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Review

Synthetic and Tissue-Engineered Vascular Grafts: Current Status, Emerging Technologies, and Clinical Prospects

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Abstract

Cardiovascular diseases (CVDs) are the leading cause of morbidity and mortality worldwide, creating an urgent demand for small-diameter vascular substitutes with durable long-term patency. Large-caliber synthetic grafts, such as polyethylene terephthalate (PET) and ePTFE, are well established in clinical practice; however, these synthetic grafts fail in small-diameter applications due to thrombosis and intimal hyperplasia. Moreover, autologous grafts are constrained by limited availability and variable quality. Recently, synthetic degradable polymers (e.g., polycaprolactone (PCL), poly(lactic-co-glycolic acid) (PLGA)), and extracellular matrix-derived natural materials (collagen, gelatin, silk fibroin, bacterial cellulose) have drawn increasing attention, as each offers distinct advantages and limitations in terms of mechanics, biocompatibility, and degradation behavior. Meanwhile, emerging fabrication technologies, including electrospinning, thermally induced phase separation, microfluidic spinning, and three-dimensional printing, are advancing the structural biomimicry and functional optimization of artificial vascular grafts. Thus, building on these developments, this review further examines the design strategies of tissue-engineered vascular grafts (TEVGs), focusing on cell sourcing, *in vitro* and *in situ* endothelialization, antithrombotic modification, and the prevention of intimal hyperplasia, while also summarizing outcomes from preclinical models and early clinical trials. Despite promising progress, the widespread clinical translation of TEVGs remains limited by prolonged manufacturing cycles, high costs, and insufficient long-term patency. Hence, future efforts toward standardized cell sources, integrated structure, function design, and multicenter clinical validation are critical to the development of next-generation vascular grafts.

Keywords: artificial blood vessels; material selection; fabrication methods; tissue-engineered vascular grafts

1. Introduction

Cardiovascular diseases (CVDs) are one of the most serious global public health challenges and are now the leading cause of death worldwide [1]. According to statistics from the World Health Organization, CVDs are responsible for approximately 17.9 million deaths each year [2]. They are associated with a variety of potential risk factors, including unhealthy lifestyle behaviors such as smoking and physical inactivity, as well as systemic conditions such as hypertension, hypercholesterolemia, hyperlipidemia, and diabetes [3]. In the context of atherosclerotic coronary artery disease, aortic pathologies, and other cardiovascular conditions, the native vasculature may become incapable of ensuring adequate tissue perfusion. Under such circumstances, surgical interventions—including vascular repair, replacement, or bypass grafting—are often required to restore blood flow. Globally, more than one million vascular bypass procedures are performed each year, and in the United States alone, the annual number of coronary artery bypass grafting (CABG) surgeries approaches 600,000, underscoring the substantial demand for vascular substitutes [4]. Synthetic materials are now widely applied in vascular grafting, with large-diameter (>6 mm) prosthetic grafts being used extensively in clinical practice. Such grafts typically achieve 5-year patency rates of 70–90% when implanted in aortic or iliac positions [5]. However, small-diameter prosthetic vascular grafts still face several challenges, such as early graft thrombosis and late-stage neointimal hyperplasia leading to luminal stenosis, with 2-year patency rates often falling below 30% [6]. Autologous vessels, such as the saphenous vein, radial artery and internal mammary artery, are therefore regarded as the first-choice of graft material for small-diameter vascular reconstruction due to their superior long-term patency and minimal risk of immunogenic rejection [7]. However, autologous vascular grafting also presents several limitations, including the restricted availability of donor vessels, suboptimal quality or pathology of the native vessels, and subpar long-term graft patency following transplantation [8,9]. Although arterial bypass grafts demonstrate superior long-term patency and clinical outcomes, their use is limited by restricted anatomical length and technical difficulty in procurement [10,11]. In contrast, venous bypass grafts, such as those using the great saphenous vein, often exhibit biomechanical incompatibility with the arterial circulation, leading to accelerated graft atherosclerosis. Clinical data indicate that saphenous vein grafts exhibit failure rates of 8–25% within the first postoperative year, and approximately 50% occlude or lose function within 10 years [12–14]. Therefore, continued research into the fabrica-

tion technologies and broad clinical applications of artificial blood vessels (ABVs), and in particular small-diameter grafts, is of great significance for advancing the field of cardiovascular surgery. While numerous studies have reported the outstanding properties of these technologies, there is a lack of comprehensive reviews that systematically summarize the developmental directions and clinical prospects in the field. This review will discuss material selection, fabrication strategies, and clinical limitations of polymer-based ABVs and tissue-engineered vascular grafts (TEVGs), with a particular emphasis on the precise development of small-diameter vascular grafts. Furthermore, it also discusses recent progress towards addressing these challenges. By directly dealing with the key issues and integrating recent advances, this review provides a deeper understanding of the developmental trajectory of the field.

2. Material Selection for Artificial Vascular Grafts

The circulatory system consists of a complex network of vessels of varying types and diameters, including the aorta and vena cava (25–30 mm), arteries and veins (0.6–16 mm), arterioles and venules (20–25 µm), and capillaries (approximately 9 µm) [15]. Anatomically, blood vessels are composed of three distinct layers: the intima formed by endothelial cells (ECs), the media composed of smooth muscle cells (SMCs), and the adventitia containing fibroblasts (Fig. 1) [16,17]. The modern use of artificial vascular grafts is widely thought to have originated in 1952, when Arthur Voorhees first employed Dacron to replace the aorta in a canine model [18]. This was followed by the first successful human implantation in 1954 [18,19]. To this day, polyester-based materials such as Dacron remain key components in the fabrication of synthetic blood vessels [20]. However, their inherent lack of biointegration, compliance, and regenerative capacity restricts their clinical application primarily to large-diameter vessels. These materials are still unable to fulfill the requirements for small-diameter grafts, particularly in terms of long-term functionality and patency [21,22]. This section provides a comprehensive overview of the advantages and disadvantages of commonly used vascular graft materials, alongside recent advancements.

2.1 Materials for Synthetic Artificial Blood Vessels

To overcome limitations of autologous vascular grafts, increasing attention is being paid to the development of synthetic polymer materials. Polymeric materials offer excellent tunability and outstanding mechanical properties, providing sufficient strength and rigidity in vascular engineering to withstand physiological blood pressure and shear stress. Among the materials in clinical use, polyethylene terephthalate (PET) and polytetrafluoroethylene (PTFE) have achieved satisfactory outcomes in large-diameter (>6 mm) vascular reconstruction [23].

