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REVIEW

Biomimetic design strategies for synthetic small-diameter vascular grafts

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Abstract

Cardiovascular diseases (CVDs) remain the leading cause of mortality worldwide. The limitations of autologous grafts, along with the long-term failure of allogeneic alternatives, underscore the urgent need for the development of synthetic vascular grafts in advanced-stage treatment. Large-diameter synthetic grafts (greater than 6 mm) have demonstrated clinical success, and synthetic small-diameter vascular grafts (SSDVGs) continue to demonstrate significant drawbacks, such as compliance mismatch, poor endothelialization, intimal hyperplasia, and thrombosis, all of which reduce long-term patency. Despite considerable progress in materials and fabrication techniques, the structural biomimetic design of SSDVGs, which is critical for mechanical performance and biological integration, has not been improved and thus continues to hinder clinical translation. This review addresses this gap by exploring design strategies inspired by native vascular architecture. It examines recent advances in synthetic material suitable for SSDVGs; structural configurations, such as fiber-based, segmented, embedded, and layered designs that improve compliance; surface topography modifications that guide endothelial cell migration and proliferation to promote in situ endothelialization; and surface functionalization involving anticoagulants, growth factors, and cellular or genetic agents to enhance hemocompatibility and prevent thrombosis. Furthermore, this paper identifies current challenges and future research directions. Overall, integrated biomimetic strategies offer a promising pathway to improve SSDVG performance and expand clinical options for the treatment of CVDs.

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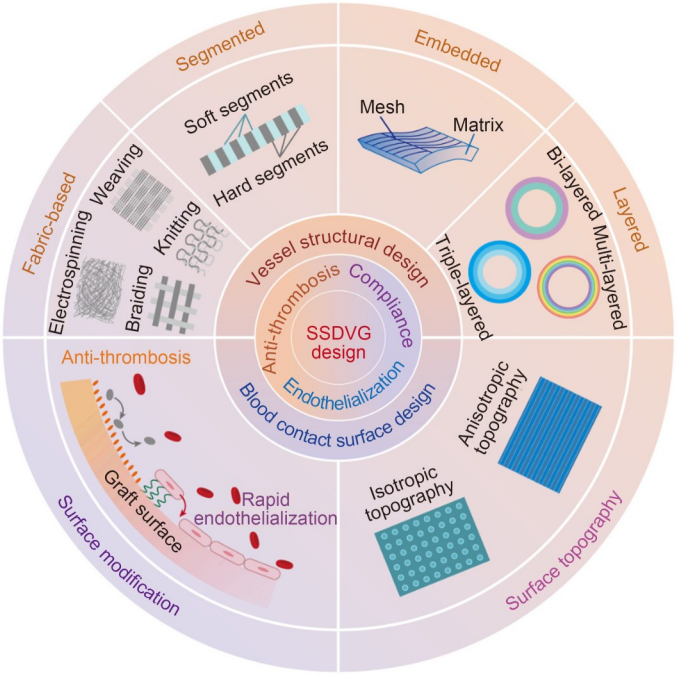
Graphical abstract



Keywords Small-diameter vascular grafts · Biomimetic design · Mechanical properties · Endothelialization · Vascular tissue engineering

1 Introduction

Cardiovascular diseases (CVDs) remain the leading cause of death worldwide. These conditions encompass a broad spectrum of heart and vascular disorders, including coronary artery disease, peripheral arterial disease, and aortic disease, which are typically characterized by vascular stenosis or embolism that leads to end-organ malperfusion or vascular wall rupture [1–3]. According to the World Health Organization, CVDs caused approximately 17.9 million deaths in 2019, and their global prevalence continues to increase [4]. Although pharmacological interventions, such as vasodilators and anticoagulants, offer symptomatic relief, bypass grafting remains the definitive and essential treatment for advanced CVD [5]. In particular, the selection of vascular grafts that closely mimic the mechanical and biological properties of native vessels is critical for the long-term success of such surgical interventions.

Three main types of grafts are currently employed in bypass procedures: autologous, allogeneic, and synthetic vascular grafts. Autologous grafts, such as those for the internal thoracic artery, radial artery, and saphenous vein, are considered the gold standard due to their biocompatibility and established clinical success [6]. However, these grafts are often limited by inadequate vessel quality, restricted availability, and harvesting-related morbidity, among others, particularly in elderly patients or those with diabetes [7]. Consequently, nearly half of patients may lack suitable autologous conduits for surgery. Moreover, vein grafts, particularly those for saphenous veins, exhibit a 10-year failure rate of approximately 50%, primarily due to endothelial hyperplasia, which limits patency [8]. The development of allogeneic vascular grafts has progressed rapidly in recent years, largely due to advancements in decellularization technologies [9]. These grafts offer reduced thrombogenicity and infection resistance, among other advantages. However, they are limited by risks of immune rejection and "vascular aging," which can cause aneurysms, restenosis, and diminished long-term patency [10]. Artificial vascular grafts, particularly those composed of synthetic polymeric materials, have emerged as a promising solution for such cases. Their advantages include mass producibility, customizable properties, and potential functional optimization, making them an attractive subject in the development of next-generation vascular grafts [11].

Commercially available large-diameter artificial vascular grafts (>6 mm), such as those made from expanded polytetrafluoroethylene (ePTFE) and polyethylene terephthalate (PET), have demonstrated excellent clinical outcomes in large-vessel reconstructions (e.g., aorta, arch vessels, and

common femoral artery) [12–14]. These procedures benefit from high blood flow and low vascular resistance, resulting in relatively low graft infection (<3%) and occlusion rates (approximately 2%), thereby enabling sustained long-term patency without requiring re-intervention [15, 16]. However, vascular graft performance significantly decreases with decreasing graft diameter. In small-diameter applications (<6 mm), particularly those used in coronary and peripheral artery bypass surgeries, ePTFE and PET demonstrate suboptimal performance due to compliance mismatch with native vessels and insufficient endothelialization. This predisposes grafts to thrombosis, stenosis, and infection at the anastomotic sites, resulting in a two-year patency rate of only 42% [17–19]. Consequently, the design and optimization of synthetic small-diameter vascular grafts (SSDVGs) must integrate multiple critical factors, including material biocompatibility, mechanical performance (especially compliance and elasticity), anti-thrombogenic surface properties, endothelial cell (EC) adhesion and proliferation capabilities, and long-term durability under physiological conditions [20, 21]. Continuing research and innovation are essential to the development of more effective SSDVGs.

The past two decades have seen the rapid evolution of various fabrication techniques for SSDVGs, including electrospinning, molding, coaxial extrusion, lyophilization, and three-dimensional (3D) printing [20, 22–24]. Synthetic materials suitable for SSDVGs are categorized based on their degradability in vivo. Bioresorbable polymers, e.g., polylactic acid (PLA), poly(L-lactide) (PLLA), polylactic-co-glycolic acid (PLGA), polycaprolactone (PCL), and poly(L-lactide-co-ε-caprolactone) (PLCL), are among such suitable materials. Biostable polymers, such as polyurethane (PU) and polyvinylidene fluoride (PVDF), are also promising candidate materials for the said applications [5, 25]. Various biofunctionalization strategies have been employed to promote endothelialization and enhance biocompatibility, including the incorporation of anticoagulants (e.g., heparin, aspirin, warfarin), angiogenic growth factors (such as vascular endothelial growth factor (VEGF), fibroblast growth factor, and hepatocyte growth factor) [26–28], stem or progenitor cell seeding, and gene-based therapies [29–31]. Furthermore, structural designs that emulate native blood vessel architecture have been developed to better replicate mechanical behavior, minimizing smooth muscle cell overproliferation and subsequent intimal hyperplasia (IH). Collectively, these advances demonstrate the strong potential of SSDVGs as effective, durable, and clinically viable solutions for vascular bypass applications.

Several reviews have significantly contributed to the field of SSDVG research by providing systematic analyses of materials and fabrication methods. Their findings underscore the central role of material development and processing in graft performance. For example, Rodríguez-Soto et al. [32] systematically evaluated fabrication techniques and biomaterial options to determine strategies for optimizing mechanical properties. Guo et al. [20] comprehensively analyzed various approaches designed to accelerate endothelialization across a diverse array of materials, highlighting opportunities for enhancing biological integration. However, achieving clinical success in SSDVGs requires more than mere advances in materials and fabrication processes. The systematic application of biomimetic design principles that emulate the structural, mechanical, and biological complexities of native vasculature is also essential. In this regard, Zia et al. [33] provided valuable insights into the biomimetic structural design of composite vascular grafts, demonstrating the importance of architecture in mimicking vascular function. However, the scope of their work was limited in two respects. First, it did not address the unique challenges associated with SSDVGs, for which clinical demand is greatest. Second, it overlooked the essential aspects of surface morphology optimization and bioactive component modification, which are critical for promoting rapid endothelialization and ensuring long-term patency. Taken together, these observations highlight the critical need for a comprehensive review investigating biomimetic design strategies for SSDVGs that integrate structural architecture, luminal surface features, and bioactive functionalization to more closely replicate native vascular properties and improve long-term outcomes.

Accordingly, the present review focuses on biomimetic strategies in SSDVG design (Fig. 1). It addresses not only the structural design of the vessel walls but also the morphology and bioactive modifications of the blood-contacting surfaces, thereby highlighting their potential efficacy in addressing persistent clinical challenges and advancing the field of vascular graft technology. First, this review outlines the core design requirements and clinical challenges of SSDVGs, delving into the multifactorial causes of graft failure. It then explores advances in material selection, structural configurations, surface topography, and bioactive modifications. These innovations enhance mechanical compliance, promote endothelialization, and reduce thrombosis risk. Finally, the review demonstrates the clinical potential of next-generation SSDVGs, emphasizing integrated strategies that optimize both mechanical and biological performance to improve patient outcomes.

2 Design requirements and current challenges

2.1 Structure and function of native blood vessels

Native blood vessels possess a complex, multilayered architecture that supports their essential physiological roles, including blood pressure regulation, blood distribution to

target organs, and the exchange of gases, nutrients, and waste products between the bloodstream and surrounding tissues (Fig. 2). The blood vessel structure is composed of three distinct layers: the tunica intima, tunica media, and tunica adventitia, each of which contributes uniquely to vascular function. The tunica intima, the innermost layer, mainly consists of ECs, which are vital in balancing coagulation and anticoagulation, maintaining blood pressure, and regulating the selective penetration of macromolecules and immune cells. The tunica media, located external to the intima, is composed of elastic fibers and smooth muscles, which regulate blood vessel contraction and dilation while lending elasticity and toughness. The tunica adventitia, the outermost layer, is primarily composed of fibroblasts and connective tissues, such as elastic and collagen fibers, and some neurons, which facilitate the anchoring of blood vessels to the surrounding tissues.

