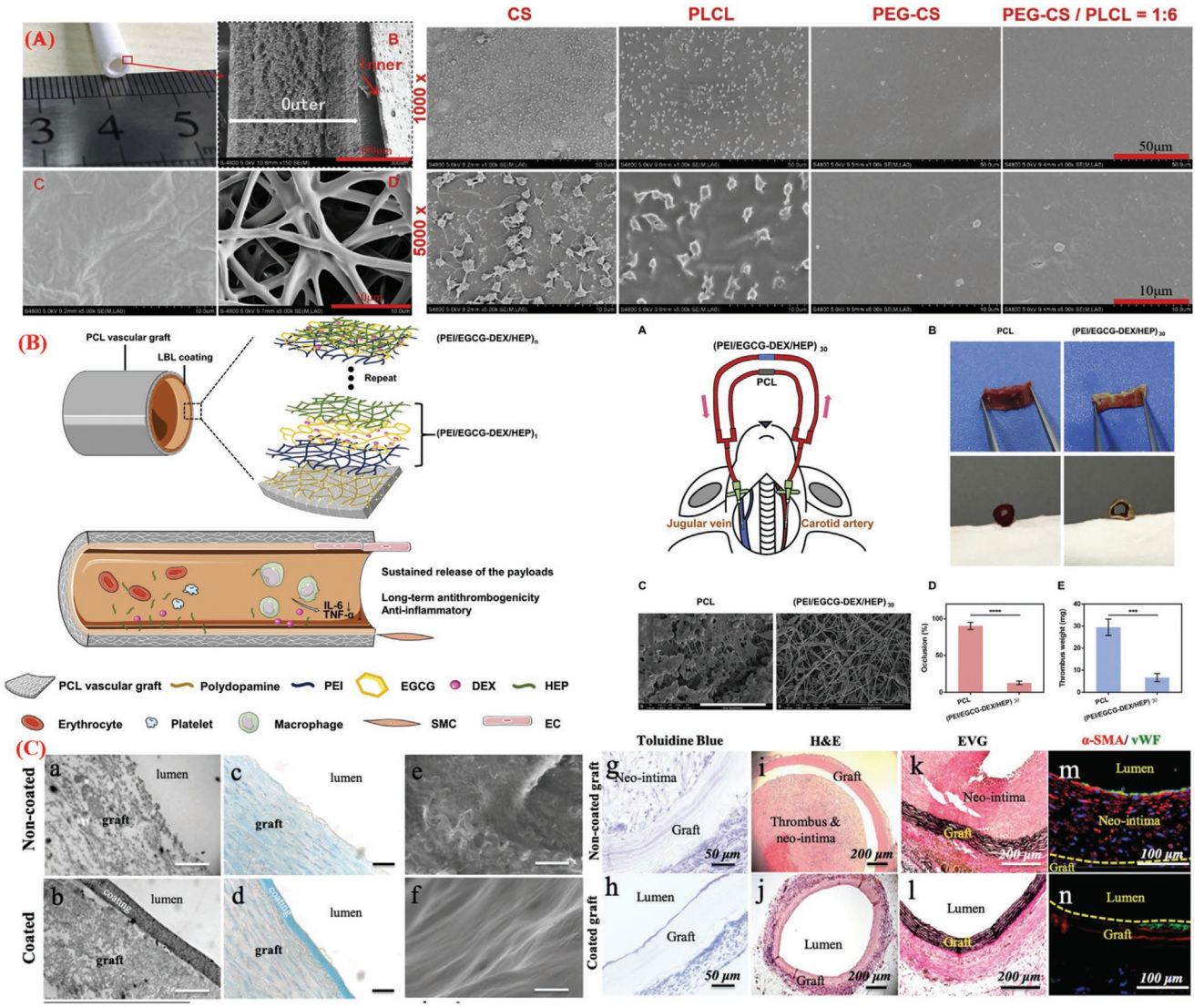

Figure 11. A) PEGylated chitosan and poly(L-lactic acid-*co*-ε-caprolactone) bilayer vascular grafts for blood vessel repair. Reproduced with permission.[223] Copyright 2020, Elsevier. B) Polycaprolactone vascular graft with epigallocatechin-gallate-embedded sandwiched layer-by-layer functionalization for enhanced antithrombogenicity and anti-inflammation. Reproduced with permission.[242] Copyright 2020, Elsevier. C) Small diameter vascular grafts with glycocalyx-like hydrogel coating for antithrombotic performance and endothelial cell promotion. Reproduced with permission.[244] Copyright 2020, Wiley-VCH.

blood vessels, and then postprocessed by CAD before printing, including editing the pore structure and geometric cues.