PET and PTFE possess strong mechanical strength, excellent durability, tunable chemical structures, and superior processability, making them among the preferred materials for constructing ABVs [24,25]. However, their hydrophobic surface limits the ability to interact with cells, leading to insufficient EC coverage. This increases the risk of thrombosis and reduces biocompatibility, thereby restricting their application in vascular grafts [16]. Current strategies to address the hydrophobic surface include modification of the surface and blending with other materials [26,27]. Some surface modification techniques are widely used to endow ABVs with antithrombotic properties. Strategies such as grafting bioactive short peptide segments [28], nitric oxide (NO) donors [29,30], and various drugs [31] can effectively exert anticoagulant effects and inhibit platelet adhesion. Multiple Antigen Peptide–Arginine-Glycine-Aspartic acid (MAP-RGD) modification achieved approximately 67% patency at 4 weeks in a rat model, showing a significant advantage over unmodified polycaprolactone (PCL)/collagen grafts (0%), with partial but incomplete endothelial regeneration observed in the lumen. Heparin-modified grafts demonstrated a patency of 64% at 1 month, but the endothelial coverage at 2 weeks was only 40%, comparable to that of untreated controls. In contrast, vascular endothelial growth factor (VEGF)-modified grafts exhibited 88% patency at 1 month and 82% endothelial coverage at 2 weeks, markedly outperforming the other groups. Overall, VEGF modification demonstrated more sustained patency and superior enhancement of endothelialization, highlighting its potential as a more promising surface modification strategy. Another approach to surface modification is to introduce hydrophilic functional groups such as –OH, –COOH, and –NH_2 through plasma treatment or surface functionalization, thereby enhancing cell adhesion and promoting spontaneous EC coverage of vascular grafts [32]. Blending of PET and PTFE with other materials is a more commonly adopted strategy by researchers. Some bioactive molecules with antithrombotic effects can also be loaded onto ABVs to significantly enhance their performance. Bivalirudin (BVLD) can directly block the active site of thrombin, thereby inhibiting downstream coagulation reactions and suppressing platelet adhesion and activation [33]. Xing *et al.* [34] improved the hydrophilicity of the material surface through the introduction of a polydopamine coating and used a peptide derived from the extracellular matrix (ECM), REDV (Arg-Glu-Asp-Val), in combination with BVLD to modify ePTFE vascular grafts. In a porcine model, the modified grafts were able to maintain patency and achieve endothelialization at 12 weeks post-implantation [34]. Traditional oil-based lubricants such as naphtha and isopar are commonly used during the fabrication of ABVs. However, these cannot dissolve water-soluble biomolecules like arginyl-glycyl-aspartic acid (RGD), heparin, and selenocystamine (SeCA). This limitation hinders their deep and

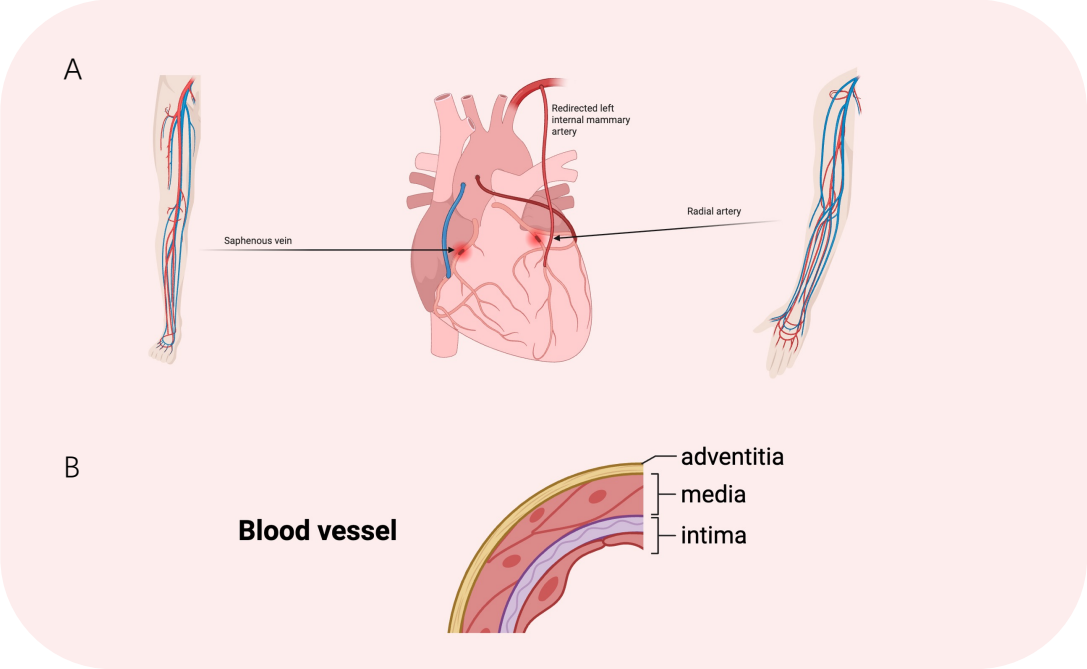

Fig. 1. Schematic illustration of CABG and structural composition of a blood vessel. (A) Main options for autologous vascular substitutes. (B) Three-layer structure of blood vessels.

uniform incorporation into the material and limits their ability to become biofunctional. To address this, researchers have recently explored the use of alcohol–water mixtures as alternative lubricants, resulting in significantly improved biological performance and safety of the vascular grafts [35].

Despite the widespread use of synthetic materials in fabricating vascular grafts, their limited biodegradability within the body often results in extended persistence that can subsequently lead to intimal hyperplasia, immune rejection, and infection. PCL and poly(lactic-co-glycolic acid) (PLGA) are two biodegradable materials that are widely used in scaffold systems [36–38], absorbable sutures [39], and drug delivery systems [40–43]. PLGA is a copolymer of lactic acid (PLA) and glycolic acid (GA). It is characterized by a faster rate of degradation, which helps to reduce adverse reactions caused by foreign body stimulation [44]. Higher GA content in PLGA (e.g., 50:50) accelerates degradation but lowers local pH and may cause inflammation, whereas higher PLA content (e.g., 75:25, 85:15) slows degradation, prolongs support, and mitigates acid accumulation [45]. However, PCL degrades more slowly, thereby offering prolonged mechanical support and enhanced lumen stability and patency [46]. Nevertheless, these materials still face several challenges in practical applications. For example, the byproducts generated during degradation may be potentially toxic to surrounding tissues. In addition, the degradation rate of biodegradable vascular grafts may not meet the necessary requirements for mechanical support [16,25].