This trilaminar architecture (Fig. 2a) is responsible for the distinct mechanical behavior of native blood vessels, which is characterized by nonlinear elasticity, anisotropy, and viscoelasticity [34]. A comprehensive understanding of these properties is essential for the realistic design of SSDVGs [35]. A hallmark feature of vascular mechanics is nonlinear elasticity, which manifests as strain stiffening, that is, initially compliant at low strain and progressively stiffer at higher strain levels. This behavior generates the characteristic J-shaped stress–strain curve observed in native arteries [36]. The nonlinear properties of blood vessels are influenced by the arrangement of elastic and rigid fibrous components in the vessel wall (Fig. 2b). Elastin is more elastic, with a modulus of 0.6–1.0 MPa, and arranged randomly, while collagen is stiffer and exhibits a wavy helical pattern oriented mostly circumferentially [37]. At low physiological pressures, the initial low modulus of blood vessels is primarily attributed to the stretching and alignment of elastic elastin fibers in a circumferential direction. As pressure exceeds the elastic limit of elastin fibers, wavy collagen fibers begin to straighten until both collagen and elastin fibers are fully stretched. Under high pressure that exceeds the physiological range, the mechanical response is dominated by the deformation of rigid collagen fibers to resist high loads [38]. Therefore, the J-shaped stress–strain behavior of native

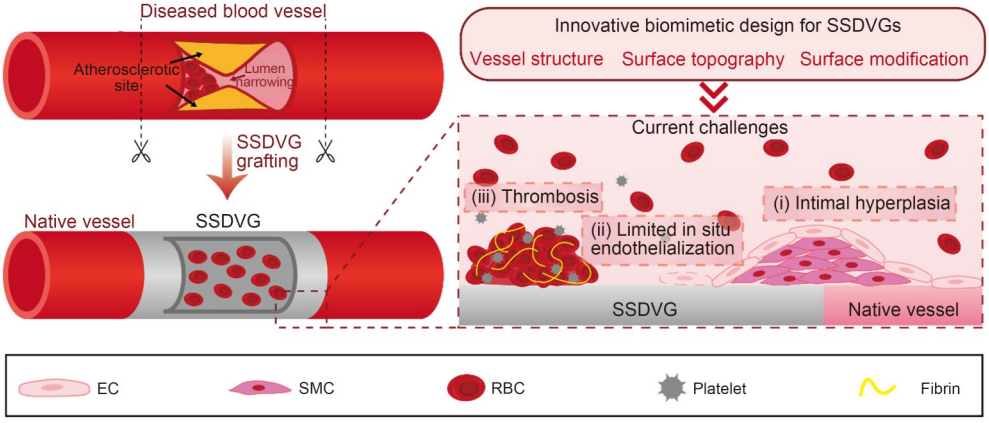


Fig. 1 Schematic diagram depicting current clinical challenges and three innovative design strategies for synthetic small-diameter vascular grafts (SSDVGs). EC: endothelial cell; SMC: smooth muscle cell; RBC: red blood cell

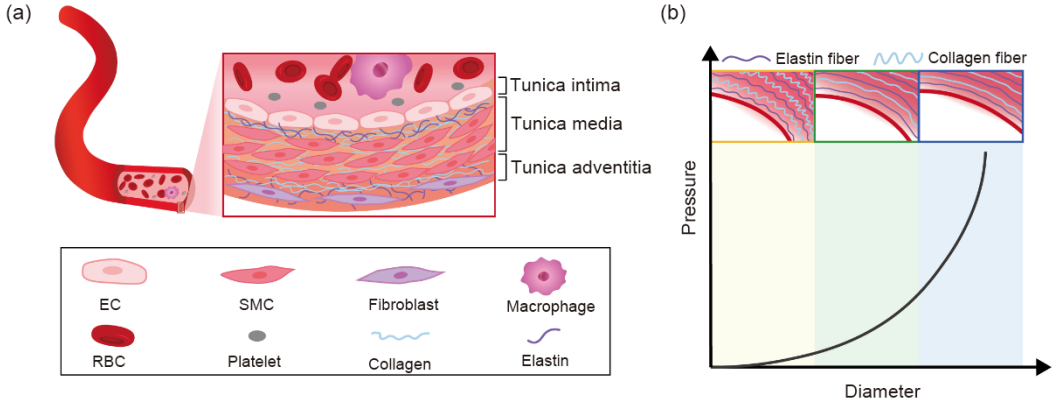


Fig. 2 Structure and mechanical behavior of a blood vessel. (a) The structure and composition of blood vessels. (b) Nonlinear mechanical behavior of the artery in response to increasing pressure. EC: endothelial cell; SMC: smooth muscle cell; RBC: red blood cell

blood vessels is critical, especially the arteries, to withstand a wide range of pressures and large deformations [37].

2.2 Design requirements

With decreasing diameter, the biomimetic design of SSDVGs necessitates more complex and more precise engineering strategies. A smaller lumen size amplifies the critical importance of replicating the intricate structural and functional characteristics of native blood vessels, as even minor deviations in design can significantly impact hemodynamic performance, mechanical stability, and biological integration. To successfully replicate the structure and function of native blood vessels, an ideal SSDVG must meet several critical design criteria: (1) sufficient mechanical strength and appropriate compliance to allow for secure suturing, withstand physiological hemodynamic stress, and maintain long-term structural integrity; (2) favorable biocompatibility, including hemocompatibility and histocompatibility; (3) superior antithrombotic and anti-infective properties, especially in small-diameter applications; (4) appropriate porosity and permeability to enable cellular infiltration and the exchange of nutrients, gases, and signaling molecules with surrounding tissue; (5) the ability to support rapid endothelialization and tissue remodeling to ensure long-term patency; (6) clinical practicality, including various available sizes to accommodate patient-specific anatomy, short manufacturing time, ease of storage and handling, and reasonable production costs to support widespread clinical use.

2.3 Unique challenges of SSDVGs

Despite the significant advancements in research and development over the past decades, SSDVGs have yet to demonstrate optimal long-term patency. Approximately 75% of SSDVGs demonstrate failure within three years of implantation [39] due to the complex interactions with the human physiological environment and specific hemodynamic and biomechanical requirements. Compared with large-diameter vascular grafts, SSDVGs are more challenging to manufacture, given the need for greater precision. SSDVGs are required to exhibit mechanical properties that match those of natural vessels, including compliance and fatigue resistance, to withstand long-term pulsatile pressures without collapsing, dilating, or rupturing. The compliance mismatch that results in the aforementioned conditions causes abnormal shear stress at the anastomotic site, which induces smooth muscle cells (SMCs) to undergo a hyper-proliferative state, consequently leading to intimal hyperplastic and luminal narrowing. The rapid post-implantation endothelialization of SSDVGs is often hindered by material surface properties, biocompatibility, and the local microenvironment, among others. Furthermore, luminal narrowing and diminished flow velocity in SSDVGs significantly increase the risk of platelet aggregation and thrombosis. Hemodynamic changes and endothelial damage induced intraoperatively trigger the coagulation process, which involves complex interactions among ECs, platelets, von Willebrand factor, and coagulation factors. The inflammatory response is further maintained by the recruitment of monocytes and macrophages, leading to thrombus formation. Over time, thrombosis causes poor patency and, in some cases, complete occlusion. Therefore, with decreasing diameter, the design of SSDVGs imposes increasingly stringent requirements on material selection, mechanical performance, antithrombotic properties, endothelialization, and durability. Thus, the development of SSDVGs is one of the most complex and demanding projects in vascular tissue engineering, given the unique challenges of IH, limited endothelialization, and thrombosis, among others, that need to be addressed.

2.3.1 Intimal hyperplasia

IH is a well-observed pathological phenomenon that results in lumen stenosis and usually occurs as early as six weeks after bypass surgery [40]. IH involves the abnormal intimal thickening owing to the abnormal migration and proliferation of vascular SMCs and excessive extracellular matrix (ECM) deposition [41]. Technological advances have identified multiple factors contributing to IH, including intraoperative endothelial injury, poor intrinsic biocompatibility of graft materials, localized stress at suture sites, and mechanical mismatch between the graft and native vessel (Fig. 3) [42–44]. Of these, compliance mismatch has been a major research focus since the 1970s, which has been investigated through both computational simulations and in vivo graft models [45–47].

Compliance is defined as the change in the internal diameter of a blood vessel in response to a pressure change [48]. As an elastic reservoir, the compliant native vessel wall can maintain dynamic blood pressure by absorbing energy during systole and releasing it in diastole [49]. Suturing rigid graft segments results in local hemodynamic changes, significantly disrupting normal function (Fig. 3a) [50]. Geometric discontinuity and compliance mismatch can cause various blood flow disturbances, including flow separation, turbulence, and wall shear stress (WSS) changes around the anastomotic area (Fig. 3b) [51, 52]. Induced by flow separation and reversal, endothelial injury and dysfunction create a thrombogenic environment by reducing the production of tissue plasminogen activator, nitric oxide (NO), and prostacyclin while upregulating that of plasma fibrinogen [53]. Under such conditions, platelets are prone to activation and capture, causing platelet aggregation downstream, further contributing to fibrin thrombus formation [54, 55].

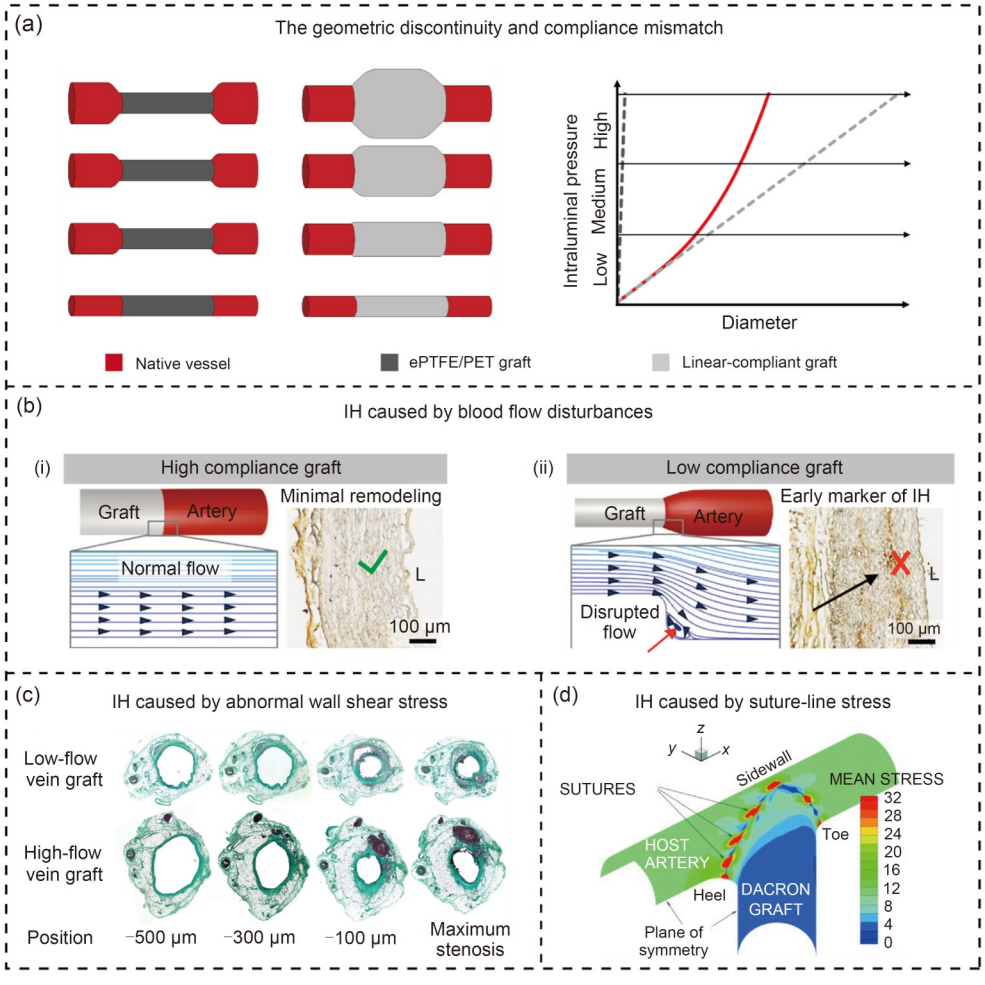


Fig. 3 Formation of IH. (a) Geometric discontinuity and compliance mismatch of SSDVGs with native blood vessels (reproduced from [50], with permission from Acta Materialia Inc.). (b) IH caused by blood flow disturbances at the anastomosis site (reproduced from [51], with permission from Acta Materialia Inc.). (c) Negative effect of abnormal wall shear stress on vascular repair (reproduced from [57], licensed under CC BY-NC-ND). (d) Increased suture-line stress due to compliance mismatch (reproduced from [60], with permission from Elsevier Science Ltd.)

