Materials Advances

REVIEW

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View Journal | View Issue

Cite this: *Mater. Adv.*, 2025, **6**, 6221

An overview of small diameter vascular grafts: from materials to fabrication

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Received 22nd June 2025,
Accepted 6th August 2025

DOI: 10.1039/d5ma00663e

rsc.li/materials-advances

Small-diameter vascular grafts (SDVGs, inner diameter ≤6 mm) are in urgent demand for treating severe vascular diseases, such as coronary and peripheral artery diseases, where autologous grafts are often unavailable. Despite the clinical success of large-diameter vascular grafts (LDVGs), SDVGs face significant challenges, including poor biocompatibility, high thrombosis risk, and inadequate mechanical properties, limiting their widespread application. Recent advances in biomaterials—ranging from synthetic polymers to decellularized scaffolds—have sought to address these limitations, yet each material presents trade-offs in durability, immunogenicity, and regenerative potential. Furthermore, innovative fabrication techniques, such as electrospinning and 3D printing, have improved graft performance but struggle with scalability and long-term patency. In this review, we systematically evaluated the current materials used for the fabrication of SDVGs and classified them based on degradability (degradable *vs.* non-degradable) and origin (biological materials *vs.* synthetic polymers), providing a comprehensive comparison of their utility in SDVG applications. Furthermore, we conducted a detailed elaboration and comparative analysis of various fabrication techniques, including cell sheet engineering, molding, bioreactor, bioprinting, and others. Most importantly, we provide clinical insights into overcoming current barriers, proposing strategies for enhancing hemocompatibility, endothelialization, and mechanical resilience to accelerate the translation of SDVGs into real-world practice.

1. Introduction

Cardiovascular diseases (CVDs), including coronary artery disease (CAD), peripheral artery disease (PAD), cerebrovascular disease, aortic aneurysm, and dissection, remain the most common causes of death worldwide. According to the American

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Heart Association, 928 714 people died from CVDs in 2023 in the United States.[1] To help treat CVDs, bypass grafts have been widely implemented. However, this approach is not a permanent solution.[2] Taking coronary artery bypass grafting (CABG) as an example, 40–50% of saphenous vein graft patients (the most commonly used conduit in CABG surgery) experience restenosis within 10 years after surgery.[3] Thus, it is likely that some patients require a secondary operation because of graft occlusion following CABG. Indeed, Lenzen *et al.* found that 3% of patients revascularized only 1 year after CABG.[4] What is worse, this rate progressively rises with duration after CABG. Nevertheless, after considering underlying diseases such as hypertension, diabetes, and hyperlipidemia, as well as the issue of insufficient target vessels due to previous use segments, it is quite possible that the patients who need secondary surgery cannot obtain satisfactory autografts.[5] In fact, based on reported statistics, no autografts are available in approximately 30% of cases, making surgeons reliant on artificial blood vessels (ABVs).[6,7]

However, according to the existing data, the practicality of small diameter vascular grafts (SDVG) still leaves much to be desired. In two single-arm trials launched by the team of Lawson, bioengineered human acellular vessels (diameter = 6 mm, 35 cm < length < 42 cm) were implanted into 60 patients.[8] One year after implantation, only 38% of these SDVG remained patent without the occurrence of thrombosis. The patency rate of SDVG compared to other ABVs is unsatisfactory, revealing a potential problem that SDVG manufacturers may need to address urgently. The synthetic polymers used to make vascular grafts may have trouble adapting to the human internal environment, which can lead to acute thrombus formation and eventually cause graft failure.[9] In contrast, biomaterials, also called natural materials, although they have good biocompatibility, have weaknesses in terms of biomechanical properties. As a result, hybrid polymers have drawn scholars' attention since they combine the advantages of different materials. However, the optimal proportion of each material to use in SDVGs remains unknown. Inappropriate ratios may result in excessively low elasticity that leads to hemodynamic instability, or overly low stiffness that increases the risk of graft rupture.[10] Moreover, the immunogenicity associated with various materials is another critical issue that cannot be overlooked. Employing appropriate fabrication methods may help address this challenge.[11,12]

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2. SDVG materials

An artery can be structurally subdivided into three layers: the tunica intima, tunica media, and tunica adventitia. Each component performs different functions, such as maintaining good blood flow, providing substantial elastic potential to generate diastolic blood pressure, and ensuring the overall structural stability of the artery. Specifically, the tunica intima possesses distinctive anti-thrombogenic properties due to the endothelial cells (ECs), that help prevent platelet aggregation and clot formation.[13] The tunica media primarily consists of numerous vascular smooth muscle cells (VSMCs) that are responsible for

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vasoconstriction and vasodilation.[13] In addition, extracellular matrix (ECM) proteins can be produced by VSMCs, to support vascular remodeling and regeneration.[14] Thus, SDVGs must possess essential characteristics that make them adaptable to the *in vivo* environment. In particular, biomechanical properties related to burst pressure, high-stress deformation, and suture strength should be similar to autografts in order to prevent aneurysms and neointima development.[15] Furthermore, noncytotoxicity and support of cell growth are necessary in allowing cell seeding, proliferation, and differentiation. Finally, SDVGs must be nonimmunogenic and ideally possess *in vivo* remodeling and regenerative properties.[16] Currently, SDVGs can be categorized into synthetic polymers, biopolymers, and hybrid polymers based on their materials.[17] Moreover, synthetic polymers fall into two categories based on their degradability: those that degrade over time and those that remain structurally stable. The following sections discuss each type in detail. Table 1 outlines the pros and cons of each material.

2.1 Nondegradable polymers

Nondegradable polymers, including expanded polytetrafluoroethylene (ePTFE), Dacron, and polyurethanes (PU), are among the earliest materials used for the production of ABVs employed in bypass surgeries. These materials were initially applied in large diameter vascular grafts (LDVGs) and achieved favorable outcomes.[18] Therefore, the potential of using nondegradable materials for SDVGs has continually drawn researchers' attention. Table 2 outlines both the advantages and disadvantages of each nondegradable material, incorporating the latest research findings.

EPTFE obtained by structurally modifying polytetrafluoroethylene has desirable mechanical strength, and excellent resistance to degradation, making it commercially viable as an LDVG. However, in a *meta*-analysis conducted by Halbert *et al.*, the patency rates of ePTFE-based SDVG at 1 year were 41%.[25] Compared to autografts, this value is significantly lower. The underlying reason for this phenomenon is that the hydrophobic surface of ePTFE prevents EC adhesion and causes platelet activation.[26] Therefore, modifying the surface of ePTFE to endothelialize rapidly and avoid restenosis is currently the focus of several studies.[27–29] In Johanka *et al.*'s study, a modified version of the standard ePTFE-based SDVG was introduced through the controlled fabrication of a fibrin mesh that incorporates covalently bound heparin along with noncovalently bound vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF).[30] Compared to the standard group, better antithrombogenic properties after contact with blood were shown in this coated prosthesis (Fig. 1). Specifically, when VEGF and FGF were bound to the fibrin/heparin coatings and exposed to fresh human blood, no plasma coagulation was detected, nor were any blood clot deposits observed on the fibrin/heparin-coated glass. In light of this, Jarkko *et al.* improved endothelialization of ePTFE-based SDVG by using growth factor therapy.[31] To elaborate, after uni- or bilateral end-to-end interposing grafts in the carotid arteries of NZW rabbits, the tissue surrounding the grafts was transduced with VEGF receptor-2 ligand. On day 28, the experimental group achieved $11.2 \pm 26.3\%$ endothelialization, compared to 0% endothelialization in the controlled group, p-value < 0.05. Moreover, synthetic grafts with high porosity have been shown to be an accessible way to increase biocompatibility and improve the patency of ABVs through enhancing endothelialization.[32,33]

Similar to ePTFE, Dacron, also called polyethylene terephthalate (PET), has excellent mechanical properties and tensile strength, enabling it to adapt to blood pressure. According to the test results of Jayendiran *et al.*, Dacron grafts exhibit greater stiffness compared to biological tissues, approximately 1.5 times that of the vascular intima layer. Additionally, the von Mises stress calculated at the junction between the aortic vessel and the Dacron graft is significantly lower than the aorta's ultimate tensile strength. Therefore, they concluded that the probability of adverse outcomes, such as delamination or rupture of the Dacron graft, is extremely low.[34] When it was used for LDVG, the prognosis was outstanding, with a five-year patency exceeding 85%.[35] However, when applied to SDVGs, the performance of this material is less than satisfactory. Given that Dacron has a hydrophobic surface such as ePTFE,

Table 1 The advantages and disadvantages of each material used to produce SDVGs

Material	Pros	Cons	Ref.
Nondegradable polymers	1. Outstanding mechanical strength enables SDVGs to withstand hemodynamic forces. 2. Maintaining remarkable stability over extended durations.	1. Demonstrating bioinertia with limited cell adhesion. 2. Predisposition to calcification/thrombosis.	25 and 34
Degradable polymers	1. Providing temporary structural support while creating pores through subsequent dissolution. 2. Exhibiting excellent processability *via* standard techniques.	1. The material shows insufficient mechanical strength. 2. Incomplete dissolution may trigger inflammatory cascades.	61, 62 and 66
Biopolymers	1. Exhibiting high biocompatibility while supporting cell migration. 2. Containing natural cell-binding motifs.	1. Suffering from uncontrollable degradation rates. 2. Requiring crosslinking to compensate for mechanical deficiency.	17, 70 and 86
Hybrid polymers	1. Balancing mechanical strength with bioactivity. 2. Recapitulating native vascular layered architecture.	1. Involving complex fabrication processes requiring precise ratio optimization.	106, 112 and 116