2.2 Natural Materials for Artificial Blood Vessels

Natural materials such as collagen, gelatin, chitosan, silk fibroin, and bacterial cellulose are also widely used in the construction of artificial blood vessels. These natural macromolecules are primarily components of the ECM and are derived from plant, animal, or human tissues. They exhibit excellent biocompatibility and cytocompatibility, effectively promoting cell adhesion and proliferation, thereby accelerating tissue repair and regeneration [47,48]. As mentioned above, blood vessels are composed of three distinct layers, with the ECM playing a critical role in maintaining normal vascular function.

Collagen and elastin are major components of the ECM and provide structural strength and stiffness to native vessels. They are also amongst the most commonly used natural materials for fabricating ABVs [49]. Collagen exhibits excellent biocompatibility and is commonly used to construct vascular scaffolds, or to serve as the outer layer of ABVs [50]. It not only provides essential structural support, but also promotes cell adhesion and proliferation [51]. The inherent biodegradability of collagen allows it to be gradually absorbed and metabolized in the body, thereby reducing adverse reactions associated with long-term implantation. Collagen scaffolds can form hierarchical nanostructures and microarchitectures similar to natural ECM, thereby serving as temporary ECM to guide tissue regeneration [52,53].

Gelatin (Gel) is a partially hydrolyzed derivative of collagen that retains many bioactive sequences, such as RGD, which enhance cell adhesion and proliferation. It

exhibits good biocompatibility and is low-cost and easy to process, making it widely used in artificial vascular grafts [54]. However, its poor thermal stability and rapid degradability necessitate crosslinking or composite strategies to improve its mechanical strength and stability. For example, PET can form a stable bond with gelatin through an intermediate polydopamine coating, which remains stable under physiological conditions for up to 24 days and promotes the adhesion and spreading of ECs and SMCs [24].

Chitosan (CS) is a naturally occurring cationic polysaccharide enriched with amino and hydroxyl groups. Its outstanding biocompatibility, degradability, and antimicrobial activity have led to its extensive use in biomedical applications such as tissue repair and drug delivery [55]. Due to its cationic nature, CS can interact effectively with cells to enhance cell adhesion and promote the regeneration process. In addition, CS can form electrostatic complexes with anionic polysaccharides, synergistically improving the mechanical properties and biocompatibility of the material [56]. Based on these characteristics, Rodrigues *et al*. [57] constructed a stable, 3D scaffold microenvironment using CS that formed a physical hydrogel network through electrostatic interactions with alginate (ALG). This provided an ideal platform for the loading and release of functional proteins such as elastin-like recombinamers (ELRs), while the cationic surface of CS also promoted attachment of ECs [57].

Silk fibroin (SF) is a natural protein derived from silkworm cocoons [58]. In addition to good biocompatibility and biodegradability, SF microspheres are also capable of controlled drug release [59,60]. Bacterial nanocellulose (BNC) is a cellulose-based biomaterial synthesized by bacteria and characterized by high crystallinity and low solubility. Compared to easily degradable biomaterials, BNC can provide prolonged structural support *in vivo*, thereby preventing vascular collapse caused by rapid degradation [61]. Bao *et al*. [58] embedded heparin-loaded SF nanoparticles onto the surface of BNC vascular grafts. This composite material exhibited superior anticoagulant properties and demonstrated enhanced endothelialization and anti-hyperplasia characteristics in subcutaneous implantation experiments in animals [58].

Although strategies involving natural materials in tissue engineering have continued to evolve, the development of biomimetic vascular grafts that simultaneously exhibit high strength, high elasticity, and excellent antithrombotic properties remains a significant challenge [62,63]. Despite their favorable biocompatibility and bioactivity, natural materials often possess low structural density and lack hierarchical organization, resulting in insufficient mechanical properties to withstand the complex shear forces present in the *in vivo* hemodynamic environment [64]. Therefore, future research should investigate more advanced fabrication techniques to enhance the architectural hierarchy of engineered blood vessels and to improve their functional performance and long-term stability in clinical applications.

Overall, synthetic materials such as PET and PTFE possess excellent mechanical strength and durability, but their hydrophobic and bioinert surfaces result in insufficient endothelialization, requiring surface functionalization to reduce the risk of thrombosis. Biodegradable polymers such as PCL and PLGA provide tunable degradation properties and better compliance, with PCL offering prolonged support due to its slow degradation, while PLGA degrades more rapidly to facilitate tissue remodeling, though its acidic by-products may induce inflammation. In contrast, natural materials such as collagen and gelatin contain RGD motifs that strongly promote cell adhesion and proliferation, but their rapid degradation and poor mechanical stability restrict their use to luminal coatings or composite layers rather than load-bearing scaffolds. Chitosan, owing to its cationic nature, enhances cell adhesion and exhibits antibacterial properties, but also requires crosslinking or blending with other materials to improve strength. Silk fibroin demonstrates good cytocompatibility and moderate mechanical performance and can be used for controlled drug release, while bacterial nanocellulose provides excellent structural stability but lacks intrinsic bioactivity, thus requiring functionalization to improve hemocompatibility. In the future, material selection for small-diameter vascular grafts will need to rely on composite designs that balance mechanical stability with biological activity. Table 1 summarizes the quantitative mechanical data of natural–synthetic composite scaffolds and native human vessels, highlighting the differences in tensile strength and Young's modulus between these materials.

Table 1. Quantitative mechanical data of natural-synthetic composite scaffolds versus native human vessels.

Materials	Tensile strength (MPa)	Young's modulus (MPa)
PET	36	-
PTFE	2.91	5.75
PCL	1.49	13.69
Collagen	-	3.7–11.5
PCL/Gelatin	3.91	8.9
HA/Gelatin	0.97	0.56
PCL/SF	2.1	23.28
BNC	1.06	3.25
Coronary artery	1.5	-

PET, polyethylene terephthalate; PTFE, polytetrafluoroethylene; PCL, polycaprolactone; HA, hyaluronic acid; SF, silk fibroin; BNC, bacterial nanocellulose.

3. Fabrication Techniques for Artificial Blood Vessels

In recent years, an increasing number of advanced technologies have been applied to the construction of ABVs. In addition to traditional casting and spinning meth-

ods, emerging techniques such as electrospinning, 3D printing, and thermally induced phase separation (TIPS), as well as their combinations, have opened up new possibilities and research directions for the design and performance optimization of vascular grafts. This section summarizes the advantages and limitations of such technologies, and presents recent advances in their application to ABV research.