5.2.2. Cell-Based Techniques

Cell Sheet Engineering: Sheet-based engineering is a method of obtaining functional tissue by using cells or polymer chips. Cell sheet rolling in sequentially and single step are used to manufacture the cell sheet rolled vascular grafts (SRVGs), which allow the use of autologous cells to avoid the immune response while mimicking the biological and structural properties of autologous BV. The aim of cell polymer sheet technology is enhancing the mechanical properties of SRVG. However, the preparation procedure of SRVGs is lengthy, first collecting cells from patients and cultivating them, and then constructing them into grafts. These complex and time-consuming steps make them unusable in emergency situations. Sequential cell sheet rolling is a classical method for constructing vascular grafts. It involves continuous culture of multiple cell membranes onto the Teflon-coated spindle, and the outer cell membrane is rolled to the first layer. Single-step cell sheet rolling is about curling a long cell sheet containing various types of cells to produce multilayer composite cell sheet. Cell–polymer sheet rolling is the simultaneous coiling of polymer and cells cultured on the polymer surface. SRVGs made from cell and polymer sheets are much easier to treat than SRVGs from cell sheet, which are delicate and easily broken during subsequent preparation. Synthetic polymer sheets prepared by molding or electrospinning, such as PLLA,[219] PCL,[230] and PDMS[219] can

be applied in combination with cell sheets composed of fetal bovine serum (FBS),[231] endothelial cells (ECs), and mesenchymal stem cells (MSCs).[232] The cell membrane also can be rolled on the prepared ESVG or MVG coating directly, as an alternative approach to improve the efficiency of cell seeding and cell function.[233]

Decellularization: Decellularization refers to the application with chemical, enzymatic, and physical agents to achieve the ECM of tissues and organs.[234] Decellularized extracellular matrix is able to retain the composition and structure of the native tissue and holds biochemical and mechanical clues, which facilitate the adhesion, proliferation, and differentiation of cell, and the organization and remodeling of tissue.[235] The main recently manufactured decellularized vascular grafts are decellularized natural vessels and decellularized engineered vessels. Native vessels obtained from pigs, cows, eggs, dogs, and humans are the most basic decellularized vessels. Decellularized engineered grafts are first cultured on scaffolds made of synthetic polymers, such as FBS,[236] smooth muscle cells (SMCs),[236] ECs, and endothelialprogenitor cells (EPCs).[237] When the cells have produced enough extracellular matrix, decellularization is performed. These vessels are able to fuse with host vessels and allow subsequent cellular infiltration and ECM deposition.

5.3. Functional Modification Strategies for Vascular Grafts

5.3.1. Antithrombogenic

Coagulopathy is the primary problem that hinders long-term vascular patency. Using natural anticoagulants to make small vascular grafts is the most basic method to avoid the formation of acute thrombosis in vascular transplantation. Heparin is a typical and widely used anticoagulant, which enhances thrombin affinity by interacting with antithrombin III, preventing platelets from adhering to the wall of the tube.[240] Wang and co-workers fabricated a heparin-loaded graft via coaxial electrospinning, and the sustained released heparin significantly improved the anticoagulant capacity of the vascular grafts.[238] It is worth noting that heparin also plays an essential role in inhibiting restenosis.[240,241] However, heparin has a short half-life in the body, which further challenges its suitability. Based on the surface chemistry of catechol, Wang and co-workers established a "sandwiched" layer-by-layer coating to enhance the stability and biological activity of heparin.[242]

At the interface between flowing blood and blood vessel walls, ECs undergo continuous shear stress, which stimulates NO release by upscaling endothelial nitric oxide synthase. It causes prostaglin 2-mediated vasodilatation and inhibits platelet aggregation.[243] In bioengineered vascular grafts, no immobilization agent has shown great potential for preventing acute thrombosis.