Table 2 The advantages and disadvantages of each nondegradable material used to produce SDVGs

Material	Advantages	Disadvantages	Application	Comments	Research team
ePTFE	1. Great mechanical properties that can adapt to natural blood pressure	1. Hydrophobic surface that resists EC adhesion and proliferation, causing acute thrombosis	*In vitro*	ePTFE modified with heparin, epigallocatechin gallate, polyethyleneimine, and rapamycin promotes HUVEC adhesion and inhibits SMC proliferation	Ding K, Yu X, Wang D, *et al.*[19]
	2. Enough suture strength to meet the requirements of the operation	2. Foreign body rejection caused by nondegradability leads to later failure of grafts	*In vivo*	Novel PTFE decreases the rate of acute thrombosis compared to ePTFE (5.73 ± 2.19% *vs.* 77.6 ± 9.5%)	Zhou S, Liu Y, Yu X, *et al.*[20]
	3. Negative charges on polymer limit the coagulation of blood proteins to some extent				
Dacron	1. Better biocompatibility, high mechanical strength, and low toxicity allow it to have better performance in the field of SDVGs	1. Lack of elasticity in the circumferential direction and high stiffness lead to loss of energy, limiting its use in SDVGs	*In vitro*	Gelatin-covalently modified Dacron has superior hemocompatibility properties	Giol ED, Van Vlierberghe S, Unger RE, *et al.*[21]
		2. Hydrophobic surfaces such as ePTFE enhance the risk of occlusion in the short term	*In vitro*	1. Higher cell viability has been observed on the surface of the Dacron/PCL/PU triad-hybrid vascular graft 2. The compliance and burst pressure of this graft are suitable for natural vessels	Jirofti N, Mohebbi-Kalhori D, Samimi A, *et al.*[22]
PU	1. Superior biocompatibility and elasticity enabling it to achieve rapid endothelialization	1. Not enough strength to support numerous soft segments embedded in polymers	*In vitro*	Hydrophilic PU elastomer developed by crosslinking hard-segment with diaminopyrimidine-capped polyethylene glycol that achieves improved biomechanical properties and bio functions, including stable catalytic release of nitric oxide and inhibition of SMC proliferation	Li S, Yang L, Zhao Z, *et al.*[23]
		2. Poor shape retention and weak pressure resistance increase the risk of aneurysm or graft rupture 3. No consideration of its thickness for balancing strength and elasticity 4. Lack of bio function and hydrophilicity	*In vivo*	Gelatin/heparin coated bio-inspired PU composite-based SDVG achieves a higher patency rate after 3 months implanted into rabbit carotid arteries	Xiang Z, Chen H, Xu B, *et al.*[24]

unmodified Dacron grafts, when used directly as SDVGs, often resist EC adhesion and proliferation. This leads to platelet activation and thrombus formation, ultimately resulting in reduced graft patency or even complete occlusion. Therefore, current modification methods for Dacron are largely similar to those for ePTFE, including in plasma treatment, binding anticoagulants, and bioactive proteins.[28,36–38]

Typically, the surface of most of these synthetic polymers lacks arginine–glycine–aspartic acid (RGD) binding sites, which means they are deficient in promoting cell adhesion.[39] After treating a 2 mm-diameter SDVG with a functional surface coating containing RGD molecules, Zheng *et al.* transplanted it into a rabbit carotid artery and monitored its patency and endothelial coverage at 2 and 4 weeks.[40] Each SDVG was patent, but 4 of 10 unmodified grafts were occluded because of thrombus formation. Additionally, confluent endothelium was observed in the intervention group, and the ECs were aligned with an order similar to the native vessel. Moreover, to eliminate factors that affect coating stability and ensure no cytotoxic damage, Elena *et al.* covalently bonded gelatin to the surface of Dacron for *in vitro* experiments.[21] Regardless of whether comparing the unmodified group or the physically bonded gelatin group, the results showed that this method indeed led to better endothelialization in 24 hours and 1 week. Another interesting phenomenon the experiment revealed was that endothelialization with human umbilical vein endothelial cells (HUVECs, cells for LDVG applications) was inferior to human dermal microvascular endothelial cells (HDMECs, cells for SDVG applications), which is contrary to the fact that Dacron performs better in LDVG applications than in SDVG. The specific mechanisms, however, have yet to be explored.

Another nondegradable material typically used for the fabrication of SDVGs is PU. With its microphase separation due to different polarity, PU facilitates superior biocompatibility, compliance, elasticity, and anticoagulation compared to ePTFE and Dacron.[18] According to the theory of Kinkert and Yasim *et al.*, the reason ePTFE and Dacron are prone to thrombosis and result in lower patency rates is due to their insufficient

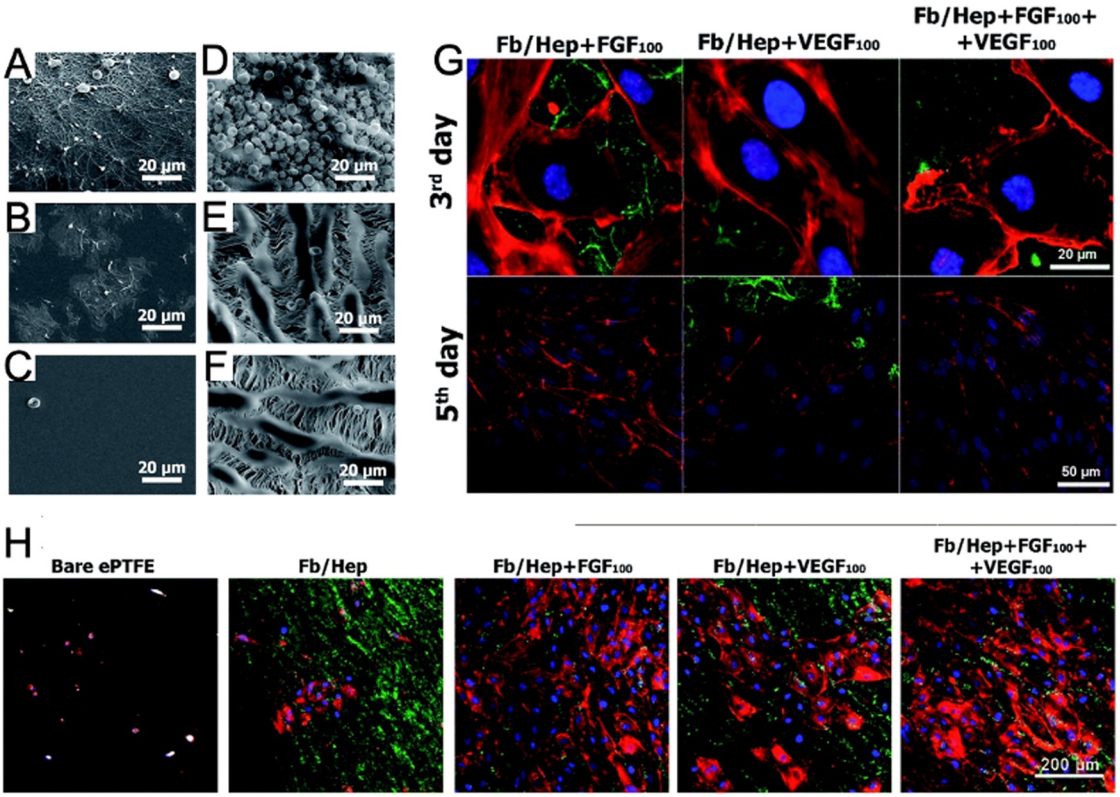

Fig. 1 Antithrombogenic property and cell-adhesive property of fibrin/heparin + FGF_{100} + $VEGF_{100}$ coat. (A)–(C) The SEM images of unmodified glass *in vitro*. (A) A blood clot composed of platelet aggregates, leukocytes and red blood cells on the bare glass. (B) Spread activated platelets on the fibrin coated glass, without leukocytes and red blood cells. (C) No blood clot deposits formed on the fibrin/heparin coated glass. (D)–(F) The SEM images of unmodified ePTFE *in vitro*. (D) An initial thrombus with platelet aggregates and many entrapped leukocytes and red blood cells on the unmodified ePTFE vessels. Only scattered red blood cells presented on fibrin/heparin coated ePTFE vessels (E) and fibrin/heparin + FGF_{100} + $VEGF_{100}$ coated ePTFE vessels (F) after 1 hour incubation with fresh heparinized human blood at 37 °C. (G) HUVECs on day 3 and day 5 after seeding on the coated glass. The blue parts on the images are the nuclei stained with Hoechst. (H) HUVECs on day 5 after seeding on the inner surface of modified ePTFE vessel walls. Adapted with permission.[30] Copyright 2021, RSC.