3.1 3D Printing

3D printing is an emerging technology capable of fabricating complex structures [65]. It allows the personalized construction of ABVs prior to surgery based on patient-specific imaging data [66,67]. The primary materials used are bioinks composed of biocompatible polymers. These must meet rigorous criteria, including excellent biocompatibility, faithful replication of the native vascular ECM, and the ability to support cell adhesion, proliferation, and tissue regeneration [16,68]. Biodegradable polymeric materials, including PLA, PLGA, and PCL, were a preferred choice for bioink formulation in previous studies due to their low cost and good biocompatibility [69]. However, as discussed in Section 2 of this paper, limitations such as insufficient mechanical strength, uncontrolled degradation rates, local effects of the degradation byproducts, and inherent hydrophobicity have restricted their application in ABVs.

ECM bioinks are a widely studied and innovative 3D printing strategy that aims to replicate the natural ECM by incorporating proteins, polysaccharides, and other biomolecules to support cell adhesion, growth, and tissue formation [70]. However, due to the inherent complexity and variability of ECM compositions from different tissue sources, the structural stability and longevity of ECM-based printed tissues require further evaluation through *in vivo* studies [71]. With the advance of bioprinting technology and the expansion of printable materials, researchers have explored the use of decellularized ECM (DECM) and cells in addition to polymers as possible bioinks [72]. DECM is derived from natural biological materials through physical or enzymatic decellularization processes, thereby preserving the native structure and function of the ECM [73,74]. DECM effectively mimics the mechanical properties of native tissues, offering robust structural support and tensile strength that regulate cell behavior and promote functional tissue formation [75]. ABVs constructed using DECM can be customized for individual-specific applications, enabling more precise and targeted tissue replacement [76]. Jang *et al*. [77] successfully implemented DECM-based 3D bioprinting in 2017 by introducing mesenchymal stem cells (MSCs) and ECs as seed cells. This also provided significant support for the development of TEVGs. Cells used in 3D bioprinting are derived from diverse sources and can be applied either individually or in combination to better replicate the complexity of native tissue structures [78]. For cardiovascular tissue engineering, the cells must exhibit several essential characteristics, including high proliferative capacity, rapid maturation, strong differentiation potential, ease of acquisition, and low immunogenicity to the host [78,79]. Stem cell engineering has shown great promise in the treatment of CVDs [80]. Human embryonic stem cells (hESCs) and human induced pluripotent stem cells (hiPSCs) can be induced to differentiate into various functional cell types, such as vascular ECs and SMCs [81,82]. Notably, hiPSCs possess the capacity to generate the three-layered structure of blood vessels—including ECs, SMCs, and fibroblasts—making them particularly suitable for vascular tissue construction [78].

A variety of advanced 3D printing technologies have been widely adopted in the biomedical field, including inkjet-based bioprinting, laser-assisted bioprinting (LAB), extrusion-based bioprinting, acoustic bioprinting, coaxial bioprinting, and stereolithography (SLA)-based bioprinting [83]. Coaxial bioprinting utilizes a concentric dual-nozzle system to simultaneously extrude two different bioink formulations in a core–shell configuration, resulting in tubular structures with circumferentially layered architecture [84]. The outer shell serves to protect the inner core, while the layered extrusion approach allows the spatial separation of bioinks containing different cell types, facilitating generation of the three-layered structure of blood vessels [85–87]. Bosch-Rué *et al*. [87] developed bilayered hollow fibers by co-extruding two cell-laden hydrogels and a sacrificial polymer through a triple coaxial nozzle. Human umbilical vein ECs (HUVECs) were encapsulated in the inner layer, and human aortic SMCs (HASMCs) in the outer layer. Both cell types showed over 90% viability after extrusion and 20 days of culture, with alignment patterns mimicking native vessel structure, i.e., HUVECs parallel and HASMCs perpendicular to the vessel axis [87]. Qu *et al*. [88] reported a Filament Diameter-Adjustable 3D Printing (FDA-3DP) strategy. Compared to traditional 3D printing with direct ink writing (DIW), the FDA-3DP method enables dynamic adjustment of printing speed and nozzle height, allowing the fabrication of structures with controllable gradient porosity and without the need for equipment replacement [88].

Artificial intelligence (AI) has recently attracted significant attention in the biomedical field [89,90]. For instance, the integration of AI can enhance the accuracy of tissue construction during bioprinting and assist in building complex *in vitro* models, as well as monitoring and analyzing cell growth [91]. However, the application of AI in tissue engineering is still in its early stages. The development of robust AI models is needed to effectively address the current limitations of 3D printing technologies, such as operational complexity and high costs [16,92,93].

3.2 Decellularization

Although DECM was introduced in Section 3.1 as a bioink for 3D printing, decellularization itself also represents an independent fabrication strategy for vascular grafts. Unlike its role as a material source, this approach directly employs whole native vessels as scaffolds by removing cellular components while preserving the natural ECM composition, three-layered structure, and vascular microarchitecture. The resulting decellularized scaffolds retain the mechanical properties and biochemical cues of native vessels, thereby providing an ideal platform for host cell repopulation and vascular remodeling [94]. However, the decellularization process may compromise biomechanical integrity and accelerate elastin deformation and degradation [95]. To address these limitations, decellularized scaffolds are often combined with other materials to restore mechanical strength. Gong *et al.* [96] reinforced decellularized aortic grafts by electrospinning PCL onto their outer surfaces. Scanning electron microscopy revealed severe damage to the medial layer of the decellularized vessel, while mechanical testing demonstrated that electrospun polycaprolactone (ES-PCL) significantly enhanced biomechanical performance. Moreover, vascular ultrasound and micro-CT angiography confirmed that the implanted grafts maintained satisfactory patency for up to six weeks in a rat model [96].