WSS, which is the stress exerted by blood flow on the vessel wall parallel to the flow direction, may be vital in regulating the function and composition of blood vessels by influencing the phenotype and integrity of ECs [40]. Under physiological WSS, the orientation of ECs is aligned with the flow direction, during which ECs produce sufficient NO to reduce the proliferation of SMCs and thus inhibit IH [56]. Extensive research indicates that both high WSS and low WSS negatively affect normal endothelial function; that is, high WSS damages the endothelium and promotes SMC proliferation, whereas low WSS indicates low blood flow velocity, minimizing EC proliferation and trapping platelets and leukocytes (Fig. 3c) [57]. In SSDVGs, ECs exposed to abnormal WSS fail to express endothelial nitric oxide synthase (eNOS). Furthermore, sharp WSS changes induce endothelial deformation at the anastomosis site [58]. Consequently, IH primarily occurs in areas with altered blood flow patterns, particularly at the arterial floor of the distal anastomosis [59]. Similarly, compliance mismatch increases vascular wall stress and suture-line stress, contributing to the development of IH (Fig. 3d) [60].

2.3.2 Limited endothelialization

Rapid in situ endothelialization on the luminal surface is crucial for achieving long-term patency in SSDVGs and remains a major focus of ongoing research. Endothelialization is the process of inducing ECs to form an intact, functional intimal layer that directly contacts blood, consistent with that in natural blood vessels, a feature that is vital for anticoagulation, anti-thrombogenesis, and IH inhibition [61, 62]. Despite its importance, achieving reliable and sustained endothelialization remains a significant challenge in the clinical application of SSDVGs.

In situ endothelialization occurs through three primary mechanisms: transanastomotic migration, transmural capillarization, and fallout endothelialization [63, 64]. Transanastomotic migration is the spontaneous endothelialization of

ECs migrating from the proximal or distal anastomoses into the grafts, which is well established in rat, rabbit, and canine models [65–67]. The length and surface structure of grafts can significantly affect the extent of transanastomotic ingrowth [68]. Transmural capillarization is the infiltration of capillaries from the perivascular tissue into the graft through pores via neovascular sprouting [69]. Unlike the other two methods, fallout endothelialization relies on circulating or peripheral blood for the recruitment and adhesion of endothelial progenitor cells (EPCs) onto the graft surface via progenitor-specific antibodies, growth factors, ligands, and adhesion peptides [70]. Subsequently, immobilized EPCs are differentiated into ECs [71, 72]. In summary, rapid in situ endothelialization strategies should integrate three mechanisms to promote the adhesion, elongation, migration, proliferation, and differentiation of EPCs and ECs through surface modification and structural design.

2.3.3 Thrombosis

Thrombosis is a key event in arterial disease associated with myocardial infarction and stroke, and contributes considerably to morbidity and mortality [73]. Occlusive thrombus in the graft lumen is an established major cause of graft failure [25]. To prevent immediate pathological inflammatory responses and thrombogenesis after implantation, a biocompatible blood-contacting surface must be developed [74].

Under physiological conditions, hemostasis refers to the dynamic balance between coagulation and anticoagulation to repair injured blood vessel walls, prevent blood extravasation, and maintain the integrity of the circulatory system after vascular damage [75]. The two main steps in hemostasis are platelet plug formation and the coagulation cascade [76]. First, platelets are activated by factors released from the injured vessel, migrate to the exposed ECM, aggregate at the adhesive site, and form an initial platelet plug [77]. Subsequently, the coagulation cascade is initiated, during which fibrinogen is converted into an insoluble fibrin mesh to strengthen and stabilize the platelet plug [78]. Because of limited endothelialization on the graft surface, the surgical injury response, and abnormal hemodynamics, the dynamic hemostatic balance is disrupted, which induces thrombus or pathological clot formation [79]. Numerous studies have also adopted various strategies for surface modification of blood-contacting implants by administering antithrombotic drugs, including heparin, warfarin, aspirin, hirudin, dipyridamole, clopidogrel, cilostazol, and glycoprotein IIb/IIIa inhibitors [80–82].

3 Biomimetic design

To improve the long-term patency of SSDVGs, biomimetic design strategies must primarily focus on three objectives: matching the biomechanical properties of native vessels, promoting rapid endothelialization, and preventing thrombosis. This section systematically reviews recent progress in these areas. First, we present typical synthetic materials suitable for preparing SSDVGs. Then, we examine innovative structural designs, along with their mechanical properties, with particular emphasis on compliance. Next, we explore the role of surface topographical patterns on the SSDVG bio-interface for effectively enhancing the cellular microenvironment. Finally, we summarize advanced surface modification strategies aimed at enhancing antithrombotic performance and accelerating endothelial regeneration.

3.1 Synthetic materials suitable for SSDVGs

While ePTFE and PET are feasible in large-diameter vascular grafts, their inherent limitations, including mismatched mechanical properties, heightened thrombosis, poor endothelialization, and inadequate biocompatibility, demonstrate impaired performance in small-diameter applications. To address these limitations, various innovative synthetic materials have been explored for the fabrication of SSDVGs, and their clinical efficacy and potential have been systematically assessed. These synthetic materials are categorized based on their degradability in vivo into bioresorbable or biostable polymers [83]. Typical synthetic materials suitable for SSDVGs are presented in Table 1.

3.1.1 Bioresorbable polymers

The degradation rates of bioresorbable polymers must be precisely controlled to match the timeline of tissue regeneration. Furthermore, their mechanical properties must be sufficient to withstand hemodynamic stresses during the transition period. Representative bioresorbable polymers include PLA, PLLA, PLGA, PCL, and PLCL.

PLA: It is a biodegradable polymer derived from renewable resources. It has emerged as a promising biomaterial with extensive applications in tissue engineering due to its exceptional biocompatibility and biodegradability [84]. PLA demonstrates excellent biosafety profiles, undergoing hydrolytic degradation into non-toxic metabolites that are completely absorbed by the host tissues [85]. Furthermore, its superior mechanical properties, including high tensile strength and modulus, make it particularly suitable for load-bearing applications [86]. Recent significant research efforts have been directed toward the development of PLA-based nanofibrous scaffolds for vascular tissue engineering [87, 88].

PLLA: It is a biodegradable synthetic polymer, gaining widespread recognition as a fundamental biomaterial in tissue engineering applications [89]. PLLA undergoes hydrolytic degradation into L-lactic acid monomers, which are

Table 1 Typical synthetic materials suitable for synthetic small-diameter vascular grafts

Material		Property	Diameter (mm)	Application	Ref.
Bioresorbable polymers	PLA	Exceptional biocompatibility and biosafety; superior mechanical properties	3	The graft supported fibroblast adhesion and proliferation in vitro, exhibited non-hemolytic properties, and demonstrated appropriate mechanical performance for its intended use.	[87]
	PLLA	Good biosafety; hydrophobicity	2.93±0.05	The addition of chitosan–collagen improved cell viability and graft hemocompatibility.	[93]
	PLGA	Customizable mechanical properties; tunable degradation; hydrophobicity	2.0	The six-week follow-up study revealed that small-diameter vascular grafts fabricated with PLGA and PEUU remained unobstructed in rabbits undergoing carotid artery defect repair.	[97]
	PCL	Exceptional biodegradability and biocompatibility; risk of calcification in vivo	2	PCL-based vascular grafts were fully endothelialized within 12 weeks but tended to develop calcification lesions after approximately 18 months in vivo.	[101]
	PLCL	Tunable mechanical properties; controllable degradation rate	2.5	Procyanidin-modified PLCL grafts showed good cell compatibility and low calcification and remained unobstructed after 30 d of carotid artery transplantation in rabbits.	[104]
Biostable polymers	PU	Superior mechanical properties; low thrombogenicity; long-term biostability	1.8–2.0	The heparin-modified PU graft demonstrated reliable cytocompatibility and substantial patency in a rat model.	[108]
	PVDF	Good mechanical strength; high chemical resistance; high biocompatibility	4	The all-in-one piezoelectric vascular graft synthesized by embedding a PVDF nanofiber mat with patterned silver nanowire electrodes between two PCL nanofiber layers exhibited native vessel-like endothelialization and mechanical performance and exceptional piezoelectric sensitivity.	[113]

PLA: polylactic acid; PLLA: poly(L-lactide); PLGA: polylactic-co-glycolic acid; PEUU: poly(ester-urethane) urea; PCL: polycaprolactone; PLCL: poly(L-lactide-co-ε-caprolactone); PU: polyurethane; PVDF: polyvinylidene fluoride

subsequently metabolized through the endogenous Krebs cycle, ensuring complete biological assimilation. Despite its favorable degradation profile, the inherent hydrophobicity of PLLA significantly limits direct implantation applications, as it hinders optimal cellular interactions and tissue integration [90]. This hydrophobic characteristic can reduce cell adhesion and compromise biocompatibility in vivo [91]. To address these limitations, researchers have developed innovative strategies that incorporate natural polymers, such as collagen, chitosan, or hyaluronic acid, to enhance the hydrophilicity, improve cell-material interactions, and promote tissue regeneration when using PLLA [92, 93].

PLGA: It is a prominent material used in biomedical applications due to its exceptional processability, which enables precise fabrication into complex geometries, and its customizable mechanical properties that can be tailored to specific needs [94]. Its predictable and tunable degradation kinetics further diversifies its applications to meet various requirements [95]. However, the inherent hydrophobicity of PLGA grafts significantly hinders cell adhesion and proliferation, limiting their biocompatibility [96]. Advanced surface modification techniques have been widely adopted to enhance cellular interactions and optimize the performance of PLGA grafts [97].

PCL: It is a highly biodegradable and biocompatible polymer well-suited for various biomedical applications [98]. Its ester groups degrade hydrolytically into water, carbon dioxide, and minor acidic byproducts [99]. Unlike other synthetic polymers, PCL degrades slowly, often taking over two years, enabling it to sustain cell adhesion and proliferation and tissue regeneration [100]. However, although PCL-based SSDVGs fully endothelialize within 12 weeks, they tend to develop calcification lesions after approximately 18 months in vivo [101].

PLCL: It is a PLLA and PCL copolymer that merges the strengths of the two constituents. It balances the rigidity and brittleness of PLLA with the flexibility and elasticity of PCL, enabling the synthesis of materials with tunable mechanical properties—from rigid to soft—by adjusting the PLLA/PCL ratio [102]. The degradation rate of PLCL can also be tailored to specific needs [103]. Both in vitro and in vivo studies confirm its excellent cell compatibility, promoting cell adhesion, proliferation, and differentiation, making it suitable for tissue engineering [104, 105].