elasticity.[41,42] As a result, PU, which possesses good elasticity, has attracted much attention from researchers.[43–45] Furthermore, SDVGs made from PU can achieve rapid endothelialization, improving the patency rate in the body.[46] Although PU exhibits excellent elasticity and biocompatibility, its relatively weak strength, attributed to the abundance of soft segments within its polymer structure, leads to poor shape retention and poor resistance to pressure, limiting its application and development.[47,48] Some researchers have proposed increasing the thickness of PU to enhance its strength.[49,50] However, the resulting reduction in elasticity compromises PU's original advantage.[51,52] Consequently, the imbalance between strength and elasticity poses a major challenge for the practical application of PU. Recently, Zhang *et al.* designed and fabricated a PU vascular graft by preparing three SDVG layers *via* the textile techniques of wet spinning and knitting. Specifically, the inner layer was formed from PU filaments produced through wet spinning, the middle layer consisted of PU tubular fabric, and the outer layer was created by spraying a PU solution. In comparison to ePTFE and Dacron, this newly developed PU SDVG exhibited decent strength, good compliance, and excellent puncture resistance.[53] This may be one of the ways to address the mismatch between PU's strength and elasticity. However, one shortcoming is that the author did not conduct biological experiments, leaving its further clinical use open to question. For this reason, a novel hybrid silk fibroin (SF)/PU SDVG was fabricated to test the biological performance by Riboldi *et al.* The novel hybrid SDVG was implanted between the common carotid artery and the external jugular vein of nine sheep. The results showed that 8 of 9 sheep presented primary unassisted patency in 90 days, and coverage by ECs was observed as well.[54] However, the radial compliances were lower than those of native vessels, decreasing from hypo- to hypertension.[55] Thus, the application of SDVGs made from PU still warrants further research.[16]

2.2 Degradable polymers

Currently, the most common materials used to fabricate degradable SDVGs are poly(lactide-*co*-glycolide) acid (PLGA), polyglycolic acid (PGA), poly-lactic acid (PLA), poly-L-lactic acid (PLLA), polyglycerol sebacate (PGS), and polycaprolactone (PCL),[56,57] which have also been used for the production of LDVGs. The primary degradation mechanism of these materials involves the hydrolysis of ester bonds within their scaffolds,

followed by the metabolic breakdown of polymers into H_2O and CO_2.[58] Thanks to this, an appropriate ECM can usually be formed after the implantation of degradable polymers.[59] Nevertheless, this degradable characteristic, although helpful in vascular remodeling, also poses potential risks. For instance, PGA is known for its fast degradation time, but this rapid degradation can compromise its mechanical properties and potentially increase the risk of graft rupture. As early as 1998, Shinoka *et al.* implanted PGA vascular grafts into the pulmonary arteries of lambs, and the scaffold was found to have completely degraded after 11 weeks.[60] Furthermore, a progressive decrease in the number of cell nuclei over 11 and 24 weeks was observed and tested by deoxyribonucleic acid assay, and this revealed ongoing tissue remodeling.[60] However, although no graft rupture was observed, possibly due to the short implantation period, the collagen, which helps maintain the vascular stability and integrity needed to resist the impact of blood flow in arteries, in the tissue-engineered vessels was only 70% of that in native vessels, indicating their unsuitability for use under higher systemic blood pressures.[60] Thus, current research has sought to focus on finding a balance between degradation and mechanical performance,[61,62] and for this purpose, certain kinds of degradable materials can be attractive.

For example, PLA, which may take several years to degrade fully, exhibits greater stiffness than PGA while offering enhanced endothelialization and patency rates.[16] Banitaba *et al.* fabricated a hollow electrospun PLA structure through a modified electrospinning method to use as vascular grafts,[63] and although the author did not mention the degradation, the mechanical performance and cell adhesion capabilities of this graft demonstrated in tests were quite satisfactory.[63] Additionally, compared to other synthetic biodegradable polymers, PCL exhibits relatively slow degradation (over 2 years) that provides sufficient time for cell adhesion, cellular ingrowth, and tissue regeneration.[64] What is more, research on hybrid polymers is also ongoing. Rohringer *et al.* created a new SDVG composed of thermoplastic polyurethane (TPU) and TP (U-urea) (TPUU).[65] In *in vitro* tests, the cell adhesion on TPU/TPUU was superior to that of ePTFE, including ECs, adipose-derived mesenchymal stem cells (ASCs), and macrophages.[65] The burst pressure of this material reached 1625 mmHg when in a dry state, even increasing after water storage, with a wall thickness of 130 μm.[65] In addition, the *in vivo* performance was also evaluated in rats. After implantation into the abdominal aorta of rats over a period of up to 6 months, the patency rate was 90%, and both the luminal and adventitial sides of the graft were covered with cells (Fig. 2).[65]

The other issue that cannot be overlooked with degradable polymers is cell adhesion and its antithrombotic properties. Similar to nondegradable polymers, one major drawback of degradable polymers is the lack of RGD binding sites, which

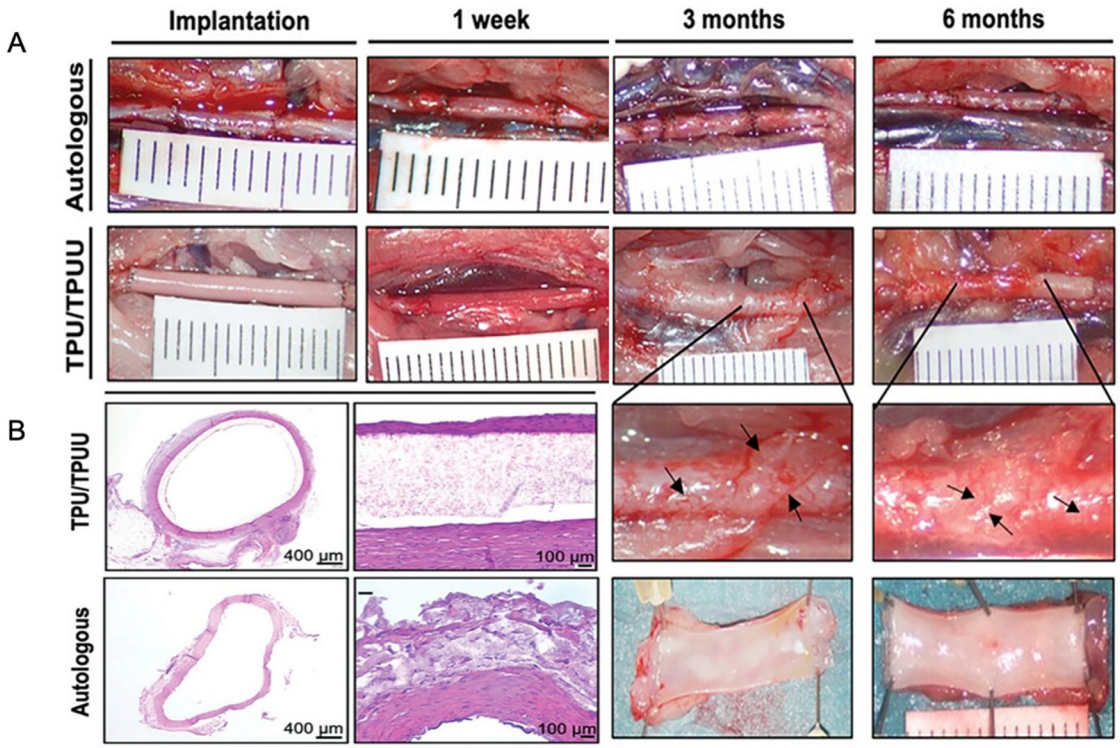

Fig. 2 *In vivo* test of a degradable polymers made SDVG. (A) There was no aneurysmal dilatation, chronic inflammation, or thrombus formation observed in the TPU/TPUU grafts and the newly formed media layer was highly vascularized *in vivo*. (B) H&E staining shows the formation of a neointimal, neomedial, and neoadventitial layer. Although the newly formed tissue did not perfectly adhere to the graft wall, the integration of the cellular layer was satisfactory. Adapted with permission.[65] Copyright 2023, Wiley.

causes problems in cell seeding and proliferation.[66] Possible approaches to solving this problem include surface chemical modification, surface biological modification with bioactive molecules, bulk biological modification, and molecular imprinting technology.[66,67] Jiang *et al.* developed a PCL scaffold applied with the dopamine-grafted hyaluronic acid (loaded and unloaded with heparin)[68] and found that the composite coating enhanced the surface hydrophilicity and mechanical properties of the PCL scaffold. Regardless of the heparin addition, the coated scaffold promoted EC proliferation and angiogenic behavior by upregulating CD31 gene expression. Additionally, it more effectively inhibited platelet adhesion and blood coagulation *in vitro*.[68] Furthermore, a PCL SDVG with high mechanical properties comprised of decellularized ECM was produced by Cuenca *et al.*, and it exhibited lower hemolysis and reduced blood coagulation compared to PCL alone.[69] Complete endothelialization was also observed by 12 weeks, and the scaffold remained patent without the formation of aneurysmal dilation. However, the amount of cellular infiltration decreased and was followed by calcification lesions after 18 months.[69] Consequently, degradable polymers still need further investigation.