3.3 Casting and Spinning

Casting and spinning are among the earliest and most widely used techniques for fabricating ABVs. However, these traditional methods struggle to precisely control pore size and distribution [16]. Consequently, many researchers have focused on trying to improve these conventional processes. Electrospinning is a specialized spinning technique that uses an electric field and a collector electrode to eject a polymer solution from a tiny nozzle, forming a fibrous network with high porosity that resembles the ECM of human tissues, thereby promoting cell adhesion and proliferation [25,97,98]. Bioactive substances and drugs can be incorporated into ABVs via electrospinning to achieve improved biocompatibility [99], including gelatin [100], rapamycin [101], heparin [102] and VEGF [103]. Electrospinning is often combined with other techniques to achieve enhanced performance. Kuang *et al.* [104] combined electrospinning and freeze-drying to construct a poly(L-lactide-co-ε-caprolactone) (PLCL)-based vascular scaffold with sustained heparin release, which enhanced endothelial adhesion and inhibited SMC proliferation. In addition, improvements in electrospinning processing techniques can enable the fabrication of blood vessels with complex geometries to meet various challenging transplantation needs [105]. Moreover, vascular grafts with intricate structures can also provide anti-torsion properties and mimic the mechanical characteristics of native vessels. Native blood vessels possess unique mechanical properties due to the wavy arrangement of elastin and collagen fibers within their walls [106]. Yan *et al.* [107] fabricated a bilayer small-diameter vascular graft composed of an inner layer of eggshell membrane and an outer layer of thermoplastic polyurethane (TPU) using electrospinning with a wavy cross-sectional rotating collector. This distinctive wavy structure resulted in a nonlinear stress–strain response and demonstrated excellent graft repeatability under cyclic loading [107]. During the electrospinning process, organic solvents such as dichloromethane, tetrahydrofuran, and N,N-dimethylformamide are commonly used to facilitate material dissolution and fiber formation [108]. However, residual amounts of these solvents may remain during fiber fabrication due to incomplete evaporation, raising potential toxicity concerns when electrospinning is used to produce ABVs. Current research efforts to address this issue mainly focus on developing solvent-free or low-toxicity alternatives, such as melt electrospinning and aqueous electrospinning, and improving the processing parameters to enhance the efficiency of solvent evaporation [108–110]. Compared with solvent-based electrospinning, which typically produces fibers in the nano to submicron range (approximately 100–1000 nm), solvent-free electrospinning (melt/MEW) generally yields fibers in the micron scale (1–20+ μm). However, these fibers exhibit higher crystallinity and lower porosity, thereby enabling slower, more sustained drug release without an obvious burst effect. In addition, the absence of residual solvents makes them more suitable for long-term implantation applications. Additionally, techniques like freeze-drying and vacuum drying are employed to further reduce residual solvents. Nevertheless, more comprehensive toxicological and animal studies are needed to evaluate the safety and clinical applicability of electrospun ABVs [108].

Microfluidic spinning is also an increasingly popular spinning technique [111]. By precisely manipulating small volumes of fluid within microscale channels, this technique enables controlled fluid processing in minimal volumes and the reproduction of complex biological structures. It therefore has great potential in tissue engineering and organoid cultivation [112,113]. Based on these features, Jia *et al.* [114] developed a microfluidic spinning approach using a coaxial glass capillary system. By adjusting the flow rate and composition of fluids in the microchannel, these authors successfully fabricated helical microfibers. The unique spiral structure induces swirling blood flow, which increases shear stress and effectively inhibits thrombosis formation. Microfluidic spinning technology enables researchers to modify vascular structures with greater precision, beyond simple straight or curved forms. This facilitates the creation of more controllable architectures that can be tailored to suit different types of blood vessels.

3.4 Thermally-Induced Phase Separation

The technique of TIPS induces phase separation between the solvent and polymer during cooling of a polymer solution, resulting in the formation of a porous structure. This method relies on temperature variation to promote polymer chain aggregation while expelling the solvent, thereby forming a 3D porous network. When combined with techniques such as electrospinning and braiding, TIPS can optimize both mechanical properties and biological functionality [115]. Ma *et al*. [116] reported a small-diameter vascular graft with a biomimetic three-layered structure in which a loose and porous PEFUU scaffold was constructed using TIPS. This porous architecture facilitated the formation of neovascular networks that exhibited superior mechanical performance compared to the control groups [116].

Overall, 3D printing technology can be tailored to fabricate complex vascular structures according to patient-specific needs, but its printing precision and the mechanical strength of bioinks still require improvement. Electrospinning enables the preparation of highly biomimetic fibrous networks that provide an ideal environment for cell adhesion; however, their small pore size hinders deep cellular infiltration, and the potential risk of residual toxic organic solvents remains a concern. Traditional casting and spinning methods are cost-effective and well established, but they lack precise control over pore distribution and structural complexity. Microfluidic spinning can generate specialized fibers that effectively prevent thrombosis, yet its mechanical performance and scalability remain limited. TIPS can rapidly produce porous scaffolds that facilitate tissue ingrowth, but its ability to finely control structural details is constrained. At present, the closest alternatives to native blood vessels are decellularized scaffolds. They preserve the natural three-layered structure and bioactivity, offering favorable compliance and biological guidance. Nevertheless, the decellularization process often compromises mechanical properties and leads to elastin degradation, while clinical applications continue to face challenges such as insufficient long-term patency and potential immune rejection.

4. Tissue-Engineered Vascular Grafts

TEVGs have attracted significant attention as an alternative for vascular transplantation. They are constructed using biodegradable polymers to form tubular scaffolds, which are then seeded with autologous cells and matured in a dynamically simulated physiological environment before being implanted into the body. Over time, the biodegradable components are gradually replaced by newly formed ECM, thus closely mimicking the properties of native blood vessels [117].

Weinberg and Bell [118] first proposed the concept of TEVGs in 1986 and successfully developed an early prototype. They constructed a tubular scaffold composed of bovine aortic ECs, SMCs, collagen, and a thin polyester mesh. Different types of cells were spatially organized within distinct layers of the scaffold in this model: ECs on the luminal surface, SMCs in the middle layer, and bovine adventitial fibroblasts in the outermost layer. Although this study laid a critical foundation for the advancement of vascular tissue engineering, the use of synthetic materials lacking bioactivity, such as polyester, limited the graft's capacity for further growth and tissue remodeling [118]. In 2001, Shin'oka *et al*. [119] carried out the first clinical trial of a cell-seeded TEVG. They implanted a biodegradable scaffold seeded with autologous vascular cells into pediatric patients with congenital heart disease, marking the first clinical translation of TEVGs [119]. However, the wider clinical application of TEVGs remains limited by factors such as long manufacturing cycles, high costs, thrombosis, and immunogenicity [120,121]. Current research efforts to address these challenges mainly focus on improving the cell sources, as well as functional modifications [122,123].

4.1 Cell Selection for TEVGs

Human blood vessels consist of three layers. The intima is mainly composed of ECs and prevents thrombosis, the media contains SMCs and provides elasticity and contractility, and the adventitia contains fibroblasts and serves to anchor the vessel. During TEVG fabrication, the cell source is therefore a key factor influencing functional performance [124].

4.1.1 Endothelial Cells

ECs are essential components of TEVGs and exhibit strong antithrombotic properties in native vessels [125, 126]. During the fabrication of TEVGs, ECs are typically seeded onto the surface of the scaffold prior to implantation in a process known as *in vitro* endothelialization [20]. Moreover, a comparative study demonstrated that EC-seeded TEVGs contribute not only to the formation of a mature endothelial layer, but also promote development of the smooth muscle layer [127].