More recently, the potential of synthetic drugs to release reactive-oxygen-induced antiplatelet ethyl salicylate, which prevents blood clotting and thus opens up over time, has been studied. In order to establish a biochemical simulation of natural endothelium, the application of hyaluronic acid colloids to acellular vascular grafts has shown protective effects against thrombosis. This new method protects the underlying collagen layer from platelet adhesion and activation.[244]

5.3.2. Rapid Endothelialization

Traditionally, seeding of autologous vascular ECs prior to transplantation has shown clinical results comparable to those of intravenous grafts.[245] Given the limitations of in vitro endothelialization of vascular grafts, the current direction of research has turned to in situ endothelialization. Recent innovative methods have concentrated on the engineering of the interface between vascular grafts and blood in order to catch EPCs in circulation and other cells involved in endothelial formation with the aim of accelerating endothelialization.[246]

Homing and Adhesion of EPCs and ECs: The most direct approach is to modify chemokines targeting chmokine cysteine-X-cysteine and integrin families on the vascular grafts to promote EPC and EC recruitment and adhesion. Biomimetic nanofibrous scaffolds are suitable to enhance the EPC adhesion due to ideal surface to volume ratio, abundant binding ligands.[247] Modification of molecules with bioactive binding or cell-capturing moieties on the surface also improves cell adhesion.[248,249]

Cell Behavior Regulation: The surface morphology of the vascular graft has a substantial impact on the biological behavior and endothelialization of ECs. Several researches have reported that axis-oriented fibers can influence the morphology and arrangement of ECs or MSCs, favoring endothelial remodeling.[250] In addition, well-aligned fibers can improve the mechanical strength of stretch, and facilitate the regular arrangement of external SMCs,[251] thus improving luminal patency.[252] The arrangement of adhesive peptides on the surface also affects behavior of ECs in terms of the migration, morphology, and proliferation.[253]

5.3.3. Inhibiting Inflammation/Intimal Hyperplasia

Endothelial hyperplasia, a pathological state, is caused by endothelial injury resulting in excessive growth and migration of the inner SMC into the endothelium, leading to thickening of the vessel wall.[254] Insufficient rapid endothelialization prevents graft wall thickening, and inflammation can lead to endothelial hyperplasia. Therefore, the degree of the postimplantation inflammatory response triggered by the vascular grafts will decide the severity of subsequent stenosis. In addition, inflammation also causes intima calcification, which threats the long-term patency of vascular graft.[255] Inhibiting the monocyte chemoattractant protein-1 (MCP-1), platelets, and natural killer cells can effectively eliminate stenosis (**Table 2**). Mismatch between vascular grafts and native vessel compliance is thought to be involved in the cause of graft stenosis. Sirolimus or rapamycin,[256] cilostazol, aspirin,[257] and paclitaxel have all been used to inhibit intimal hyperplasia.[258] Bioabsorbable grafts that are functionalized with platelet-rich growth factor and c-kit receptor kinase inhibitors have also shown potential in reducing neointimal tissue generation.[259]

Table 2. Strategies for the functional modification of small vascular grafts.

Purpose	Strategies	Agents/technique	Ref.
Antithrombogenic	Antiadsorption	PEG Zwitterionic polymers	[260,261]
	Anticoagulation	Heparin NO	[242,246,262]
	Synthetic drugs	Tissue plasminogen activaor Warfarin Clopidogrel	[263]
Rapid endothelialization	Homing and adhesion of EPCs and ECs	VEGF MCP-1 stromal cell derived factor 1 antibody Fibronectin	[264]
	Cell behavior regulation	Aligned nanofibers Surface patterns	[250,251]
	Promoted proliferation and activation	VEGF FGF-2 polypeptide containing arginine–glycine–aspartic acid REDV	[264]
Anti-inhibiting inflammation/intimal hyperplasia	Rapid endothelialization		
	Inhibit inflammation	MCP-1 Rapamycin Cilostazol Aspirin Platelet-rich growth factor Dexamethasone	[242,259]

5.4. Future of Vascular Grafts

Over the years, although current techniques for the fabrication and modification of artificial vascular grafts have shown remarkable results under laboratory conditions, their demonstration in the clinical setting has still to be thoroughly investigated. Moreover, their availability requires the combined efforts of biologists, engineers, and clinicians. More in-depth biological mechanistic studies, as well as developmental explorations, greatly facilitate a deeper understanding of the artificial vascular graft remodeling process, as well as the various regulatory factors required for it. In addition, emerging approaches to immunomodulation are critical and promising. A deeper understanding of the association between graft design factors and following immune response could offer a new perspective on the control of healing and remodeling. Artificial vascular grafts need to be integrated with emerging technologies as they develop. In the long term, more convenient and customized products will also require more effort to adapt to the needs of diverse patients with diverse pathological environments.