3.1.2 Biostable polymers

Biostable polymers have extensive tissue engineering applications due to their superior mechanical properties, chemical

stability, and biological inertness. However, when these materials come into direct contact with blood, they trigger mild coagulation responses or immune rejection. Consequently, surface functionalization is often employed for enhanced biocompatibility. Common biostable polymers used for SSDVGs include PU and PVDF.

PU: It has been used as a vascular graft material since the 1960s. Its unique flexible molecular architecture yields mechanical properties remarkably similar to those of natural blood vessels and supports rapid endothelialization [106]. Compared with conventional materials, such as ePTFE and PET, PU-based vascular grafts are superior in terms of elasticity, compliance, and biocompatibility [107]. Furthermore, its exceptional suture retention and self-healing capabilities minimize plasma leakage post-anastomosis, thereby ensuring low thrombogenicity [108]. A new generation of polycarbonate-based PU that has been recently developed incorporates soft polycarbonate segments that enhance long-term biostability [109].

PVDF: It is a promising biomaterial that combines exceptional mechanical strength, outstanding chemical resistance, and favorable biocompatibility [110]. Its high tensile strength and flexibility allow it to endure dynamic vascular stresses, while its chemical inertness ensures long-term stability under physiological conditions [111]. Notably, surface-modified PVDF promotes cellular adhesion and proliferation, thus facilitating graft patency and preventing thrombus formation [112]. Furthermore, the exceptional resistance of PVDF to biological degradation further enhances its suitability for long-term implantation, addressing a critical challenge in small-diameter graft applications [113].

3.2 Structural design of the vascular wall

The structural design of vascular grafts is inherently complex and must be tailored to meet patient-specific requirements by considering mechanical performance, material selection, structural configuration, and manufacturability [33]. Table 2 presents the mechanical properties of autologous vessels commonly used in bypass surgery, offering a critical reference point for the biomimetic design of SSDVGs. These data provide mechanical benchmarks that synthetic alternatives must replicate or surpass to ensure long-term clinical performance comparable to native vessels.

Vascular grafts fabricated using a single material or manufacturing technique often fail to replicate the complex mechanical behavior and porosity of native vessels. However, the performance of SSDVGs can be enhanced through rational structural design and integration of advanced materials and manufacturing technologies. This combined approach facilitates improvements in elasticity, compliance, fatigue resistance, and antithrombogenicity, thereby bringing synthetic grafts closer to the functional profile of native blood vessels. Accordingly, structural design-driven optimization offers a scientifically grounded pathway for enhancing graft performance and supports ongoing innovation in vascular tissue engineering. In this subsection, we review recent structural design advances for optimizing the mechanical behavior of SSDVGs. These designs utilize composite materials and various fabrication techniques. Vascular graft structures are designed and characterized using various modalities, including fabric-based, segmented, embedded, and layered structures. The compliance values of different structural designs of small-diameter grafts are summarized in Table 3, demonstrating the impact of design variations on biomechanical performance.

3.2.1 Fabric-based structures

Fabric-based vascular grafts are engineered using optimized fiber arrangements. They have attracted significant attention due to their favorable mechanical performance and biological compatibility (Fig. 4) [119]. These grafts can be fabricated using textile or non-textile fiber production techniques [120]. In particular, textile-based methods are widely used for their ability to produce grafts with compact architecture, dimensional stability, and controllable wall thickness. Common textile techniques include weaving, knitting, and braiding, each offering distinct structural and mechanical features depending on various parameters, such as yarn twist, interlacing pattern, and fabrication geometry (Fig. 4a) [121].

Weaving involves the interlacing of two sets of mutually perpendicular yarns, the warp and weft, to form a tightly packed fabric structure (Fig. 4a). Mechanical and physical

Table 2 Mechanical properties of autologous vessels commonly used in bypass surgery

Autologous vessel	Tensile modulus (MPa)	Tensile strength (MPa)	Burst pressure (mmHg)	Compliance (%/100 mmHg)	Suture retention (N)	Ref.
SV	4.2±3.3	1.8±0.8	1680–2476	1.77±1.20	1.92±0.02	[114–116]
RA	2.68±1.81	–	2001–2617	3.68±2.05	1.41±0.55	[114, 115, 117]
IMA	8.0±3.0	4.1±0.9	1932–4460	5.22±5.13	1.35±0.49	[114–116]
CA	1.48±0.24	1.44±0.87	2031–4225	4.06±3.16	1.96±1.17	[114, 115, 118]

SV: saphenous vein; RA: radial artery; IMA: internal mammary artery; CA: coronary artery. 1 mmHg≈133 Pa

Table 3 Synthetic small-diameter vascular grafts with various structural designs

Structural feature	Manufacturing method		Material	Compliance (%/100 mmHg)	Specific consideration	Ref.
Fabric-based	Weaving		Cell-assembled extracellular matrix	2.9–4.8	Optimize grafts by varying sheet strength and weaving parameters (such as warp count, weft ribbon width, and weft tension).	[122]
	Knitting		Collagen/PLA	3.98±1.94	Design a hybrid vascular graft utilizing the excellent mechanical properties of synthetic fibers and the biological properties of collagen fibers.	[125]
	Braiding		Silk fibroin	2.6	Develop a novel covered graft with biocompatible and comprehensive mechanical properties.	[130]
	Electrospinning		TPU	5.1±1.1	Study the thin-walled TPU grafts and show their long-term performance characteristics after implantation.	[134]
	Melt electrowriting		PCL	12.9±0.6	Manufacture highly porous, biocompatible microfiber scaffolds with physiological anisotropic mechanical properties and high compliance.	[135]
Segmented	Knitting Electrospinning		PET/Spandex PU	15±2.1	Achieve an optimum balance between structural robustness and flexibility, and reveal good in vitro biomechanical properties.	[140]
	Knitting		PET/NT/PU	5.89–9.80	Present a new knitted graft design and demonstrate significant improvement in biomechanical and procedural parameters.	[139]
Embedded	Wrapping Crosslinking		Collagen/ Alginate	4.88±0.99	Develop biocomposite material grafts and demonstrate both mechanical and biological compatibility.	[141]
	Knitting Crosslinking		PLA/GelMA	3.03±0.69	Engineer a textile-reinforced hydrogel vascular graft favoring the reendothelialization and enhancing macrophage activation and upregulation.	[142]
Layered	Bi-	IL: extrusion printing OL: electrospinning	IL: GelMA OL: PCL/PLCL	7.87±1.22	Prepare a high-compliant vascular graft, similar to human muscular arteries.	[149]
	Triple-	IL: electrospinning ML: electrospinning OL: braiding	IL: silk fibroin ML: PLCL OL: silk fibroin	3.60±0.15	Fabricate a novel three-layer vascular graft to mimic the structure of human blood vessels, exhibiting excellent mechanical strength, biocompatibility, and anticoagulant properties.	[158]
	Multi-	Dip spinning Solution blow spinning	PCL/GEAL	6.3–12.9	Mimic the media and adventitia layers of native arteries and exhibit the J-shape mechanical response and compliance of human coronary arteries.	[164]

IL: inner layer; ML: middle layer; OL: outer layer; PLA: polylactic acid; TPU: thermoplastic polyurethane; PET: polyethylene terephthalate; NT: nitinol; PU: polyurethane; GelMA: gelatin methacryloyl; PCL: polycaprolactone; PLCL: poly(L-lactide-co-ε-caprolactone); GEAL: gelatin-alginate. 1 mmHg≈133 Pa

properties are influenced not only by the material but also by weaving parameters, such as thread spacing, weave type, linear density, and yarn twist direction [122, 123]. Woven grafts exhibit smooth surfaces, permeability, ease of handling, chemical stability, favorable bio-healing response, and sufficient mechanical strength. However, the organized orthogonal arrangement structures exhibit poor radial compliance and low axial elongation, limiting long-term applications in vivo [124].

Knitted grafts, which are constructed from interlocking yarn loops (Fig. 4a), offer radial distensibility and compliance superior to those of woven structures [125]. Their mechanical and structural properties can be modulated by adjusting loop density, pore size, and distribution [126], which enhances cell infiltration and vascular tissue remodeling. However, their application is limited by their high porosity and tendency for rapid dilation, which often requires preclotting procedures to reduce blood leakage during early implantation [127].

Braided grafts are produced by intertwining multiple helical yarns into a cylindrical structure (Fig. 4a), which offers high flexibility, low porosity, and excellent shape retention [128]. Key parameters, such as braiding angle and braid density, significantly influence mechanical behavior [129]. Increasing the braid angle with the axial direction enhances the circumferential stiffness of the scaffold but reduces its axial stiffness [130]. Furthermore, the number of yarn ends and the number of picks per square inch influence void space and are positively correlated with bulk stiffness [131]. Overall, textile-based fabrication provides precise

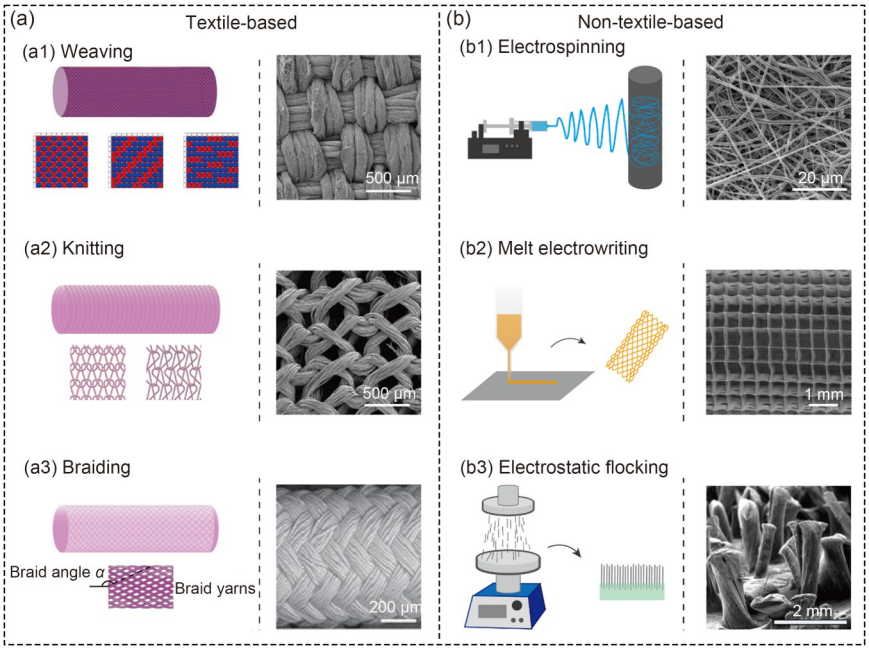


Fig. 4 Fabric-based structures. (a) Textile-based fabric structures produced by weaving (a1), knitting (a2), and braiding (a3). Left column: reproduced from [121], licensed under CC BY 4.0. Right column: (a1) is reproduced from [123], with permission from the American Chemical Society; (a2) is reproduced from [127], with permission from the Japanese Society for Artificial Organs; (a3) is reproduced from [131], with permission from Wiley-VCH GmbH. (b) Non-textile-based fabric structures produced by electrospinning (b1), melt electrowriting (b2), and electrostatic flocking (b3). (b1) is reproduced from [133], with permission from Elsevier B.V.; (b2) is reproduced from [135], licensed under CC BY 4.0; (b3) is reproduced from [136], licensed under CC BY-NC-ND

control over scaffold architecture, porosity, and mechanical properties, which are critical for replicating the anisotropic and nonlinear mechanical behavior of native vessels, thereby enhancing the functional success of SSDVGs.