However, the sourcing of autologous ECs is challenging due to patient-specific limitations and difficulties in cell isolation [128,129]. To address this, researchers have explored the use of HUVECs as an alternative [130]. Umbilical cord tissue provides an abundant supply of immature, highly proliferative cells that can form complex vascular networks within the host. Nevertheless, challenges in purifying and stabilizing HUVECs have limited their widespread application in vascular grafting. In addition to HUVECs, researchers are also investigating the use of less differentiated stem cells, such as induced pluripotent stem cells (iPSCs) or endothelial progenitor cells (EPCs), which can be induced to differentiate into ECs *in vitro* and subsequently used for TEVG endothelialization [125,131,132].

In addition to *in vitro* endothelialization, the inner surface of the vascular graft can also be modified to capture

host cells and promote *in situ* endothelialization [2]. By modifying material surfaces with capture molecules that mimic natural homing factors, circulating EPCs can be effectively recruited [133]. Various ligands have been applied to material surfaces to allow them to directly capture EPCs from the patient's bloodstream, including monoclonal antibodies [134], functional peptides [135,136], and certain bioactive factors [137].

4.1.2 Smooth Muscle Cells

The tunica media of blood vessels is primarily composed of SMCs and ECM, forming the main structural component of most vessels and playing a key role in regulating vascular contraction to control blood flow [138,139]. The incorporation of SMCs into TEVGs is a key factor in ensuring their successful application. Current strategies include seeding SMCs onto surface-modified scaffolds, and introducing stem cells followed by their differentiation into SMCs [140–143]. Ardila *et al*. [144] developed an electrospun scaffold loaded with transforming growth factor β2 (TGFβ2), which enabled the sustained release of low concentrations of TGFβ2 and promoted the proliferation and migration of SMCs seeded onto the scaffold. In addition, the function of SMCs is also influenced by mechanical stress induced by blood flow, including cyclic stretch and hydrostatic pressure [145]. Studies have confirmed that the magnitude of cyclic stretch can increase the expression of SMC-specific differentiation markers and enhance the proliferation of SMCs [124,146]. Hydrostatic pressure can also increase the proliferation of SMCs and promote the expression of certain proteins in the ECM [147,148].

4.1.3 Fibroblasts

Fibroblasts are spindle-shaped cells primarily found in connective tissues [124]. They are capable of synthesizing ECM components, particularly collagen and elastin, and serve as the predominant cell type in the tunica adventitia of blood vessels [149,150]. Fibroblasts can differentiate into myofibroblasts in response to environmental stimuli, effectively enhancing the mechanical strength of TEVGs [151]. They can be obtained from the skin and exhibit strong proliferative potential [152]. Torres *et al*. [153] generated ABVs by culturing human fibroblasts to form cell-assembled ECM sheets, which were then rolled and matured. These grafts were used clinically for dialysis and remained functional for up to 20 months [153].

4.1.4 Human Induced Pluripotent Stem Cells

hiPSCs have stem cell functions and are obtained by inducing somatic cells to express stem cell factors [154,155]. They can be guided to differentiate into various cell types, including SMCs [156,157]. Compared to embryonic stem cells, hiPSCs exhibit lower immunogenicity and are more readily accessible [124]. In previous applications of hiPSC-TEVGs, the low degree of SMC differentiation led to insufficient ECM synthesis, as well as reduced mechanical strength and radial dilation after implantation [158–160]. In a study published in 2020, Luo *et al*. [132] reported that a culture medium containing only TGF-β1 (excluding platelet-derived growth factor-BB (PDGF-BB)), combined with mechanical stretching after static culture, effectively improved the survival of hiPSC-derived SMCs. The resulting optimized hiPSC-TEVGs exhibited mechanical strength comparable to that of the saphenous vein [132]. Nevertheless, the hiPSC-TEVGs produced by this method still lack mature elastin fibers, and their mechanical strength has not yet reached the biomechanical level of human arteries. Moreover, the potential risk of tumor formation associated with hiPSCs, safety concerns related to the cell reprogramming process, and high manufacturing costs still limit the clinical application of hiPSCs. Therefore, further research is urgently needed to improve the safety and cost of hiPSCs [125,161,162]. At present, various factor-based regulatory strategies can significantly improve the efficiency of hiPSC differentiation into vascular lineage cells. Dash *et al*. [163] demonstrated that a multi-stage process, in which hiPSCs are first differentiated into MSCs and then directed toward VSMCs, can expand the intermediate cell population and thereby facilitate efficient downstream SMC differentiation. In addition, the use of PDGF-BB alone markedly upregulates the expression of the SMC marker gene calponin, and when PDGF-BB is combined with shear stress, it can further enhance the orientation and functionality of hiPSC-derived VSMCs [160,164].

4.2 Functional Modification of TEVGs

4.2.1 Enhancing Anti-Thrombotic Properties

Thrombosis is a major challenge for small-diameter vascular grafts [165]. The inflammatory response triggered by vascular grafts can lead to platelet aggregation, ultimately resulting in thrombus formation and graft occlusion [166]. Heparin, a potent anticoagulant used to prevent acute thrombosis after vascular implantation, has been widely applied as a coating on the inner layer of TEVGs through various methods [167]. Heparin has also been shown to promote the proliferation of ECs within TEVGs [168], and NO secreted by ECs plays an important role in inhibiting platelet aggregation [169]. The surface density of heparin immobilized on PU–PEG–Hep grafts was reported as 1.21 $\pm$ 0.29 $\mu g/cm^2$, retaining only ~22% of the anticoagulant activity of free heparin, yet still achieving a 71.4% patency rate at 60 days in a rabbit model. Yang *et al*. [170] developed an AuNP–ChOX–Arg cascade system that catalyzed cholesterol into NO, reaching 18.95 $\mu mol \cdot L^{-1}$ within 20 min at a flux of 4.5×10^{-10} $mol \cdot cm^{-2} \cdot min^{-1}$, comparable to endothelial cells. In a hyperlipidemic rat carotid model, it markedly reduced platelet adhesion, an effect reversed by 2-(4-carboxyphenyl)-4,4,5,5-tetramethylimidazoline-1-

oxyl-3-oxide (carboxy-PTIO), and maintained graft patency for 60 days [170].