6. Bioresorbable Cardiac Occluders

Congenital heart disease is a heart defect that exists since birth. An abnormal heart structure will interrupt the one-way flowing of blood in the heart and thus affect the normal way the heart works. Several most common kinds of congenital heart diseases include atrial septal defect (ASD), ventricular septal defect (VSD), patent foramen ovale (PFO), patent ductus arteriosus, etc., which are manifested as a hole located on the wall of atrium, ventricle, or vessel. Surgical closure and device closure are two common treatments for congenital heart defects. The number of device closures steadily increases because occluder devices can be delivered through a catheter for less morbidity, lack of a scar, and shorter hospital stay. Commercially available occluders are made from nondegradable metal (usually Ni–Ti alloy) that is responsible for anchoring to a defect site and polymeric fabric membrane (usually PET) that is responsible for blocking the abnormal shunt of blood.[265,266] However, all these occluders are designed to exist in the human body lifelong, which might lead to long-term foreign body response, a lasting releasing of Ni ions, and mechanics mismatch between occluders and adjacent tissues. The reported occluder-device-related complications include tissue erosion, device embolization, thrombus, and arrhythmias, with an overall occurrence rate varying from 0.1% to 8.6%.[267,268] Bioresorbable cardiac occluders as a disruptive new device can provide temporary occlusion and induce in situ tissue regeneration in the hope of solving the problems with traditional cardiac occluders.

6.1. Principles for Degradable Cardiac Occluders

The concept of bioresorbable occluders are built on the "in situ" tissue regeneration theory.[269] At the early stage of occluder implantation, the function of a occluder is anchoring to the tissue around a heart defect and providing immediate closure.

Also, it is hypothesized that a bioresorbable occluder can function as an instructive scaffold for endogenous cells to infiltrate, migrate, and generate a new tissue through an inflammation-mediated process. Over time, the defect is filled by new tissue with the occluder inside. At this moment, there is no need for the occluder to withstand the hydrodynamic loads and it is slowly resorbed, with one's own normal heart left. Especially in the field of blood vessels,[270,271] and heart valves,[272] the concept of in situ tissue engineering has been demonstrated technically feasible. However, huge challenges remain in developing bioresorbable occluders with good effectiveness and safety. In particular, taking into account the need for transcatheter delivery, bioresorbable occluders put a higher demand on the mechanical performance of materials.

6.2. Components of Degradable Occluders

Framework and the membrane attached to it are two main components of the bioresorbable occluder. A framework provides the fixation force to resist the pressure between the heart chambers or vessel lumens. A membrane is dense to stop the blood flow from passing through a heart defect. Additionally, the framework and membrane should meet the requirements for catheter delivery. A cardiac occluder should keep intact when it is crimped into a sheath, and it should recover the predesigned shape completely when it is pushed out from the sheath. In this section, we will particularly discuss the applicability of materials to bioresorbable occluders from the aspect of mechanics and degradability.