2.3 Biopolymers

Biopolymers, including collagen, SF, fibrin, chitosan, gelatin, elastin, and bacterial cellulose (BC), offer an attractive 3D microenvironment with appropriate binding sites for various cellular populations compared to non- and degradable polymers, and they show better bioactivity and biocompatibility as well.[70] Thus, these materials have become widely researched in recent years. Collagen type I is the most often used as a biopolymer for its abundance in the body and because it offers a group of integrin binding sites. It can control cell adhesion, differentiation, and overall cellular behavior.[71–73] Similarly, gelatin, due to its excellent biocompatibility, biodegradability, low cytotoxicity, immunogenicity, and cost-effectiveness, has been widely used as a biomaterial in tissue engineering. However, it has one notable drawback: the need for chain reticulation in order to maintain stability. As a result, it is often combined with other materials for use as a vascular graft.[74–76] Aside from biocompatibility, fibrin can limit immunological reaction risks because it can be isolated from a patient's plasma.[77] Elastin can also be used as a biomaterial since it can inhibit the excessive proliferation of SMCs, thereby limiting intimal hyperplasia. Additionally, it possesses excellent antithrombotic properties.[78,79] SF, mainly produced by insects, is characterized by its resistance to traction and controllable degradability and has recently gathered interest in the field of producing ABVs.[80–82] Moreover, chitosan is commonly combined with other materials in the field of ABV due to its antibacterial and controllable degradability, although its mechanical properties do not meet the requirements of native vessels.[83,84]

However, before any of these materials can be put into formal use, several issues need to be addressed. An ideal vascular graft made from biomaterials should possess certain specific characteristics that meet the requirements for *in vivo* application, encompassing sufficient strength, controlled degradation and remodeling, a balance between complexity and efficacy, and translational feasibility.[17] To overcome the problem of insufficient strength, while maintaining biocompatibility, researchers have proposed cross-linking with fixative agents.[85] In 2019, Cai *et al.* reported a decellularized porcine carotid artery cross-linked with *N*-(3-dimethylaminopropyl)-N^0-ethylcarbodiimide hydrochloride and *N*-hydroxysuccinimide to improve the mechanical properties.[86] The results demonstrated that the suture strength in the cross-linked arteries was a little lower than in native arteries with no significant differences and the burst pressure.[86] However, although the application of cross-links with fixative agents indeed improved the materials' strength, their potential cytotoxicity cannot be ignored.[87] In 2016, Hass *et al.* reported that glutaraldeyde reduced cell viability.[88] Thus, when this method is applied, the effects of the cross-linking agent on cells must be carefully considered.

Many other fabrication methods have been attempted as well, among which physiological mechanical stimulation has been proven to be an effective approach.[18] In a recent study by Camasão *et al.*, a cellularized collagen trilayered vascular graft was produced and cultured under physiological mechanical stimulation that showed better cell alignment, remodeling, and viscoelastic properties compared to grafts matured under static conditions.[89] Another way to improve mechanical properties is to hybridize biomaterials with different synthetic polymers. In this field, Ma *et al.* reported a brand-new vascular graft composed of PCL, collagen, and heparin that was produced through electrospinning in 2022.[90] This PCL/collagen/heparin composite vascular graft combined the respective advantages of various materials. To be specific, this composite not only had similar mechanical properties to native vessels but also presented good biocompatibility. What is more, a synergistic effect between collagen and heparin released during degradation was observed when used as an ABV, which promoted appropriate tissue regeneration.[90]

Gelatin is another commonly used biomaterial. As mentioned above, it has the drawback of insufficient stability, so it is primarily utilized in a functionalized form, gelatin methacryloyl (GelMA).[74] In a 2021 study, Peng *et al.* reported an even stronger GelMA achieved through a combination of photo-cross-linking and enzymatic cross-linking after 3D bioprinting.[91] In their research, this reinforced material was observed to have a smaller calculated pore diameter in SEM images and a HUVEC viability of 82% (Fig. 3).[91] According to Wei *et al.*'s theory, enlarged pore size is commonly correlated with a decrease in stiffness.[92] Thus, the authors[91] concluded that this material has better mechanical properties and biocompatibility than the one with large pore size. No other biomechanical tests were conducted, so the biocompatibility of this material still requires *in vivo* experiments for validation. Combining gelatin with other materials is also used to achieve stability. For example, Joy *et al.* fabricated an electrospun tubular scaffold based on an *in situ*, cross-linked blend of gelatin-oxidized carboxymethyl cellulose (OCMC) in 2017.[93] In

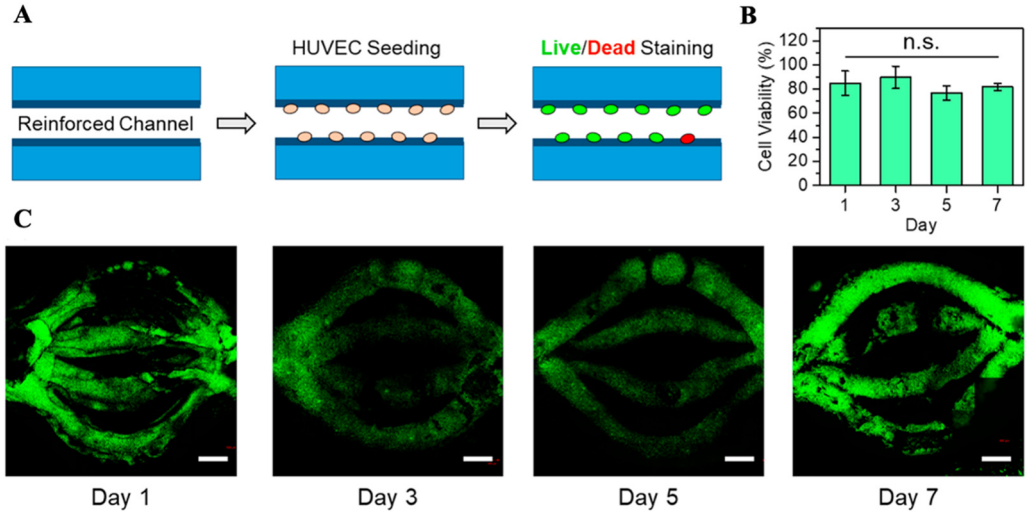

Fig. 3 A biocompatibility test for SDVG. (A) The approaches to test the biocompatibility of grafts. Live cells were stained with calcein AM (green fluorescence). Dead cells were stained with EthD (red fluorescence). (B) Cell viability of HUVECs was not significantly different at day 1, 3, 5, and 7. (C) The confocal laser scanning microscope images obtained at certain days to test the viability of HUVECs. Adapted with permission.[91] Copyright 2021, American Chemical Society.

their plot of load *vs.* extension graph, they discovered that the tensile properties achieved with their optimized 90-minute condition closely resembled the ultimate tensile strength of the human coronary artery intima.[93,94] Furthermore, they also tested its biocompatibility in both *in vitro* and *in vivo* experiments. In particular, BALB/c-3T3 cell viability was preserved at over 70% no matter the sample extract concentration in the *in vitro* test, demonstrating its nontoxicity.[93] The authors then implanted this graft subcutaneously into Wistar rats and observed cell colonization of the gelatin-OCMC scaffolds 7 days after implantation. Interestingly, there was no scaffold visible after 15 days of implantation, indicating a complete resorption.[93] Finally, use in combination with other synthetic polymers was proposed in order to avoid the impact of rapid degradation on mechanical properties. Similarly, Huang *et al.* prepared a bilayered scaffold composed of PCL and gelatin.[95] In their study, a satisfactory mechanical property was achieved, and a continuous endothelial monolayer was formed on the luminal surface. What is more, there was another phenomenon observed in which SMCs colonized from outer layers, demonstrating the potential of this scaffold in terms of remodeling and regeneration.[95]

The same method has also been applied to other materials to enhance their mechanical properties. For instance, considering fibrin's excellent biocompatibility and the good biomechanical properties of PU, Yang *et al.* mixed PU and fibrin to prepare PU/fibrin grafts through electrospinning technology in 2020.[96] They tested this graft *in vitro* first and found that its mechanical properties increased with the addition of PU. Moreover, cell staining was used to investigate the viability of mesenchymal stromal cells (MSCs) on the graft, and these results showed that the number of living cells on PU/fibrin (15 : 85) was similar to that of pure fibrin at 3 and 5 days.[96] They also implanted this graft (PU/fibrin, 15 : 85) into SD rats, and the pure PU grafts were used as the control group and found that patency and viability in PU/fibrin were significantly higher than in the control group. Additionally, immunofluorescence experiments revealed cell infiltration and neo-tissue formation in the experimental group.[96] Consequently, this vascular graft could be used as an ideal SDVG if similar or even better results are demonstrated in longer *in vivo* studies.

Controlled degradation and remodeling is also a key requirement of SDVGs. This necessitates that degradation is counterbalanced by new tissue formation, ensuring the replacement of lost material with native proteins. However, it seems to be a challenge for the target population, because older and sicker patients typically exhibit a diminished capacity compared to younger individuals.[97] To address the issue of biopolymers undergoing more rapid and uncontrolled degradation compared to synthetic polymers, recent studies have focused on hybrid polymers and advanced fabrication processes. In the absence of hybrids, manipulating stand-alone biomaterials such as silk through various processing parameters can improve degradation, and may help strike a balance between degradation and new tissue formation. As an example, silk prepared from the organic solvent hexafluoroisopropanol showed no degradation up to 1 year in one study, but water-dissolved silk grafts fully degraded in 6 months.[98] Furthermore, the porosity that these grafts possess is considered to have a direct relationship with its remodeling properties.[99] Specifically, grafts with higher porosity facilitate faster cell colonization and infiltration, resulting in increased ECM deposition.[100]

Replicating the structure of native blood vessels is also considered a viable approach to addressing the mechanical and controlled remodeling requirements of SDVGs. Alessandrino *et al.* designed a tri-layered graft composed of electrospun silk for the inner and outer layers, with a braided silk fiber intermediate layer.[101] They used ECs, SMCs, and adventitial

fibroblasts to test their biocompatibility and found good cell adhesion and no relevant hemolytic activity or complement activation *in vitro*.[101] Furthermore, they implanted this graft into the carotid artery of one minipig (unilateral) and one sheep (bilateral) for 4 weeks and evaluated the formation of thrombi, the degradation, and the general performance of the graft. In the grafted minipig, there was no formation of thrombi observed though a slight stenosis near the proximal anastomosis because of an intimal hyperplasia, and the grafted sheep carotid did not show any luminal stenosis or thrombi formation. Endothelization was seen in both animals. However, different from the grafted minipig, the grafted sheep had an area of restricted endothelization (3 mm-wide beyond end-to-end anastomotic sites). Signs of positive tissue remodeling such as a newly formed vascularized connective tissue colonized in the middle layer were also observed.[101]

To meet the requirements of normal human physiological conditions of burst pressure over 1000 mmHg and high tensile strength, scholars usually commit to enhancing the mechanical properties of biomaterials. However, good mechanical properties are often accompanied by a longer degradation time, and longer degradation can lead to foreign body responses, including inflammation, that may influence the performance of grafts. Currently, no consensus has been reached regarding the optimal degradation rate of these materials. Experimental simulations still primarily focus on short-term studies, making it difficult to predict the long-term performance of grafts and their optimal degradation times.