4.2.2 *In Situ* Endothelialization

Endothelial cells can secrete bioactive substances such as NO and heparin to maintain vascular patency [171]. Section 4.1.1 provided a preliminary introduction to the construction of an endothelial layer on TEVGs. Among the current strategies, *in situ* endothelialization has become a major focus of research as it avoids the need for *ex vivo* isolation and cultivation of ECs [172]. Yan *et al.* [135] used 1,2-dimyristoyl-sn-glycero-3-phosphoethanolamine-N-[poly(ethylene glycol)] (DMPE-PEG) as a lipid-anchoring structure to immobilize an EPC-capturing peptide on the luminal surface of TEVGs, significantly enhancing the adhesion of EPCs under dynamic flow. The DP structure also reduced nonspecific plasma protein adsorption, preventing the masking of EPC-binding sites (Fig. 2A) [135]. Platelet-rich plasma (PRP) is enriched with VEGF, TGF-β1 and PDGF, and effectively recruits EPCs to accelerate endothelialization [173,174]. Li *et al.* [175] developed a PRP-poly(L-lactic acid) (PLLA)/gelatin composite scaffold that achieved an intimal coverage rate of 80.17% after one week in a rabbit common carotid artery transplantation model. Moreover, a 5% PRP-loaded scaffold achieved an intimal coverage of approximately 80% at 1 week and over 90% at 4 weeks, with functional $eNOS^+$ endothelial cell coverage reaching 95%. *In vitro*, 2–5% PRP significantly promoted vascular endothelial cells (VECs) proliferation (EdU^+: ~60% vs. 36%) and migration (32 vs. 10 cells per field), whereas excessive concentrations (10%) suppressed the growth of both VECs and SMCs, showing a dose-dependent effect. PRP-TEVGs were able to continuously release growth factors for over 25 days, with VEGF as the predominant component [175]. Current research primarily aims to enhance endothelialization by loading growth factors such as VEGF and fibroblast growth factor (FGF) [20]. However, these strategies are costly and have poor stability [176]. Some researchers have also explored the regulation of bioactive ion release as an alternative to growth factors [177]. Bioactive glass (BG) is an inorganic silicate material with excellent biocompatibility and bioactivity [178]. Different types of BG can be doped with various ions to exert distinct biological functions [179]. However, certain components commonly found in typical BGs (e.g., Ca, Si, and P) can induce coagulation, thus limiting the application of BGs in vascular grafts [180]. Alasvand *et al.* [181] developed Cu-doped BGs with Ca, P, and Si removed. This resulted in enhanced EC proliferation, migration, and VEGF secretion, while also providing strong antibacterial effects (Fig. 2B).

4.2.3 Prevention of Endothelial Hyperplasia

Following TEVG implantation, SMCs may proliferate abnormally at the anastomosis, leading to intimal injury and vascular stenosis [182,183]. Surface modification of TEVGs with drug-loaded coatings is a common strategy to address this issue [184]. Various agents including NO, small peptides, and traditional Chinese medicine compounds have been widely used to prevent SMC-related endothelial hyperplasia [185,186]. Portulaca flavonoid (PTF) is a drug that can inhibit the PDGF-induced abnormal proliferation of SMCs. Xie *et al.* [187] employed PCL scaffolds loaded with PTF, which effectively suppressed SMC proliferation without cytotoxicity.

4.3 Animal Models and Clinical Translation of TEVGs

Mice and rats are the most commonly used experimental animals in current preclinical studies of TEVGs [188]. However, due to significant differences in physiological mechanisms, immune environments, and hemodynamics compared to humans, the experimental results obtained from these small animal models may still differ from actual clinical outcomes [20]. Large animals such as dogs, pigs, sheep, and baboons are widely used in TEVG research due to their anatomical structures and hemodynamic characteristics being similar to those of humans [189]. Computational fluid dynamics (CFD) studies have revealed significant interspecies differences in hemodynamic parameters. For example, in porcine coronary arteries, wall shear stress (WSS), time-averaged WSS (TAWSS), and relative residence time (RRT) are largely comparable to humans, but oscillatory shear index (OSI) differs markedly. In pulmonary artery models, sheep exhibit TAWSS values very close to humans (median ~1.5 Pa vs. 1.2 Pa; $p = 0.42$), whereas pigs show significantly higher TAWSS (~1.7 Pa; $p < 0.05$) [190]. However, both pigs and sheep demonstrate OSI values that differ significantly from humans. Therefore, specific interspecies differences must still be considered when using large-animal models. What's more, sheep exhibit a stronger tendency toward coagulation [127], while pigs are more difficult to handle and also grow very rapidly, making them less suitable for long-term studies [191]. Non-human primates, such as baboons, closely resemble humans in terms of anatomy and thrombotic behavior [192–194], but their use is limited by the high costs and ethical concerns associated with animal experimentation.

To date, the application of TEVGs in humans remains limited. Shin'oka *et al.* [195] conducted a clinical study in which TEVGs composed of biodegradable scaffolds combined with autologous bone marrow cells were used to repair congenital heart defects in 25 pediatric patients. The median follow-up period was 11 years, during which no graft-related deaths were reported. However, 7 patients developed asymptomatic graft stenosis [195,196]. Bockeria *et al.* [197] directly implanted cell-free biodegradable vascular grafts into five patients. Postoperative follow-up revealed favorable structural and functional outcomes for the grafts, with no graft-related adverse events reported [197]. Gutowski *et al.* [198] evaluated decellularized TEVGs