6.2.1. Framework

Currently, FDA-approved biodegradable polymer materials that can be implanted into the human body mainly include poly-*p*-dioxanone (PDO), PLA, PCL, and poly(4-hydroxybutyric acid) (P4HB). Their basic properties are listed in Table 4. Considering the main role of the framework is anchoring to tissue and preventing the device from slipping out under the condition of a blood strike, it requires robust mechanical properties of framework materials especially the modulus. As listed in **Table 3**, the tensile modulus of polymers is significantly lower than Ni–Ti alloy, so the polymeric biodegradable occluder has a weak fixation force and may involve a higher risk of detachment. Increasing the framework mass and volume can reinforce the biodegradable occluders but may negatively affect the delivery performance. Based on the modulus distinction, PDO and PLA are superior to PCL or P4HB for constructing the framework of the biodegradable occluder because the former possesses a higher modulus. Another challenge is the incompatibility of degradable polymer mechanics with catheter delivery due to their poor shape memory effect. Unlike Ni–Ti alloy, most degradable occluders fail to recover the predesigned geometry shape when being released from a sheath. The geometry bias of an occluder to the design will not only decrease the fixation force but also perturb the normal flowing of blood by the protrusion of the frame disk into the heart chambers or vessel lumens. Therefore, most biodegradable occluders adopt a design of mechanical lock for geometry maintenance and fixation force compensation. Besides, a key factor that should be deliberately considered when developing a biodegradable occluder is the match of degradation rate and tissue generation rate. The mechanical strength of degradable frameworks declines as the degradation proceeds. If the framework loses its mechanical support before being covered by tissue, the occluder will slip out and lead to embolization. Previous animal studies reported that the biodegradable occluder could be covered by intima tissue in 3–6 months which is significantly shorter than Ni–Ti alloy counterparts.[273] This result suggested that temporarily mechanical support for as long as 3–6 months might be enough for a biodegradable occluder.

6.2.2. Membrane

The membrane attached to a framework can be crimped for delivery and unfolded for blocking blood together with the framework. A basic requirement for the mechanical performance of membrane materials is to withstand the pressure in the atrium, ventricle, or other chambers, ranging from 3–100 mmHg. Besides, a membrane should be able to be conveniently crimped within a sheath. Quite a few degradable materials including polymers listed in Table 3 and collagen-based materials might meet this mechanics threshold. And similar to a framework, the membrane must maintain enough mechanical strength until being covered by newborn tissue. For increasing the rate of tissue regeneration, the membrane usually possesses porous morphology allowing for rapid cell repopulation.

6.3. Clinical Progress in Bioresorbable Occluder Devices

The clinical progress of several typical bioresorbable cardiac occluders is summarized in **Table 4**. Most bioresorbable

Table 3. The basic properties of framework materials used in cardiac occluders.

Materials	Tensile modulus[GPa]	T_g [°C]	T_m [°C]	Degradation time	Ref.
PDO	1.5	–10–0	110	6–12 months	[273]
PLA	1.9	60–65	173–178	12–36 months	[273]
PCL	0.4	–65–60	58–63	>24 months	[273]
P4HB	0.07	–48–51	53–60	8–52 weeks	[274]
Ni–Ti	48 (austenitic phase)	–	–	–	[275]

Table 4. The clinical trials of various bioresorbable cardiac occluders.

Manufacturer	Product name	Framework	Membrane	Application	Clinical result
NMT	BioSTAR	MP35N Stainless steel	SIS	PFO/ASD	Successfully implanted in 57 (98%) of 58 patients with ASD or PFO. High closure rate at 1 month (92%) and 6 months (94%).[274] Implanted in 9 patients with ASD. No residual shunts at 0 and 30 days postimplantation. No major complications.[279]
atHeart Medical	reSept	PLGA	PET	PFO/ASD	Successfully implanted in 14 patients without complication. Complete closure in 4/6 PFO patients and 6/7 ASD patients at 6 months. No recanalization at 12 and 24 months. No major complications.[280]
Mallow Medical	Pancy	PDO	PET	PFO	Limited data are available. Effective defect closure and no leak postimplantation.[281]
Lifetech	Absnow	PLLA	PLLA	ASD	Implanted in five patients. Complete defect closure rates at 30 days, 3 months, and 6 months were 60%, 80%, and 80%, respectively. Residual shunts were detected in 3 of 5 patients at 2 and 3 years and the residual shunt size increased over time.[277,278]
Shanghai Shape Memory Alloy	MemoSorb	PDO	PLA	VSD	Successfully implanted in 53 of 55 patients with VSD. The closure rate at 6 months and 1 year were all 100%. No device-related major complication.[a)]

[a)]Provided by Shanghai Shape Memory Alloy.