2.4 Hybrid polymers

Functional SDVGs can be produced by an appropriate combination of synthetic and natural polymers. Some of these materials have been discussed above. In general, these conduits are characterized by improved biomechanical, antithrombogenic, and cell adhesion properties.[102] PCL is widely regarded as the benchmark synthetic polymer most frequently used in vascular graft research because it exhibits degradable properties while also providing stability, giving it major potential for vascular remodeling. However, due to the slow degradation rate of PCL, typically taking 18 months to degrade by 70–80%, incidents of calcification and stenosis have been frequently reported.[103,104] In addition, chitosan, characterized by its controlled degradability and antibacterial antifungal properties, was found to have a similar structure to ECM, and it can undergo rapid remodeling to a neo-artery, giving it greater potential for clinical application.[105] However, it is limited by its poor mechanical properties.[83] Thus, the combination of these two materials has attracted the attention of many researchers.

In a study conducted by Fukunishi *et al.*, hybrid PCL/chitosan was fabricated with two diameter lengths (D = 1 and 5 mm and different composite ratios of 5 : 2 and 5 : 1), then implanted in rat and sheep models respectively.[106] Mechanical testing yielded promising results that showed significant difference in burst pressure between the native carotid artery and the graft (1.46 ± 0.52 MPa *vs.* 1.37 ± 0.36 MPa, p-value = 0.0224), though the graft 6 months after implantation was less compliant than native carotid artery (6.58 ± 1.76% *vs.* 11.98 ± 2.02%, p-value = 0.0125).[106] Furthermore, the histological assessment illustrated that cellular infiltration was extensive in the graft, including collagen and elastin deposition, indicating the formation of vascular neo-tissue.[106] Indeed, on the graft lumen surface, a cellular monolayer that stained positively for von Willebrand Factor was observed, demonstrating endothelial cell layer formation.[106] In addition, modification of grafts with heparin and aspirin has also been implemented to improve the anti-thrombogenic characteristic of grafts,[107–109] and ECs have been found to perform better in terms of adhesion and skeleton morphology on finer nanofibers.[110,111] With an increase in the proportion of PU proportion, especially higher than 50%, the diameter of the fibers increased to the micron level. However, there was a phenomenon observed that the degradation process became more and more difficult when this happened. Thus, considering the mechanical properties of grafts, Zhou *et al.* selected PCL90/PU10 as the optimized composite ratio of PCL/PU and modified it with a heparin–aspirin compound.[112] In their *in vitro* experiment, PCL/PU modified with heparin and aspirin (PCL/PU-HepA) had the highest and most stable blood clotting index, even maintaining 79.5% after contact with blood for 45 minutes, showing potent antithrombotic ability.[112] Moreover, the proliferation rate of ECs on membranes of PCL/PU-HepA was significantly faster than that on pure PCL/PU.[112] The superiority of PCL/PU-HepA was also demonstrated in *in vivo* experiments. The internal blood flow of PCL/PU-HepA assessed by CDFI was stable and kept at 60.1 mL min^{-1}, which was close to native blood (73.5 mL min^{-1}).[112] Tissue regeneration was also observed to have occurred *via* histology staining.[112]

Additionally, hybrid polymers can be combined with growth factors that can accumulate in the vascular wall, affecting cellular functions such as cell migration and growth.[113–115] In a 2020 study, Emechebe *et al.* reinforced a dual-layer ABV made of polydioxanone (PDO) and PCL, functionalizing the surface of the graft with VEGF to inhibit thrombus and aid rapid endothelialization.[116] Their hemocompatibility test showed that the VEGF-modified surface was able to bind specifically to fibrinogen with high affinity.[116] Furthermore, confluent cells were observed in VEGF-containing samples at 7 day,[116] confirming previous reports that VEGF induces faster endothelization through binding with VEFG receptor 1 or 2 present at the surface of cells.[117,118] Considering that no single material has yet been discovered that can meet the diverse needs of blood vessels, hybrid materials are very promising in the field of ABVs. However, a large number of tests are needed to evaluate the feasibility of this approach before it is officially put into clinical use.

3. Fabrication technologies

Since the first attempt of Weinberg, Bell, and Rosenberg *et al.* to manufacture vessel conduits,[119] a number of researchers

have explored a variety of technologies to fabricate suitable engineered vascular grafts. There is already a consensus that no matter what method is used, any prepared ABV should have enough burst pressure to adapt to the natural physiological environment, high porosity to support cell seeding, an adequate degradation period to transition to vascular remodeling and regeneration, and excellent biocompatibility to prevent thrombosis.[17,120,121] Current methods that meet these requirements include cell sheet engineering, electrospinning, molding, bioprinting, decellularization (Fig. 4) and bioreactors.[5,18,122,123] Using these methods, the production and transplantation of LDVGs have been found to be efficient based on clinical trial performance.[124] However, the same testing results for SDVGs remain unsatisfactory, and further explorations are needed. The specific difficulties lie in the formation of natural ECM structures and appropriate mechanical characteristics.[5] Table 3 shows the characteristics of each fabrication method.

3.1 Cell sheet engineering

Cell sheet engineering technology was developed by L'Heureux *et al.*[125–127] In general, this method relies on the use of cell sheets that contain fibroblasts, MSCs, ECs, and VSMCs that are shaped around a mandrel to produce a tubular formation without vascular scaffolds to provide support.[128] A cell sheet-rolled vascular graft (SRVG) can be fabricated using either sequential or single-step cell sheet rolling. The sequential method involves culturing multiple cell sheets on a mandrel and, after maturation, rolling the outer sheet onto the preceding layer. In contrast, the single-step approach entails rolling a long cell sheet containing different cell types in one step to create a multilayer, multicell SRVG.[129,130] Since these grafts

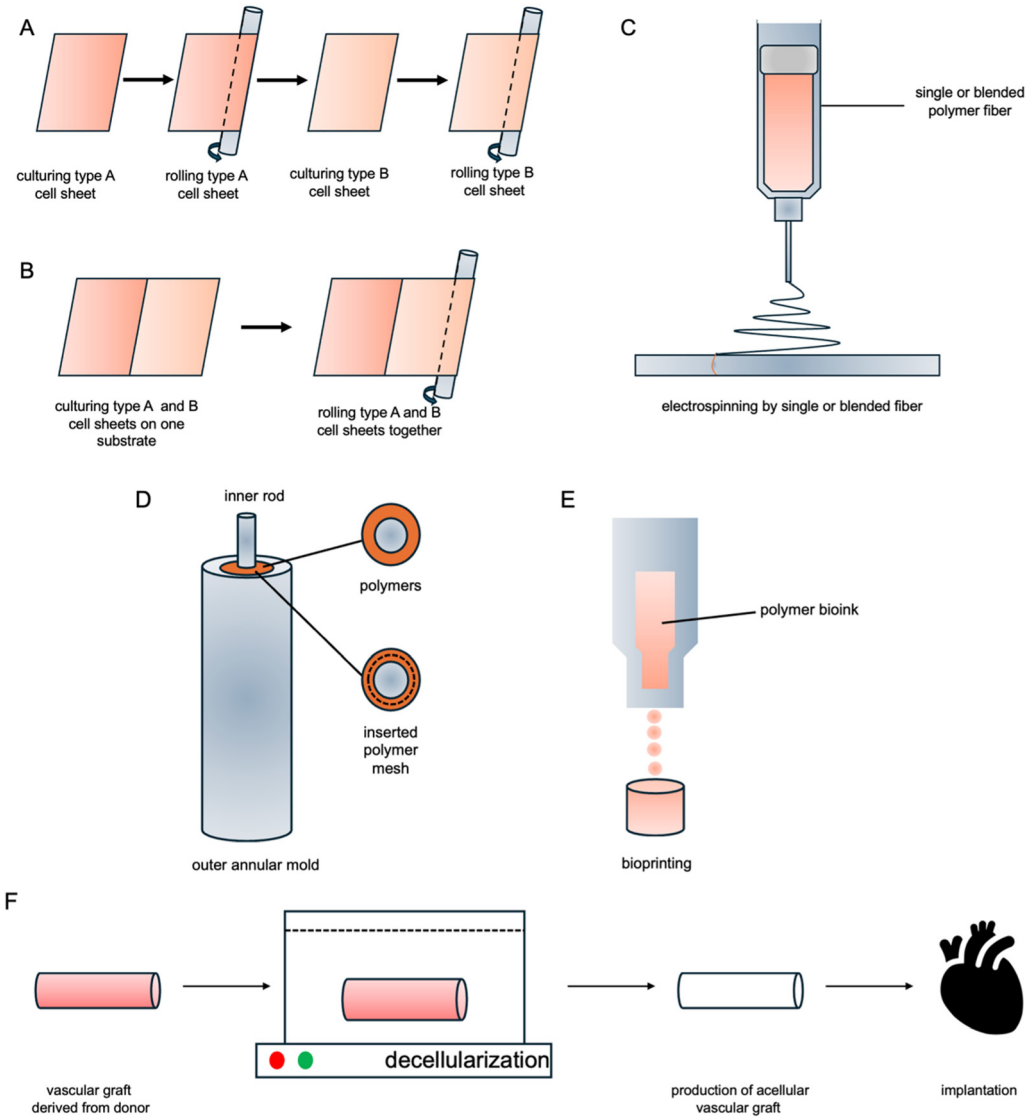

Fig. 4 (A) Fabrication using sequential rolling of multiple cell sheets. (B) Fabrication using single-step rolling of a combined cell sheet rolling of a cell sheet formed on top of a polymer sheet. (C) Fabrication of SDVGs using the electrospinning method. (D) Fabrication of SDVGs using molding. (E) Fabrication of SDVGs using bioprinting. (F) Fabrication of SDVGs using decellularization.