Non-textile fabrication methods, such as electrospinning, melt electrowriting, and electrostatic flocking, offer advanced structural design capabilities that often produce grafts with random fiber arrangements (Fig. 4b) [132]. For example, electrospinning enables the selection of a wide range of natural and synthetic polymers to construct structures with greater flexibility to mimic the properties of native blood vessels (Fig. 4b) [133]. Nanofibrous scaffolds, which are composed of fibers ranging from nano- to micrometer scales, offer a high surface-area-to-volume ratio, which is conducive to cell growth [134]. Emerging techniques, such as melt electrowriting and electrostatic flocking, further expand capabilities for SSDVG fabrication by enabling the construction of scaffolds with physiological compliance (Fig. 4b) [135, 136]. These advanced fabrication methods thus present significant opportunities for developing next-generation vascular grafts with biomimetic architectures and enhanced functional outcomes.

3.2.2 Segmented structures

Segmented structures, often referred to as "caterpillar" designs, are a novel class of vascular grafts resulting from advancements in knitting technology. These grafts consist of alternating high-modulus (hard segments, HSs) and low-modulus (soft segments, SSs) segments that facilitate the dynamic modulation of stiffness and flexibility along the graft length (Fig. 5) [137]. The mechanical characteristics of each segment can be finely tuned by selecting appropriate materials and adjusting structural density (Fig. 5a) [138].

Compared with conventional Dacron-woven grafts, segmented structures provide superior compliance that closely matches that of native vessels, such as the human aorta. This enhanced compliance stems from the high elasticity of the SS, which facilitates radial expansion in response to pressure changes (Fig. 5b) [139]. The design also exhibits unique biomechanical properties, including bidirectional expansion, a negative Poisson's ratio, and volumetric expansion under circumferential stress, all of which further enhance its functional performance (Figs. 5c and 5d) [138, 140]. Collectively, these characteristics improve hemodynamic performance and mechanical adaptability.

Notably, the caterpillar configuration minimizes bending resistance and prevents kinking because the SSs accommodate localized deformation while the HSs maintain the circular geometry of the graft [139, 140]. In this design, the HSs provide mechanical integrity, while the SSs facilitate critical functionalities, such as compliance, distensibility, flexibility,

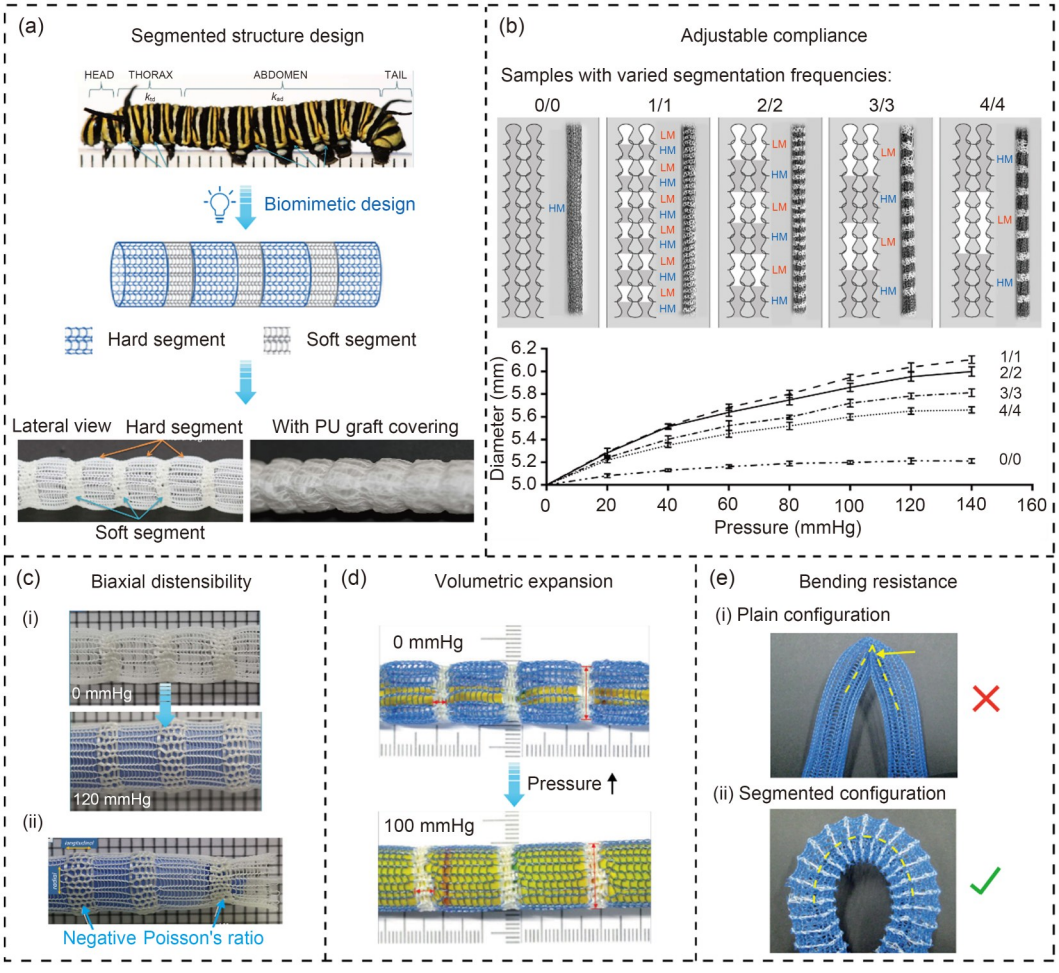


Fig. 5 Segmented structures. (a) Biomimetic segmental geometry resembling a caterpillar cuticle. Reproduced from [138] (with permission from SAGE Publications Ltd.) and [140] (with permission from Elsevier Ltd.). (b) Pattern and structure of plain (0/0) and segmented (1/1, 2/2, 3/3, 4/4) knit mesh designs and their corresponding pressure–diameter curves over a pressure range of 0–140 mmHg (reproduced from [139], with permission from Elsevier Ltd.). (c) Biaxial distensibility behavior and negative Poisson's ratio of the structure (reproduced from [140], with permission from Elsevier Ltd.). (d) Volumetric expansion effect after internal pressurization from 0 to 100 mmHg (reproduced from [138], with permission from SAGE Publications Ltd.). (e) Bending resistance of the segmented structure compared with that of the plain configuration (reproduced from [138], with permission from SAGE Publications Ltd.). 1 mmHg≈133 Pa

and bending and kinking resistance (Fig. 5e) [138]. By harmonizing HS and SS, the design establishes a well-balanced interplay between structural stability and functional adaptability. However, despite its promising performance, this design has yet to be evaluated in vivo, necessitating further experimental studies to establish its clinical potential.

3.2.3 Embedded structures

The embedded structure is a significant innovation in vascular graft design, which integrates a flexible yet robust backbone within a soft, biocompatible matrix (Fig. 6). The embedded mesh framework acts as the backbone, and the primary load-bearing component of the graft provides essential reinforcement and structural stability during implantation and physiological loading (Fig. 6a). Materials commonly used for the backbone include PET, PLA, collagen, and biocompatible metals (Fig. 6b) [141–144]. Strategic backbone architecture enables the precise tuning of graft mechanical properties, such as burst pressure, suture strength, and radial compliance, to more closely replicate those of native blood vessels (Fig. 6c) [142, 144].

Embedded structures have been validated through extensive experimental studies and finite element simulations. The latter, which model sinusoidal fiber architectures with varying amplitudes, offer valuable insights for structural optimization (Fig. 6c) [145, 146]. Overall, embedded structures enhance mechanical performance while meeting the physiological demands of small-diameter vascular applications, offering a robust, durable, and functionally adaptive graft option.

The surrounding matrix, often composed of hydrogels or similar soft biomaterials, complements the backbone by

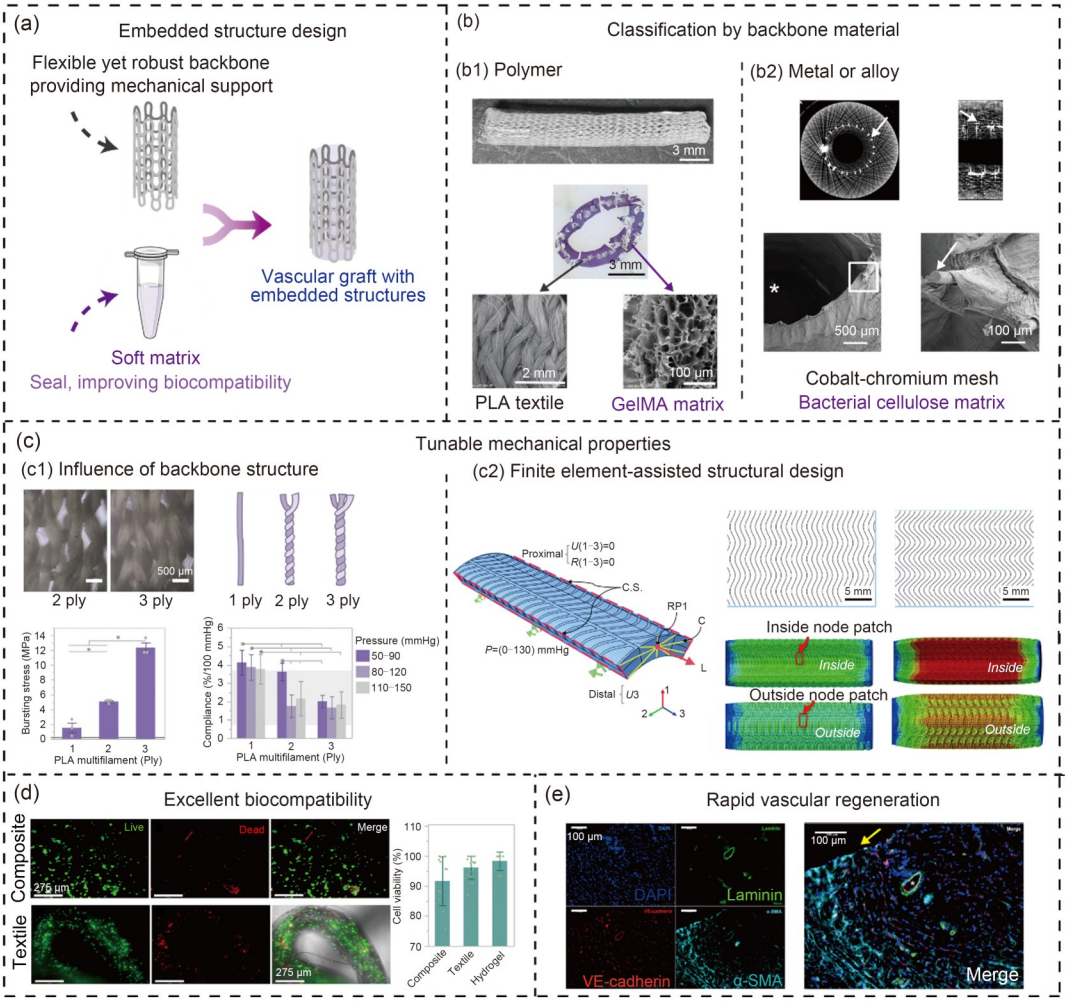


Fig. 6 Embedded structures. (a) Scheme of the embedded vascular graft (reproduced from [142], with permission from The Royal Society of Chemistry). (b) Different types of embedded grafts categorized according to the backbone material: (b1) polymer mesh (reproduced from [142], with permission from The Royal Society of Chemistry); (b2) alloy mesh (reproduced from [143], licensed under CC BY 4.0). (c) Tunable mechanical properties: (c1) influence of backbone structure (reproduced from [142], with permission from The Royal Society of Chemistry); (c2) finite element-assisted design (reproduced from [145], with permission from The Royal Society of Chemistry). (d) Excellent biocompatibility of embedded grafts compared with textile grafts (reproduced from [142], with permission from The Royal Society of Chemistry). (e) Vascular repair capacity for coronary artery bypass grafting in a pig model (reproduced from [143], licensed under CC BY 4.0)

providing critical biological functions. It directly contacts blood and cells, exhibiting excellent inherent biocompatibility and optimizing the adhesion, proliferation, and survival of ECs on the graft surface (Fig. 6d) [142]. Moreover, the matrix enhances macrophage activation and precisely regulates the expression of M1- and M2-related genes, fostering a conducive environment for vascular regeneration and immune modulation, contributing significantly to successful vascular graft integration and long-term patency [142]. Embedded structures promote a dual focus on structural integrity and biocompatibility and are crucial to improving the design and efficacy of vascular grafts. Some large animal model studies have successfully demonstrated the considerable potential of small-diameter embedded structure grafts for coronary and peripheral bypass grafting (Fig. 6e) [143].