occluder devices have similar disk-like geometry to traditional metal occluders because they close the defect in a similar fashion. The components of cardiac occluders mainly include framework and membrane, either or both of which can be made by degradable materials for biodegradability. The development of bioresorbable occluders undergoes from partially bioresorbable ones to fully bioresorbable ones.[276] BioSTAR and reSept as two typical examples of the early partially bioresorbable occluder possess a degradable membrane (small intestinal submucosa (SIS)) and a degradable framework (poly(lactic-*co*-glycolic acid) (PLGA)), respectively. The early term clinical study showed that these devices could be successfully delivered into the human body and great postoperation closure of the defect was achieved.[277] At present, BioSTAR is discontinued and reSept has only received the investigational device exemption approval of FDA for a clinical trial in 2020. No further clinical result is revealed until now. A partially bioresorbable PFO occluder (Pancy) developed by Shanghai Mallow Medical has a degradable framework made from PDO and a nondegradable membrane made from PET polyester. Lifetech Scientific company developed a fully bioresorbable ASD occluder (Absnow) composed of PLLA framework and PLLA membrane. The device has medium self-expansion properties. However, the shape memory effect of the PLLA framework might be not enough to ensure a complete shape recovery, so a physical locking stick as a bridge between the two disks is designed to enhance the shape retention.[278] The first-in-man study showed that the device had the desired immediate closure.[279] However, there was a higher proportion (20–40%) of the residual shunt in patients after 1 year implantation. The proportion expanded to 60% after 2 and 3 year implantations and the size also increased over time.[279] The weak mechanical properties and poor geometry fitness between disks and tissue may contribute to the problem. The leak deteriorates as the mechanics of occluders declines during the period of late-term implantation. Meanwhile, there is no sufficient new tissue generated to compensate for the loss of fixation force and fill the defect. The match between the mechanics' decline curve and the profile of tissue regeneration over time is vital for the success of developing a bioresorbable occluder. Wang and co-workers at the National Engineering Research Center for Biomaterials in the Sichuan University worked closely with Shanghai Shape Memory Alloy Inc. and Fuwai Hospital, and have developed a bioresorbable VSD occluder (MemoSorb) fabricated by the PDO framework and PLA membrane. MemoSorb is expected to be covered by newborn tissue within 3 months after implantation and have a life span of ≈12 months in the human body. A prospective, multicenter, randomized, noninferiority clinical trial was conducted to evaluate the effectiveness and safety of this device. 1 year follow-up result demonstrated that 100% closure rate was achieved at 6 and 12 months postimplantation. No device-related major complications were encountered in the study. Memosorb VSD occluder is not inferior to traditional Ni–Ti occluders in the treatment of ventricular septal defect of congenital heart disease, and has been approved by National Medical Products Administration (Chinese) in February 2022, which became the first bioresorbable cardiac occluder approved by national regulatory agencies worldwide. The approval of MemoSorb is expected to stimulate the rapid development and application of degradable materials in medical devices for structural heart diseases.

6.4. New Concepts of Biodegradable Occluders

3D printing technology provides a rapid, cost-effective manufacturing way for personalized medical devices. The high variety of heart anatomy makes it difficult for the standard-sized device to cover all the patients' conditions. Recently, Lin et al. constructed a biodegradable occluder using PLLA and magnific Fe_3O_4 nanoparticle by 3D printing technology,[282] which could provide a personalized occluder customized to a patient's anatomy (**Figure 12**). Due to the addition of magnific nanoparticles, this occluder showed a good shape memory effect under the stimulation of the magnific field. In