Table 3 The pros and cons of each fabrication method used to produce SDVGs

Fabrication methods	Pros	Cons	Ref.
Cell sheet engineering	1. Scaffold-free fabrication *via* cell self-secreted extracellular matrix (ECM) enables superior biocompatibility and native-like tissue microstructure. 2. Forming confluent endothelial layer ensures excellent thromboresistance, critical for long-term graft patency.	1. While demonstrating adequate baseline mechanical properties, current constructs require multilayer reinforcement to achieve clinical-grade strength. 2. The extended maturation period remains a challenge for acute clinical applications, motivating research into accelerated culture protocols.	125, 126, 132 and 135
Electrospinning	1. Enabling precise modulation of fiber diameter and porosity. 2. Demonstrating outstanding mechanical properties, meeting the clinical demands for SDVGs.	1. Limited cellular infiltration capacity. 2. The absence of endogenous bioactive signaling molecules necessitates exogenous stimulation to achieve functional vascularization.	146–148 and 150
Molding	1. The precisely controlled biomimetic architecture replicates native vascular layered structures. 2. Scalable fabrication demonstrates batch-to-batch consistency, enabling clinical-grade production throughput.	1. Material selection is currently constrained by the requirement for castable polymers with specific rheological properties, limiting the diversity of applicable biomaterials. 2. Inhomogeneous cellular distribution remains a key challenge for achieving consistent tissue maturation.	122, 159, 160, 164 and 165
Bioprinting	1. Engineered complex 3D architectures enable multicellular coculture systems with biomimetic gradient distributions. 2. Demonstrates significant potential for patient-specific customization through tunable structural/biological parameters.	1. The current printing resolution threshold presents a fundamental limitation in replicating the native vascular microarchitecture, necessitating further development in precision deposition technologies. 2. Bioink stability challenges significantly compromise fabrication fidelity, highlighting the need for novel crosslinking mechanisms or material formulations.	167, 173, 177 and 178
Decellularization	1. Preservation of native ECM components maintains biomechanical and bioactive properties critical for vascular remodeling. 2. Effective decellularization ensures minimal immunogenicity, as confirmed by *in vivo* host response assays.	1. The reliance on xenogeneic or allogeneic sources introduces potential immunogenicity risks and batch-to-batch variability, underscoring the need for alternative cell sources.	197, 198, 203 and 206
Bioreactors	1. Promoting cellular maturation and functionalization. 2. Enabling 3D bioprinting or decellularized scaffold culture to address nutrient diffusion limitations in thick-walled vascular constructs.	1. Experiencing asynchronous scaffold degradation and cell proliferation during dynamic culture, potentially leading to structural collapse. 2. Exhibiting significant variability in key parameters across studies, hindering cross-experimental comparisons.	208–210

incorporate autologous cells from patients themselves, the grafts produced by this method will probably not induce immune responses.[131] However, the most obvious drawback lies in the fact that, due to the absence of a supporting structure, its mechanical properties fail to meet the required standards. As a result, further maturation in a pulsatile bioreactor is needed to enhance burst pressure and overall mechanical properties.[126,132]

The initial work of L'Heureux *et al.* produced a biological tissue-engineered human blood vessel with fibroblasts and SMCs wrapped around an inert tubular structure. This vessel was then placed in a bioreactor that was designed to provide both luminal flow of culture medium and mechanical support.[125] Testing results were impressive in terms of cellular populations localizing properly and burst pressure over 2500 mmHg.[125] As a result, these tissue-engineered vascular grafts were implanted into dogs' femoral arteries. After 7 days, the patency rate remained 50% though the graft implanted was not endothelialized. However, intramural blood infiltrations were observed in all grafts, revealing that the grafts produced through this technology were susceptible to failure for dilation and delamination,[125,133] despite the fact that this method biologically and structurally mimics the native blood vessels. The ECM produced was also different from that made of proteins extracted from living tissues, leaving room for better *in vivo* integration and remodeling.[134] Another disadvantage of this approach is its prolonged cell culture period, ranging from 6 to 26 weeks,[132,135] which limits its use in emergencies.

3.2 Electrospinning

The electrospinning method was first proposed in 1930 and provided an economical solution for graft fabrication.[136] An electrospinning device typically consists of a syringe filled with polymer solution, a syringe needle for polymer ejection, a metal collector for fiber deposition, and a high-voltage power source to create an electric field.[136,137] There is an electric field created by high voltage power between the needle tip and the collector, and this electric field influences the polymer solution in the

syringe. As the voltage increases, the hemispherical polymer solution held at the needle tip by surface tension elongates to form a Taylor cone. When the repulsive force generated by the electric field is high enough to overcome the surface tension, a charged jet of liquid is ejected from the Taylor cone toward the metal collector. As the liquid moves from the needle to the collector, the solvent evaporates, resulting in the formation of continuous fibers that are randomly deposited onto the metal collector, creating a thin fibrous film.[122,138] During this process, many parameters affect the morphology of the electrospun fibers, including the polymer flow rate, solvent system, surface tension, supplied voltage, tip-to-collector distance, humidity, and temperature.[139–144] For example, fiber formation during electrospinning is influenced by the viscosity of the solution after polymer dissolution in the solvent. Excessive viscosity can cause the fibers to become twisted and entangled, whereas insufficient viscosity may lead to the generation of particles instead of fibers upon solvent evaporation, a phenomenon known as electrospraying.[145] The main advantages of electrospinning technology are that it mimics natural ECM for cell adhesion, proliferation, and differentiation, despite the risk that the solvent may be toxic and that coaxial electrospinning causes interface effects.[146–148]

The polymer materials used in the electrospinning approach can be either synthetic or natural. However, important differences do exist between these different materials. For example, Kang *et al.* fabricated an electrospun collagen vascular graft modified with hyaluronic acid oligosaccharides in 2019 that promoted endothelialization.[149] Unfortunately, the study lacked any mention of the mechanical properties of the graft. Tracing back to an article in 2012, the mechanical properties of an electrospun elastin and silk vascular graft were found to be inferior to those of autologous grafts such as coronary arteries and saphenous veins, though endothelialization and SMC infiltration were observed.[150] In contrast, when using synthetic polymers alone to fabricate electrospun vascular grafts, the mechanical strength is comparable to native vessels in terms of tensile strength and strain, Young's modulus, and burst pressure, but other complications such as thrombotic occlusion, hyperplasia, and calcification may occur due to low biocompatibility.[151] To combine the advantages of each type of material, electrospinning with hybrid polymers in the same solvent has become the choice of many researchers. To design a vascular graft with both good biocompatibility and sufficient mechanical strength, Lu *et al.* constructed a three-layer electrospun vascular graft that consisted of PCL, collagen, and gelatin[152] and found that not only did the longitudinal maximum stress of this hybrid material reach 2.63 MPa but HUVECs also adhered more easily to this material, giving it great potential for vascular tissue engineering.[152]

To accommodate different treatment needs, several types of electrospinning technology have been created. One such method is co-electrospinning, which utilizes two electrospinning systems to deposit fibers onto a single rotating mandrel. This approach allows independent control of electrospinning parameters for each polymer solution, enabling the fabrication of fibers with distinct morphologies that can achieve tailored mechanical properties and degradation rates.[153] For instance, the slow degradation rate of PCL in a co-electrospun PCL/PU nanofibers maintains the integrity of the graft, avoids the presence of aneurysm and dilation, and the PU fibers provided improve compliance of the scaffold.[154] Simultaneous electrospinning/electrospraying is also used to create pores that promote cell infiltration.[155] Wang *et al.* employed this combined approach and successfully fabricated electrospun SF scaffolds with larger macropores and higher porosity by utilizing electrosprayed poly(ethylene oxide) microparticles.[156] As a result, cell infiltration was observed *in vitro*, and more efficient tissue ingrowth was observed *in vivo*.[157] Another method is coaxial electrospinning. This technique utilizes two concentrically aligned syringe needles to deposit polymer fibers in a core–shell structure, with synthetic polymers forming the core to ensure mechanical strength. Natural polymers serve as the shell to enhance biocompatibility.[158] Hu *et al.* employed this axial electrospinning method and produced a triple-layered vascular graft with both sufficient mechanical characteristics and biocompatibility.[147]

3.3 Molding

Molding, with a device such as a tubular concentric cylinder, is normally used to produce molded vascular grafts. The polymer solution is cured in an annular mold, the internal rod is used to set the inner diameter, and the outer tube limits the wall thickness of the graft.[159] This approach can also be combined with pore-generating methods such as salt leaching, gas foaming, and phase separation to produce high porosity molded vascular grafts for better cell infiltration.[122] Among these, thermal-induced phase separation is a common approach to achieve the high porosity mentioned before. Through the combination of molding and thermal-induced phase separation, researchers have already developed an SDVG that consisted of PLLA that was found to be beneficial for cell seeding, cell growth, and cell function.[160] Moreover, Zhen *et al.* found that PU with 40 μm pores is better than either that with 100 μm pores or a nonporous structure with regard to angiogenesis and cellularization, revealing the importance of pore size.[161] Methods to enhance mechanical strength are essential for molded grafts, however, especially for natural materials. Currently, dynamic conditioning of cell-seeded scaffolds through cycles of inflation and contraction, along with the application of centrifugal force to compress the scaffolds, has been employed to enhance the mechanical properties of molded vascular grafts created from natural polymers, allowing these molded vascular grafts to withstand *in vivo* implantation for six months without failure.[162,163] However, both natural and synthetic polymer-based molded vascular grafts still have room to improve in terms of mechanical strength compared to native vessels.[164,165]

3.4 Bioprinting

Bioprinting has attracted significant attention from researchers over recent decades due to certain properties such as the potential for the produced grafts to be used immediately,

allowing cells to be spatially arranged in the constructs without the need for cell seeding.[166,167] The principle of fabrication by bioprinting is building objects through layer-by-layer deposition of polymer materials under the guidance of computer-aided design models.[168] Furthermore, both synthetic and natural polymers can be used with this method.[5] Different approaches including three-dimensional (3D) bioprinting and four-dimensional (4D) bioprinting are also developed to meet different needs.