3.2.4 Layered structures

The layered structure design offers a promising strategy for developing SSDVGs that more closely replicate the structural and functional complexity of natural blood vessels. Unlike conventional single-layer grafts, which are often limited by low compliance and biocompatibility, layered designs integrate distinct materials and functionalities across multiple layers (Fig. 7a), enabling the simultaneous optimization of mechanical integrity, compliance, and biological performance, ultimately improving graft durability and long-term patency. Here, layered structures are categorized based on the number of layers employed: bi-layered, triple-layered, and multi-layered configurations (Fig. 7).

Bi-layered structures: They achieve the desired mechanical properties and biocompatibility by selectively matching two

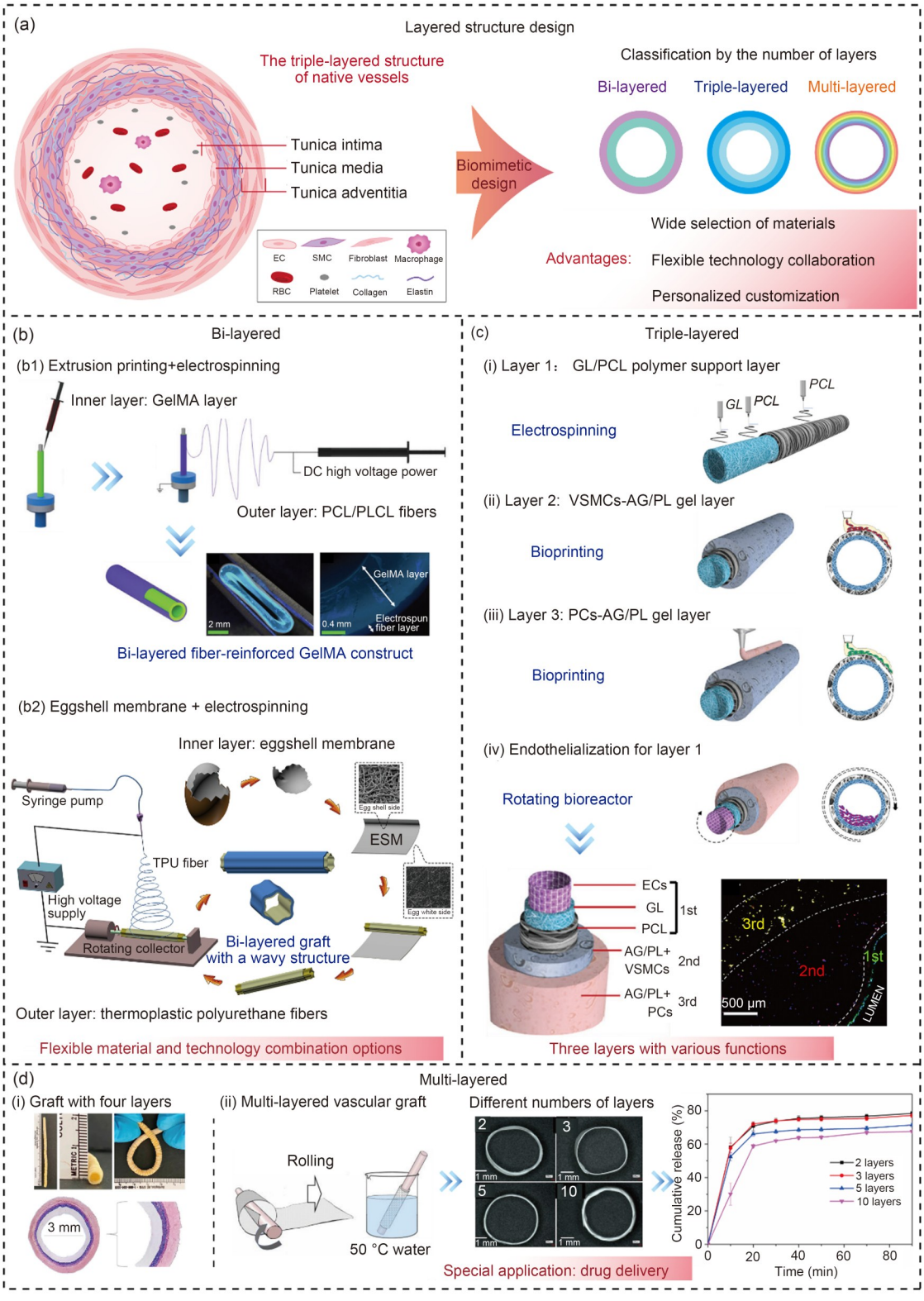


Fig. 7 Layered structures. (a) Schematic diagrams of the layered structure design, mimicking the triple-layered structure of natural blood vessels. (b) Bi-layered vascular grafts constructed using different techniques and materials: (b1) bi-layered fiber-reinforced gelatin methacryloyl construct (reproduced from [149], licensed under CC BY 4.0); (b2) bi-layered graft with a wavy structure (reproduced from [151], with permission from Elsevier B.V.). (c) Triple-layered vascular graft with various functions (reproduced from [161], licensed under CC BY 4.0). (d) Multi-layered vascular grafts (reproduced from [162], licensed under CC BY 4.0) and their applications in drug delivery (reproduced from [165], with permission from Elsevier B.V.)

different layers in terms of material, structure, orientation, or manufacturing method (Fig. 7b). Typically, the inner layer is designed to facilitate endothelialization and reduce thrombogenicity, often by incorporating bioactive or biocompatible components [147–150]. For example, natural biomaterials, such as eggshell membranes, have been used as inner layers because of their unique fiber structure, excellent biocompatibility, and ability to promote EC adhesion and proliferation (Fig. 7b) [151]. The outer layer must offer structural integrity, mechanical recovery, and compliance, ensuring optimal alignment with the mechanical behaviors of native vessels [152, 153]. Numerous studies have demonstrated the advantages of double-layer structures designed according to specific requirements. First, the bi-layered design enables a wide range of material combinations with various degradation properties. Popryadukhin et al. [154] successfully fabricated bi-layered electrospun vascular grafts with an inner diameter of 1.1 mm that featured a bioresorbable inner layer designed to promote cellular infiltration and vascular regeneration. This layer was complemented by a non-absorbable outer layer that effectively prevented aneurysm formation. Furthermore, the bi-layered design integrates the advantages of different fabrication techniques to the greatest possible extent. Navarro et al. [150] combined molding and electrospinning to fabricate a bi-layer graft with a porous, nanofibrous inner layer for cell growth and a dense outer layer for structural support. Moreover, the bi-layer structure facilitates the independent functional optimization of each layer. Wang et al. [155] developed a bi-layer graft with spatiotemporal NO/H_2S co-delivery for anti-inflammation and anti-calcification. A keratin-based H_2S donor was electrospun with PLCL to form the outer layer, while sodium hyaluronate was modified with copper ions to mimic the endothelial glycocalyx and support sustained NO generation in the inner layer. Overall, a bi-layer structural design enhances design versatility for SSDVGs.

Triple-layered structures: Similar to the bi-layered structures, the inner layer of a triple-layered structure must facilitate anticoagulation and endothelialization, while the middle and outer layers should be engineered to deliver robust mechanical support and optimal compliance [156]. However, compared with bi-layered grafts, the triple-layer structure provides even greater flexibility in the selection of materials and manufacturing methods (Fig. 7c) [157–159]. Therefore, triple-layer grafts offer a more precise simulation of the natural triple-layer vascular structure, more closely replicate nonlinear mechanical properties, and exhibit a more uniform mechanical stress distribution, thereby significantly reducing the risk of graft failure or deformation [160]. Furthermore, customization of the characteristics of each layer expands the diversity of possible biological functions [161].

Multi-layered structures: The multi-layered graft architecture represents another innovative layered approach, with increased precision in replicating the complex structure and functional properties of natural blood vessels, achieved by precisely tuning the mechanical properties, diameter, and wall thickness of the graft (Fig. 7d) [162–164]. Multi-layered vascular grafts exhibit the J-shaped mechanical response and excellent compliance, such as those previously constructed for human coronary arteries [164]. Multi-layered structured grafts also offer significant advantages in drug release (Fig. 7d) [165]. The multifunctionality of multi-layered SSDVGs positions them as highly versatile and clinically promising options for vascular reconstruction.

3.3 Surface topography design

In biomimetic SSDVGs, the wall structure and luminal surface topography function as two interdependent and critical design components. Wall structural design focuses on replicating the macroscopic mechanical properties of native blood vessels to achieve appropriate flexibility, durability, and compliance under physiological conditions. Luminal surface topography is concerned with microscale biological interactions, particularly those involving ECs. These differences in design focus, from mechanical performance to surface biofunctionality, underscore the increasing importance of strategies that enhance endothelialization, reduce thrombogenicity, and prevent IH. Surface topography design facilitates the precise replication of the micro- and nanoscale features of native vessel endothelium, such as microgrooves, microprotrusions, and geometric patterns. The design can enhance blood flow and replicate physiological conditions, thereby improving graft biocompatibility and in vivo performance. A substantial body of evidence demonstrates that ordered and repetitive biomimetic surface topography accurately mimics the cellular microenvironment and significantly enhances local vascular regeneration, offering a promising therapeutic option for CVDs.

This subsection provides a comprehensive overview of luminal surface topography as a critical factor influencing vascular cell behavior, particularly that of ECs. Surface morphologies and patterning strategies are categorized based on spatial distribution into isotropic and anisotropic topographies (Fig. 8) [166–168]. Then, we summarize key in vitro findings that demonstrate the impact of surface morphology on essential cellular processes, such as adhesion, proliferation, differentiation, and overall functionality. Lastly, we discuss successful in vivo applications of topographically enhanced SSDVGs, demonstrating the translational potential and clinical relevance of surface topography modification.