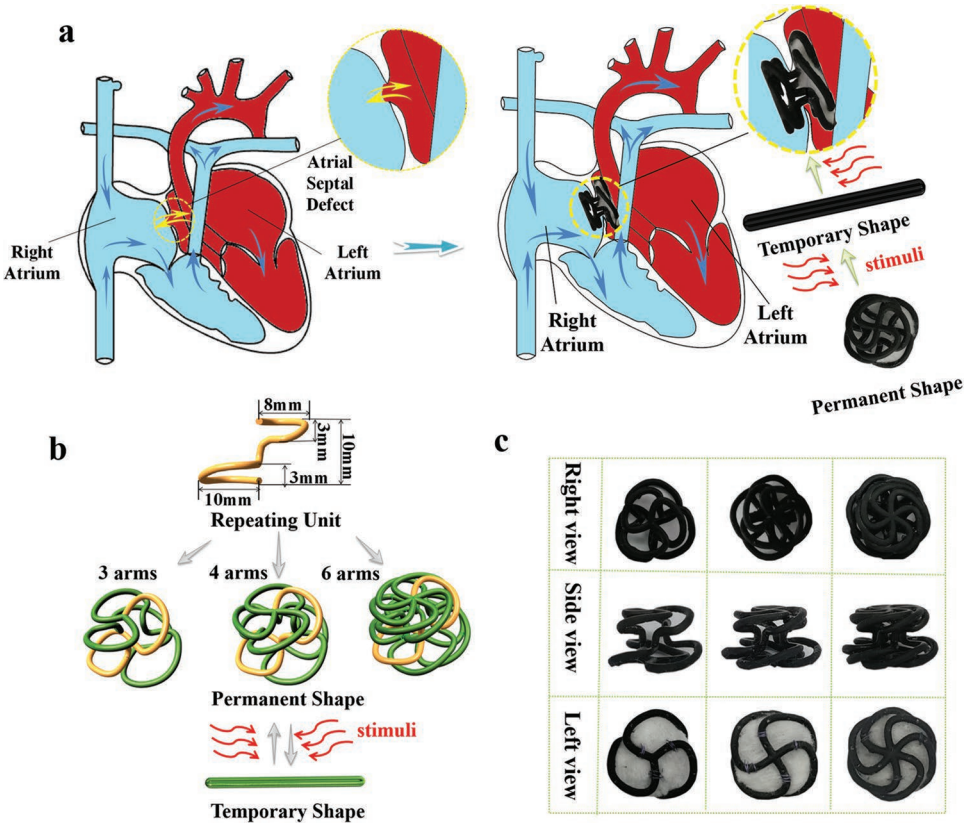

Figure 12. A) Schematic illustration of the ASD prototype before and after interventional therapy with an occluder. B) Schematic illustration of the design of three types of occluder frames with different arms. C) 4D-printed occluders with frame and membranes. A–C) Reproduced with permission.[282] Copyright 2019, Wiley-VCH.

vitro closure simulation also demonstrated this device could be delivered by a catheter and effectively close the ASD. Sun et al. printed a biodegradable occluder with a poly(lactic acid) (PLA) copolymer consisting of PLA, trimethylene carbonate, and glycolide.[283] In vitro and in vivo experiments demonstrated that the occluder had good biocompatibility. Up to now, the 3D printed occluder still stays conceptual stage and needs to be further evaluated for its feasibility in a large animal model.

6.5. Outlook of Cardiac Occluders

In recent decades, a rapid progression has been made in the development of biodegradable cardiac occluders. The major challenge faced by the development of a successful biodegradable occluder is to achieve the early term retention of sufficient mechanical anchoring, raid heart tissue generation, and fast resorption late in implantation. Therefore, the current bioabsorbable cardiac occluders mainly aim to achieve the orchestration between mechanical properties' evolution of devices and the growth rate of new tissue to make sure the completed closure of defects during implantation. More studies are needed to confirm whether these occluders can induce the generation of cardiac tissue recapitulating the exact microstructure and function of naive tissues. In addition, a long-term and large-scale cohort study is still needed to show how a biodegradable occluder can restore the normal physiological function of the heart as well as providing more benefits than a traditional occluder.

7. Conclusion

The innovative biomaterials and devices have provided powerful solutions for the treatment of various cardiovascular diseases. The development of cardiovascular biomaterials and devices is an interdisciplinary field involving materials, machinery, biology, medicine, and other disciplines, and the emergence of new material, the birth of relevant new clinical technology, and the progress of clinical surgery techniques may all promote the generation and development of innovative cardiovascular medical devices. Looking forward, the further investigations of cardiovascular biomaterials and devices should focus on the following aspects: 1) biodegradable cardiovascular stents and cardiac occluders with tissue regeneration function; 2) synthetic polymeric valves with biosafety and durability; and 3) injectable hydrogels with tissue regeneration for heart failure therapy. With the development and improved performance of new cardiovascular biomaterials and devices, more advanced treatment options will be available to bring new hope to the cardiovascular patients.

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Conflict of Interest

The authors declare no conflict of interest.

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