3.4.1 3D Bioprinting. As mentioned before, bioprinting can spatially arrange cells arbitrarily in constructs. The realization of this depends on the addition of cells to the depositing material, a formed substance known as bioink.[169] Over the past few decades, bioinks have undergone significant changes. Overall, these changes have evolved in a direction that better protects cells and ensures that cells can fully differentiate and grow after printing.[170,171] Currently, types of bioinks include single-component hydrogel bioinks, decellularized matrix-based bioinks, multi-component bioinks, and hydrogel microspheres-based bioinks.[172] Each type has distinctive properties that meet the demands of vascular grafts. For instance, the high water content of hydrogel enables the material to mimic natural ECM under biological conditions.[173] Decellularized matrix-based bioinks can promote cellular function by preserving their ECM,[173] and the multi-component bioinks can enhance cell viability and function while also maintaining a certain amount of mechanical strength.[169]

The specific methods of 3D bioprinting can be categorized into extrusion, injection, laser-assisting, and stereolithography, each with its advantages and disadvantages.[174–176] Extrusion is frequently used for generating ABV. Here it is important to deposit cell–laden polymers at a physiological temperature or below because the process of this technology involves heating, which can harm both cells and bioactive substances in the bioink.[177] Furthermore, the size of the nozzle and the extruder movements control the resolution of the product. A smaller nozzle does facilitate high-resolution printing, but the risk of clogging increases.[178,179] In addition, through manipulation of the printing parameters, the pore geometry and interconnectivity within the grafts can be controlled. Specifically, the porosity and pore size increase with slower filament flow rates.[180] The resolution of products fabricated in the inject bioprinting approach is usually higher compared to that of extrusion-based products. However, the high shear stress generated by rapid injection reduces cell viability. Moreover, the low cell density needed to prevent printer blockage compromises mechanical strength.[181] In contrast, laser-assisted bioprinting enables relatively high cell densities across various viscosities within the nozzle, minimizing cell loss due to shear stress, but here the preparation of metallic absorbing layers and donor layers is time-consuming. Residual metal particles may also pose risks to tissue constructs.[182,183] Stereolithography, also known as photopolymerization, utilizes UV or visible light to cross-link a polymer solution, either with or without embedded cells.[122] Through this approach, printed vascular grafts with controlled geometries of curvature, diameter, and wall thickness can be generated.[184] However, the risk that cell viability may decrease due to exposure to UV exists.[185] Furthermore, the polymers often need chemical modification to become reactive to light.[186]

3.4.2 4D Bioprinting. 4D bioprinting is an advanced fabrication that includes 3D bioprinting as well as a fourth dimension: time. The main difference between 3D bioprinting and 4D bioprinting has been called the smart behavior of produced scaffolds by Rastogi *et al.*[187] Smart behavior means that the 4D printed scaffolds can change their physical and chemical properties on their own when exposed to stimuli.[188] The parameters of the external stimuli that the grafts are exposed to can be varied, including potential of hydrogen (PH), heat, magnetic field, light, and humidity.[189] Polymers such as collagen and keratin are responsive to PH, changing the polymer chain arrangement from globule to coil form under different PH, inducing shape change.[190,191] This change occurs because the initial structure of these materials contains acidic or basic groups, allowing anionic or cationic compounds to fluctuate in response to pH variations.[192] Recently, a bioink for 4D printing made from sodium alginate (SA), collagen, and ECs was synthesized by Pfarr *et al.*[193] The length of these bioprinted grafts can reach 30–40 centimeters which is comparable to the saphenous vein used for CABG.[194,195] Moreover, the results of Pfarr presented not only a well-organized matrix in which embedded endothelial progenitor cells or HUVECs were observed but also biomechanics comparable to human saphenous veins.[193] The coagulation analysis revealed low thrombogenicity as well, indicating that this method is promising.

3.5 Decellularization

Decellularization is an approach to obtaining an ECM that advances the process of cell adhesion, migration, proliferation, differentiation, organization, and remodeling.[196] Therefore, decellularized vascular grafts should be free from immunological responses under ideal conditions while also preserving the mechanical properties of native vessels.[197,198] Decellularized vascular grafts can be native vessels or synthetic grafts.[122] The process of decellularization can be summarized in three steps: first, cell disruption occurs through the dissolution of the cytoplasmic membrane or DNA fragmentation; second, cellular and nuclear debris are removed; third, the resulting graft is sterilized.[199,200] Currently, the decellularization approach includes methods such as snap freezing, use of ionic and nonionic detergents, trypsin addition, and mechanical agitation or sonication.[5] The most often used decellularized native vessels are gained from animals. However, an extended immune response typically exists due to the presence of alpha-gal-epitope (Galalpha1-3Galbeta1-(3)4GlcNAc-R), which results in graft failure.[201] Genome editing with CRISPR-Cas9 may assist in this field.[202] Moreover, if the decellularized scaffold is not pre-endothelialized *in vitro* before implantation, the graft is likely to trigger acute thrombosis.[203] Decellularized vascular grafts that undergo recellularization with ECs or bone marrow-derived cells before implantation have demonstrated a 60%

improvement in patency rates when compared to acellular grafts.[204]

Other native vessels have been used to fabricate decellularized vascular grafts derived from humans. Among these, human umbilical vessels (HUV) are considered an alternative source for the production of SDVGs.[205] Mallis *et al.* successfully produced a decellularized human-umbilical-artery-derived vascular graft with better mechanical properties than native vessels in 2020.[206] However, the compliance of this graft exhibited a slight limitation.[206] There were no *in vivo* experiments conducted in this study, so it requires further investigation. In addition, much effort has been focused on the decellularization of synthetic polymer derived grafts. Liu *et al.* created a decellularized human amniotic membrane (HAM) graft with PCL/SF (HPS Graft) in 2022[207] and used a decellularized porcine small intestinal submucosa-integrated PCL/SF graft (SPS Graft) for control. *In vitro* experiments revealed that HAM created a bioactive environment that supported rapid proliferation of endothelial cells while inhibiting fibroblast-driven collagen production. The PCL/SF scaffold offered a biocompatible structure conducive to cellular infiltration and exhibited mechanical characteristics similar to those of the rat aorta.[207] The results of these *in vivo* studies are encouraging. More specifically, the HPS graft promoted faster functional endothelialization and exhibited reduced ECM deposition compared to the SPS graft, which correlated with a milder inflammatory response and foreign body reaction observed 4 weeks post-implantation. Over 24 weeks, it maintained patency by gradually stabilizing its remodeling structure, closely resembling native tissue.[207] This bioengineered graft enhances the possibility that allogeneic matrices can be combined with degradable electrospun polymers for long-term *in situ* vascular applications.

3.6 Bioreactors

Structurally, bioreactors consist of four key components (a chamber, pumps, nutrient exchange modules, and sensors, Fig. 5), which collectively enhance the mechanical properties and biocompatibility of SDVGs through mechanical stimulation, dynamic culture conditions, and real-time regulation.[208] More notably, bioreactors significantly reduce the *in vitro* maturation time of SDVGs—a breakthrough addressing urgent clinical demands and offering a promising avenue for further exploration. When cultured within the bioreactor chamber, SDVGs are subjected to controlled shear stress and fluid dynamic forces. These biomechanical stimuli promote endothelial cell alignment and accelerate sprouting angiogenesis, thereby enhancing vascular tissue formation.[209,210] Moreover, the stretching pressure provided by bioreactors endows SDVGs with stable mechanical properties, enabling them to withstand surgical suturing and post-implantation hemodynamic stresses.[211,212]

Pulsatile flow bioreactor is a specialized system designed to apply precise shear stress and pulsatile stimulation to SDVGs, thereby enhancing their biochemical and biomechanical properties.[213] This technology was successfully implemented as early as 2006, demonstrating its longstanding utility in vascular tissue engineering.[214] Specifically, pulse rates of 120 or 60 beats per minute (bpm) were set to simulate adult and fetal hemodynamics, respectively. By configuring a flow rate of 2 mL s^{-1} to represent small-diameter vessel conditions, the shear stress acting on 3-mm inner diameter diacrylated derivatized PEG (PEGDA)-based SDVGs was maintained at ~6 dynes per cm^2. Results demonstrated that, compared to static constructs, SDVG in bioreactor-conditions exhibited significantly higher cellularity, indicating that pulsatile conditioning enhanced cell survival/proliferation.[214] Furthermore, in a recent *in vivo* study, human induced pluripotent stem cell-derived SDVG (hiPSC-SDVG) fabricated using a pulsatile flow bioreactor demonstrated excellent performance. The grafts maintained patency for 4 weeks post-implantation in the aortic position of nude rat models.[215]