3.3.1 Anisotropic topography

Anisotropic topographies are engineered by precise fabrication to establish directional surface patterns using various advanced spinning techniques (Fig. 8). These patterns include gratings, grooves, ridges, and fiber networks formed by aligned micro- or nanofibers [169–172]. Anisotropic topography integrates directional guidance for the growth of ECs [173]. On unpatterned substrates or those with randomly oriented stress fibers, ECs typically adopt a rounded, cobblestone-like morphology. In contrast, when cultured on grooves or fibers, ECs exhibit significant polarization and orientation, consistently assuming elongated forms with reduced aspect ratios along the axis of gratings or grooves [174]. Although findings are inconsistent, the expression of EC genes, including endothelial nitric oxide synthase (eNOS), platelet endothelial cell adhesion molecule-1 (CD31), and von Willebrand factor (vWF), is generally strongly correlated with surface morphology [175, 176]. Nevertheless, several recent studies demonstrate that ECs progressively exhibit reduced sensitivity to contact guidance with increasing cell density [177]. Furthermore, the impact of varying microgroove dimensions on EC behaviors, including proliferation and migration, was examined. Smaller groove sizes (3–5 μm) significantly enhanced cell proliferation relative to flat substrates within the initial 24 h [174, 178]. Several studies emphasize the importance of enhanced cell–cell junction stability in promoting EC migration and monolayer integrity on anisotropic topography. This effect is attributed to the upregulation of the adherens junction proteins, such

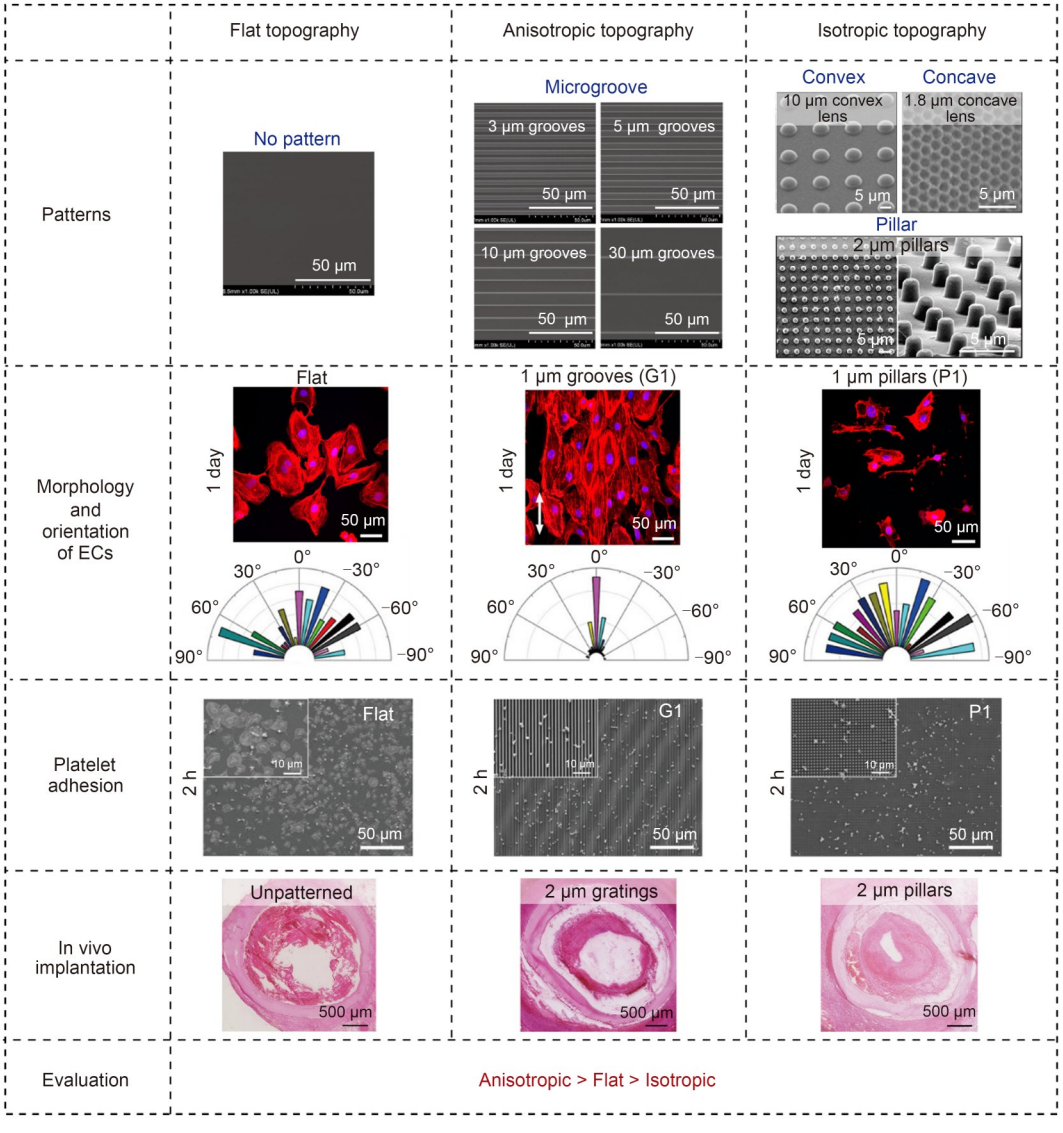


Fig. 8 Diverse surface topography designs and their effects on endothelial cell morphology and orientation, platelet adhesion, and in vivo implantation. Reproduced from [182] (with permission from the American Chemical Society), [183] (with permission from Elsevier Ltd.), and [174] (with permission from the American Chemical Society)

as VE-cadherin [177, 179]. Furthermore, anisotropic topography effectively reduces platelet adhesion and activation, highlighting its unique antithrombotic capability and potential to prevent thrombotic events [180, 181].

3.3.2 Isotropic topography

Isotropic topographies are characterized by a lack of directional guidance. This category of patterns includes pillars, wells, holes, pits, pores, cones, and randomly aligned fibrous mesh [182–184]. Isotropic topological structures exert negligible influence on EC orientation. The ECs mainly exhibit an elliptical morphology with numerous pseudopods extending to contact the micropillars [182]. The effect of isotropic topologies on EC proliferation depends significantly on size. The smaller the size of the micropillar, the greater the inhibition of intercellular contact formation and impairment of EC monolayer function. Despite the progressive improvement of EC phenotype with increasing dimensions, micropillars remain inherently less favorable than microgrooves in promoting the EC behavior [183].

3.4 Surface modification

Surface modification is a key aspect of biomimetic SSDVG design, as functionally optimized blood-contacting surfaces are essential to minimize thrombogenicity and ensure long-term patency [185]. Extensive research efforts have been devoted to exploring diverse strategies, with the overarching design objectives centered on two key aspects: promoting rapid in situ endothelialization and enhancing antithrombogenic properties (Fig. 9). The specific molecules used for bioactive surface modification and their loading approaches are summarized in Table 4.

3.4.1 In situ endothelialization strategies

Promoting in situ endothelialization during vascular remodeling is a significant priority for maintaining physiological vascular function and has thus attracted considerable research interest. Bone marrow-derived EPCs can migrate into the peripheral circulation and subsequently differentiate into ECs, thereby significantly contributing to

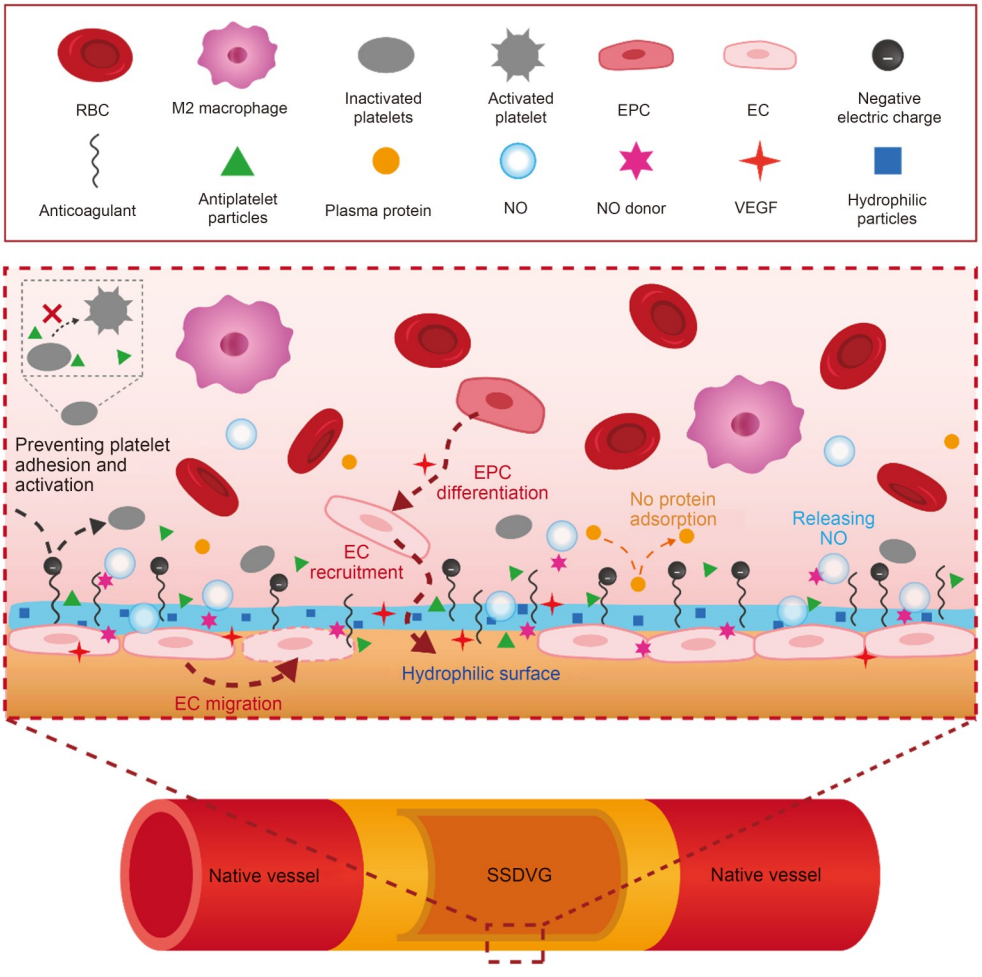


Fig. 9 Surface modification strategies of synthetic small-diameter vascular grafts (SSDVGs). EC: endothelial cell; EPC: endothelial progenitor cell; RBC: red blood cell; NO: nitric oxide; VEGF: vascular endothelial growth factor

endothelialization [186, 187]. EC migration from anastomotic sites is another key mechanism for endothelialization. Engineering the optimal vascular graft requires functional surface modification strategies that effectively recruit both ECs and EPCs, enhance EC migration, and promote their adhesion, proliferation, and activation.

Multiple chemokines targeting receptors on EPCs can facilitate their homing to neovascularization sites. These include stromal cell-derived factor-1α (SDF-1α) and dickkopf-3 (Dkk3), which target CXC family receptors; fibronectin (Fn), which targets integrin family receptors; and VEGF, which targets vascular endothelial growth factor receptor 1 (VEGFR1) and vascular endothelial growth factor receptor 2 (VEGFR2) [188–192]. However, more specific chemotactic factors that enhance EPC recruitment and homing efficiency effectively still need to be developed. Notably, the availability of circulating EPCs in human patients, particularly in elderly individuals or those with chronic conditions, is often significantly reduced [193–196]. Several studies have addressed this deficiency by implementing strategies to enhance EPC mobilization or function, such as pharmacological interventions or cell therapy, which can improve treatment outcomes for these patient groups [197, 198].