However, despite the remarkable achievements of bioreactors in fabricating SDVGs, several critical limitations hinder their practical translation:

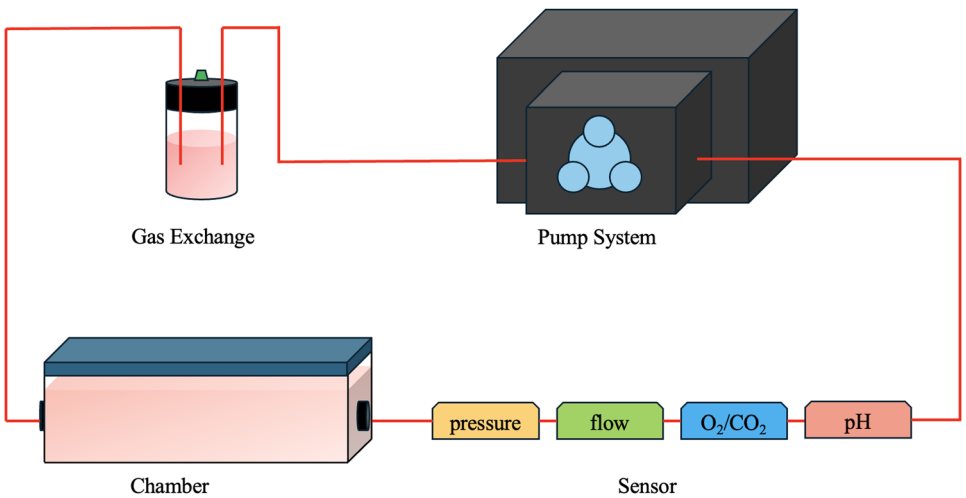

Fig. 5 Common components of typical vascular bioreactor setups including a chamber, pump, nutrient exchange, and sensors.

(1) High technical complexity: the precision control systems required for hemodynamic conditioning impose significant operational barriers, limiting accessibility.

(2) Asynchronous degradation-proliferation kinetics: mismatched rates between scaffold degradation and cellular proliferation during culture may lead to structural collapse.

(3) Parameter heterogeneity: substantial variability in bioreactor protocols across studies complicates cross-experimental comparisons and *meta*-analyses.

(4) Scalability constraints: current systems predominantly operate at benchtop scales, failing to address clinical-scale production demands.

4. Challenges and perspectives

Though the research associated with SDVGs is proceeding with high momentum, including the exploration of different materials and fabrication techniques, the reported findings remain unsatisfactory compared to autografts, especially when it comes to long-term outcomes, leaving substantial room for improvement. Restenosis, thrombus formation, and dilation are the usual reasons for graft failure. What is more, infection is also a major cause of late graft failure, with the inflammatory response to infection potentially promoting restenosis.[216] To avoid these problems, mechanical strength, appropriate stiffness, biocompatibility, and antibacterial activity are essential to the success of SDVGs. Unfortunately, SDVGs made of a single material have so far failed to strike the right balance between mechanical strength and elasticity. A higher stiffness may significantly improve a material's performance in withstanding blood pressure, but it also has a notable impact on the material's elasticity. Insufficient elasticity can lead to hemodynamic changes, enhancing the possibility of intimal hyperplasia.[124] Consequently, many researchers have experimented with different combinations in order to find a balance, representing major approach to it. Another way to improve the mechanical properties and elasticity simultaneously is to mimic the structure of native blood vessels. Numerous efforts have been made in this direction, and such three-layered SDVGs do have better performance in terms of both mechanical properties and elasticity.[217–219]

Similar to autografts, the failures of SDVGs can be classified into acute failure and late failure, which can both be caused by thrombus formation, dilation, rupture, or intimal hyperplasia respectively.[220] Basically, synthetic materials are prone to formate thrombus to varying degrees.[221] As such, strategies to limit thrombus formation are required for these materials. The normal approaches include surface modification and rapid endothelialization. Regarding the former, combining heparin with the material is a common practice.[222–224] However, given that most reported experiments stay in the short term (from days to months), the usefulness of this strategy in the long term (from months to years) remains to be demonstrated. As for the latter, it can be realized by incorporating growth factors into the grafts and more precise fabrication methods such as molding and bioprinting.[225–228]

The anti-thrombosis strategies mentioned above can also draw upon commonly used clinical anti-platelet measures, such as the application of medications like aspirin and clopidogrel.[229,230] However, due to the lack of effective strategies to deal with it, intimal hyperplasia caused by SMC activity that includes migration from the media to intima and hyperproliferation[231] warrants more attention. Thus, aiming to limit the activity of SMCs may hold promise in improving intimal hyperplasia, thereby extending the long-term patency of a graft. Efforts such as reducing the compliance mismatch between native arteries and vascular grafts that have proven to be beneficial for limiting intima hyperplasia formation have been examined already but again only in short-term expoeriments.[232]

In addition, the application of anti-bacterial materials such as chitosan and fabrication technologies such as decellularization to reduce immunological responses can reduce the harm from the body's inflammatory response. Therefore, future research should focus on identifying the critical balance point in the integration of various materials to achieve an equilibrium between strength and pliability. Furthermore, improving graft endothelialization to reduce the risk of early thrombosis remains a crucial aspect. Implementing preventive strategies targeting SMCs is indispensable for achieving favorable long-term outcomes.

Notably, the VEST clinical trial demonstrated that incorporating an external support device around vein grafts significantly reduces intimal hyperplasia, suggesting potential to improve long-term patency rates.[233,234] This evidence provides a compelling rationale for adapting similar supportive strategies in SDVG development to systematically validate this approach.

To our knowledge, a novel 15-cm-long, 4-mm inner diameter restorative bypass graft (designated XABG) has recently been developed, comprising a supramolecular ureidopyrimidinone-based bioabsorbable polymer integrated with a nitinol microskeleton. Successful implantation was achieved between the aortic root and left anterior descending artery in Suffolk sheep models.[235] Angiographic follow-up at 12 months demonstrated maintained patency of XABG conduits, with microscopic findings confirming satisfactory endothelialization coverage.

5. Conclusion

The evolution of SDVGs represents a pivotal advancement in the field of vascular surgery since they have the potential to address critical challenges in vascular reconstruction and repair. This review highlights the paramount importance of material selection and fabrication techniques in optimizing the performance of these grafts. Biocompatible materials play a crucial role in enhancing mechanical properties and promoting favorable biological interactions, as demonstrated in recent studies, and innovative fabrication techniques, including electrospinning and bioprinting, have emerged as powerful tools for mimicking the native vascular architecture, significantly improving a graft's functionality and integration with host

tissues. For instance, electrospun scaffolds have shown enhanced cell adhesion and proliferation that have led to better long-term patency rates. This emphasizes the necessity of tailoring the microstructure and surface characteristics of ABVs to facilitate endothelialization and reduce thrombogenicity.

Looking forward, the integration of smart biomaterials that respond dynamically to physiological stimuli offers exciting possibilities for the development of next-generation vascular grafts. Such materials could enhance graft longevity and performance, mitigating the risks of complications associated with SDVGs. Additionally, ongoing research into the mechanisms of graft failure and host response is critical to refining design strategies and optimizing clinical outcomes. In summary, SDVGs hold immense potential for transforming vascular surgery by providing reliable solutions for vascular defects and diseases. Continued interdisciplinary collaboration among materials scientists, bioengineers, and clinicians is essential for translating laboratory innovations into effective clinical applications. As we progress in this field, the ultimate goal remains clear: to improve patient outcomes through enhanced vascular repair and reconstruction strategies, paving the way for a future where SDVGs can seamlessly integrate into the human body.

Author contributions

Qian Li and Kui Zhang conceived of the idea of the review and drafted the manuscript. Xili Ding, Cong Chen and Ran Dong revised the manuscript, and made substantial contributions to conception and design. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for aspects of the work.

Conflicts of interest

The authors declare no conflicts of interest.

Abbreviations

CVD	Cardiovascular disease
CAD	Coronary artery disease
PAD	Peripheral artery disease
CABG	Coronary artery bypass grafting
ABV	Artificial blood vessel
SDVG	Small diameter vascular graft
MDVG	Medium diameter vascular graft
LDVG	Large diameter vascular graft
ECs	Endothelial cells
VSMCs	Vascular smooth muscle cells
ECM	Extracellular matrix
ePTFE	Eexpanded polytetrafluoroethylene
PU	Polyurethanes
VEGF	Vascular endothelial growth factor
FGF	Fibroblast growth factor
PET	Polyethylene terephthalate
HUVECs	Human umbilical vein endothelial cells
HDMECs	Human dermal microvascular endothelial cells
SF	Silk fibroin
PLGA	Poly lactide-co-glycolide acid
PGA	Polyglycolic acid
PLA	Polylactic acid
PLLA	Poly-l-lactic acid
PGS	Polyglycerol sebacate
PCL	Polycaprolactone
TPU	Thermoplastic polyurethane
ASCs	Adipose-derived mesenchymal stem cells
BC	Bacterial cellulose
PDO	Polydioxanone

Data availability

No primary research results, software or code have been included and no new data were generated or analyzed as part of this review.

Acknowledgements

The research was supported by the National Natural Science Foundation of China (82270408), and a grant (CX23YZ01) from the Chinese Institutes for Medical Research. The authors thank AiMi Academic Services (**https://www.aimieditor.com**) for English language editing and review services.

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