Following EPC homing, EC and EPC adhesion and migration to the graft surface must be enhanced. This can be achieved by incorporating bioactive binding sites or through specific molecular modifications that use similar biological pathways [199]. Natural polymers, known for their excellent biocompatibility, can provide sufficient cell-binding ligands. Thus, surface modification of synthetic polymers with natural polymers may significantly improve cellular adhesion in vascular graft fabrication [199]. Gelatin, collagen, elastin, and fibroin are common alternatives for vascular graft applications [200–203]. However, these materials also interact with other blood components, such as platelets, leukocytes, and SMCs, potentially triggering thrombosis and IH. Thus, more specific binding coatings must be developed to achieve optimal in situ endothelialization. Antibodies, cell adhesive peptides, and aptamers have been extensively investigated for their ability to promote cell-specific adhesion [61]. Of these, anti-CD34 antibodies are the most widely utilized for EPC capture and have been combined with drugs like sirolimus to reduce IH [204, 205]. Cell-adhesive peptides also play a crucial role in mediating biological identification between cell membranes and their ligands to facilitate both cell capture and adhesion. Various peptide sequences have been successfully employed in surface modification strategies, including Arg-Gly-Asp (RGD), Cys-Ala-Gly (CAG), Arg-Glu-Asp-Val (REDV), and Tyr-Ile-Gly-Ser-Arg (YIGSR) [206–210]. These bioactive peptides exhibit specific adhesion for ECs and EPCs while

Table 4 Specific molecules for bioactive surface modification

Design objective	Specific molecule	Loading approach	Effect	Ref.
In situ endothelialization	SDF-1α	Immobilized onto heparin	EPC recruitment	[190]
	Dkk3	Co-electrospinning	EPC recruitment and differentiation	[189]
	Fibronectin	Coating on synthetic polyester	EPC homing	[191]
	VEGF	Co-axial electrospinning	EPC homing and capture, and EC proliferation and activation	[216]
	Collagen	Extrusion	EPC and EC adhesion	[202]
	Elastin	Blending	EPC and EC adhesion	[201]
	Anti-CD34 Abs	Immobilized on the surface	EPC capture	[205]
	RGD	Thiol-ene click reaction	EPC and EC adhesion	[210]
	CAG	Grafting and thiol-ene click reaction	EPC and EC adhesion	[209]
	NO	Catalyzed by copper ions	EPC homing, and EC proliferation and activation	[223]
Antithrombosis	PEG	Covalent grafting	Reducing protein adsorption	[227]
	Zwitterionic polymers	Covalent grafting	Resistance to protein adsorption, and preventing platelet adhesion	[226]
	Heparin	Co-axial electrospinning	Preventing platelet adhesion	[236]
	Clopidogrel	3D printing	Preventing platelet deposition	[232]
	Gastrodin	Co-hybrid casting	Inhibiting blood clot formation, and anti-inflammatory	[231]
	pHEMA	Photo-polymerization	Inhibiting plasma protein adhesion, and preventing platelet adhesion	[153]

SDF-1α: stromal cell-derived factor-1α; Dkk3: dickkopf-3; VEGF: vascular endothelial growth factor; CD34: cluster of differentiation 34; anti-CD34 Abs: anti-CD34 antibodies; RGD: Arg-Gly-Asp; CAG: Cys-Ala-Gly; NO: nitric oxide; PEG: polyethylene glycol; pHEMA: poly(2-hydroxyethyl methacrylate); EPC: endothelial progenitor cell; EC: endothelial cell

effectively minimizing platelet attachment [211]. Furthermore, aptamers are short oligonucleotide sequences that are highly effective for EPC capture; however, they can potentially induce inflammatory responses [212, 213].

To enhance the proliferation and activation of ECs and EPCs following adhesion, the incorporation of bioactive molecules may be a promising strategy. VEGF is crucial to regulating EC behavior, which is in turn essential for vascularization. Sustained VEGF release from vascular grafts facilitates endothelialization via multiple mechanisms, such as promoting EPC homing and differentiation, while simultaneously stimulating EC proliferation and activation [214]. VEGF loading onto vascular grafts can be employed through various advanced techniques, such as nanoparticle delivery, coaxial electrospinning, and direct blending electrospinning [215–217]. Furthermore, NO can significantly enhance EPC homing and stimulate EC proliferation and activation. These effects make NO donors and catalysts highly attractive for vascular tissue engineering applications [218]. Promising NO donors that can be applied in biomaterials include N-diazeniumdiolates and S-nitrosothiols [219]. NO generation can be improved using typical catalysts, such as selenocystamine, metal-phenolic surface, and copper ions [220–223].

3.4.2 Antithrombosis strategies

At the initial stage of transplantation, the EC-deficient surface of vascular grafts directly interacts with circulating blood components as a foreign material, which triggers plasma protein adsorption and cellular adhesion, subsequently initiating the coagulation cascade [224]. The resulting thrombus reduces the lumen diameter and eventually blocks the blood vessel. Effective surface modification strategies are needed to inhibit thrombogenesis and promote patency during the initial post-implantation phase. Hydrophilic surface modifications have been significantly effective in inhibiting protein adsorption and platelet adhesion [225]. Various biocompatible hydrophilic biomaterials have been employed for vascular graft surface functionalization, such as polyethylene glycol and zwitterionic polymers [226, 227]. These hydrophilic moieties can be incorporated through direct coating, blending, or covalent grafting onto the graft surface [228, 229]. Surface modification of vascular grafts with anticoagulant agents through coating or immobilization techniques is also highly effective. Commonly employed anticoagulants include heparin, clopidogrel, warfarin, poly(2-hydroxyethyl methacrylate), tissue plasminogen activator, gastrodin, and argatroban [74, 153, 230–232]. Of these, heparin remains the most widely utilized [233–236]. Its mechanism of action involves binding to antithrombin III to potentiate the inhibition of thrombin and coagulation factor Xa. This dual inhibition collectively enhances its antithrombotic effects.

4 Conclusions and further perspectives

The development of SSDVGs that promote rapid endothelialization, anti-thrombogenesis, IH prevention, and long-term patency remains a major challenge in vascular tissue engineering. Compared with large-diameter prostheses, which benefit from higher flow and lower resistance, SSDVGs carry increased risks of compliance mismatch, delayed endothelialization, and thrombosis under low-shear conditions, thereby necessitating stringent design requirements. Recent efforts to address such challenges integrate innovative biomimetic designs and advanced fabrication techniques that accurately replicate the biomechanical and biological properties of native vessels. This review evaluated the current landscape of SSDVG development by focusing on four essential design strategies: material selection, structural configuration, surface topography, and bioactive surface functionalization. Each strategy is vital for enhancing mechanical performance, hemocompatibility, and regenerative capacity. Our work comprehensively examined different synthetic materials appropriate for SSDVG fabrication and categorized them according to their in vivo degradation characteristics. We classified graft structures as fabric-based, segmented, embedded, or layered, highlighting their respective advantages in optimizing compliance and stress distribution to better match native vascular mechanics. We found that surface topographies can be engineered to guide EC migration and proliferation and promote efficient in situ endothelialization. Finally, bioactive surface modification enhances EC recruitment and function through biomolecule immobilization while reducing thrombogenicity by integrating hydrophilic coatings and anticoagulant agents that limit protein adsorption and platelet adhesion. By improving vascular graft integration and function, these strategies thoroughly address the small-diameter core barriers to clinical translation.

Based on the comprehensive analysis presented in this review, significant advancements are needed for SSDVGs to achieve clinical viability and meet patient-specific requirements. To reflect the stringent requirements of small-diameter conduits, future studies should prioritize investigations in the following directions:

(1) Developing precise and controllable fabrication methods at the sub-6-mm scale to regulate graft diameter and wall thickness, anisotropic architecture, and porosity via advanced techniques, such as computer-aided design systems, precision extrusion, and microfluidic platforms. Furthermore, standardized and automated production workflows must be established to ensure batch-to-batch consistency, high quality, and low error rates. These safeguards enhance the reliability and reproducibility of graft manufacturing and facilitate the streamlined transition from research and development to large-scale clinical application.

(2) Applying biomimetic design strategies specific to small-diameter hemodynamics to enhance structural organization, porosity, and tissue integration. Compliance matching must be ensured at the anastomosis site to minimize wall shear stress gradients and oscillatory shear under low-flow conditions. Surface modification strategies must be developed for the efficient immobilization of bioactive molecules, such as heparin and growth factors. Furthermore, antithrombotic function must be balanced with timely endothelial coverage to suppress IH in small lumens.

(3) Developing and optimizing biomaterials with optimal biocompatibility, mechanical properties, and controlled degradation profiles tailored for thin vascular walls and matched to tissue regeneration rates. These reinforce hoop strength and fatigue resistance during graft remodeling due to pulsatile loading at small calibers. The use of composite materials would maximize the synergistic advantages of multiple material components, further enhancing the functional performance and adaptability of grafts across coronary and distal applications.

(4) Establishing standardized and comprehensive evaluation systems specific to small-diameter conditions, including standardized in vitro platforms and long-term testing under low shear, physiological pulse pressure, and end-to-side anastomotic geometries. Parallel in vivo studies should assess graft performance through key indicators, such as lumen patency, inflammation response, thrombosis formation, endothelialization, neovascularization, and tissue remodeling in coronary or below-knee flow models. The integration of standardized in vitro and in vivo evaluation systems would accelerate the development of high-performing SSDVGs, ultimately improving patient outcomes.

(5) Integrating artificial intelligence (AI) technologies in designing and optimizing biomimetic SSDVGs for sub-6-mm targets. AI analysis of extensive datasets on material properties, biological responses, and performance metrics can accelerate the identification of optimal biomaterials with appropriate mechanical properties, biocompatibility, and degradation rates. AI-driven computational models combine fluid dynamics and structural mechanics to simulate hemodynamic behaviors under physiological conditions, predict SSDVG performance, and facilitate the development of designs that closely mimic natural blood vessels. In manufacturing, AI helps ensure consistent quality and reproducibility through real-time monitoring and control of parameters, such as inner diameter, fiber alignment, porosity, and luminal topography. Personalized customization can also be achieved by integrating patient-specific imaging and genetic data to customize grafts to individual anatomical and physiological needs for improved suturability and long-term functionality. Furthermore, AI may be used to monitor clinical outcomes by analyzing in vivo graft performance and predicting long-term effects or complications, thereby enhancing decision-making. As AI technology progresses, its integration into SSDVG design would streamline research, reduce costs, and accelerate the development of more effective, durable, and patient-specific vascular grafts, ultimately enhancing outcomes for patients requiring vascular reconstruction.

By integrating the coordinated advancement of these domains, biomimetic small-diameter grafts would more accurately replicate the intricate structural and functional properties of native blood vessels, including mechanical compliance, biochemical signaling, and dynamic responsiveness to physiological conditions. Such improvements would accelerate the clinical translation of SSDVGs and ensure sustained long-term patency. Future advances in SSDVG design will rely on biomimetic design to fully integrate biomechanics with tissue engineering. Such developments would help overcome the dual challenges of material limitations and functional constraints and ultimately facilitate the synergistic optimization of vascular regeneration. The current findings offer a foundational reference for future progress in tissue-engineered vascular substitutes.

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Declarations

Conflict of interest HZZ is a young academic editor of *Bio-Design and Manufacturing* and was not involved in the editorial review or the decision to publish this article. The authors declare that they have no conflict of interest.

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