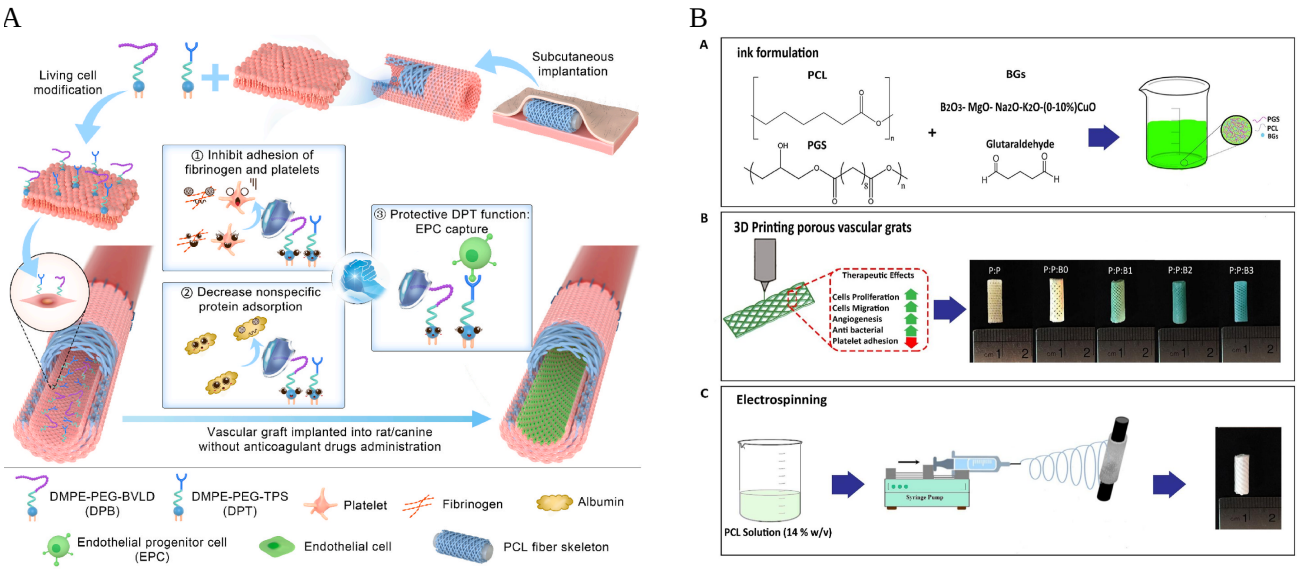

Fig. 2. Schematic representations of dual-modified PB vascular grafts and bilayer 3D-printed vascular scaffolds. (A) Combined modification of the luminal surface of *in vivo* engineered PB grafts with DPB and DPT significantly promoted *in situ* endothelialization without the need for anticoagulant therapy [135]. (B) Schematic illustration of the construction of a bilayer vascular graft. The inner layer consists of a 3D-printed porous structure composed of PGS, PCL, and modified bioactive glass (BG) to accelerate vascular remodeling [181]. EPC, endothelial progenitor cell; PB, poly(butylene)-based; DPB, 2,2′-dithiodipyridine–based biofunctional linker; DPT, dual-peptide treatment; PGS, poly(glycerol sebacate).

seeded with human vascular SMCs for peripheral artery bypass in 20 peripheral artery disease (PAD) patients with SFA occlusion. Over 24 months, 26 graft-related complications occurred in 10 patients, but no amputations, infections, or aneurysmal changes were observed. The primary and secondary patency rates were 58% and 74%, respectively [198].

In recent years, great advances have been made with TEVGs and they have become a key focus of tissue engineering. However, to truly solve the clinical challenges presented by small-diameter grafts—like low long-term patency rates and limited treatment success—better materials and more reliable manufacturing methods must first be developed. Moreover, it is crucial that such grafts be thoroughly tested in large animal models and clinical trials to verify their safety and effectiveness before they can be widely used in patients.

4.4 Challenges and Barriers to the Clinical Translation of TEVGs

Although TEVGs have demonstrated potential in animal experiments and early clinical studies, they still face numerous unresolved challenges. The inability to ensure long-term patency remains the primary limitation hindering their clinical application. Early stenosis typically occurs within a few weeks after implantation, as most biomaterials used in TEVGs possess hydrophobic and negatively charged surfaces that can activate the intrinsic coagulation pathway, leading to acute thrombosis [199–201]. In addition, biofilm formation resulting from bacterial adhesion may also contribute to early stenosis of TEVGs [202]. Late stenosis is mainly caused by incomplete endothelialization and fibrosis with intimal thickening induced by persistent foreign body stimulation from the graft [203].

Insufficient mechanical performance and compliance are critical factors restricting the clinical application of TEVGs. In the human body, blood vessels are constantly subjected to multiple complex physiological forces, including blood flow pressure, pulsatile pressure, and external forces from surrounding tissues [204]. Therefore, artificial blood vessels must possess adequate mechanical strength and compliance to maintain stable elastic expansion and contraction under such conditions [25,205]. However, current TEVGs often exhibit significant compliance mismatch compared with autologous vessels. This mechanical discrepancy at the anastomosis can lead to disturbed blood flow, aggravating platelet aggregation and fibrin thrombus formation [206]. Post *et al.* [207] demonstrated using an *in vitro* model that compliance mismatch not only reduces wall shear stress but also induces intimal thickening, thereby severely compromising long-term patency.

Besides, TEVGs usually require long periods of *in vitro* culture and preparation to ensure their mechanical strength, which also represents a major obstacle to their clinical translation [208]. Although TEVGs have shown promise in both preclinical and early clinical studies, long-term patency and mechanical compliance remain major barriers to clinical translation. The outcomes of completed

Table 2. Completed clinical studies of TEVGs.

	Patients (n)/Age	Indication	Implantation site	Graft type	Diameter	Follow-up	Patency/Interventions	Refs
Bone marrow cell–seeded TEVG	n = 42; 1–24 y	Complex CHD	Fontan conduit	PGA/PLLA PLCL	12–24 mm	Mean 16.3 months (max 31.6 months)	No occlusion	[195]
Bone marrow cell–seeded TEVG	n = 25; 1–24 y	Single-ventricle CHD	Fontan conduit	PLA (n = 12) PGA (n = 13)	12–24 mm	Mean 5.8 years (4.3–7.3)	6/25 stenosis (24%); 4 balloon dilatations, 1 stent; 1 mural thrombus	[196]
UPy-PCL TEVG	n = 5; 4–12 y	Single-ventricle CHD	Fontan conduit	UPy-PCL	18–20 mm	12 months	No stenosis; 2 APC occlusions (non-graft related)	[197]
Human acellular vessel	n = 20; 54–79 y	PAD SFA occlusion (TASC B/C)	Femoral–popliteal/SFA bypass	Decellularized human ECM (types I/III collagen, FN, VN)	6 mm	Mean 20.7 months (up to 24 months)	12-mo: 63% primary, 84% secondary; 24-mo: 58% primary, 74% secondary; 6/20 interventions	[198]

TEVG, tissue-engineered vascular grafts; ECM, extracellular matrix; CHD, congenital heart disease; PGA, poly(glycolic acid); PLLA, poly(L-lactic acid); PLCL, poly(L-lactide-co-ε-caprolactone); FN, fibronectin; VN, vitronectin; APC, anticoagulant protein C.

clinical trials, summarized in Table 2 (Ref. [195–198]), further illustrate these challenges in different patient populations and graft designs.

5. Emerging Technologies

In recent years, various emerging technologies such as engineered cells, artificial intelligence and 4D printing have been applied to the construction of vascular grafts. ECs exhibit remarkable immunological plasticity. In their quiescent state, ECs display low immunogenicity and secrete anti-inflammatory mediators such as NO, which also inhibit platelet aggregation [209]. The maintenance of a stable endothelial phenotype is therefore essential for ensuring the long-term patency and immune tolerance of TEVGs. Park *et al*. [210] reported that physiological shear stress induced hiPSC-ECs into a quiescent, anti-inflammatory phenotype, with increased antithrombotic factors (endothelial nitric oxide synthase (eNOS), krüppel-like factor 2,4 (KLF2, KLF4)) and reduced pro-thrombotic molecules (intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1)). The implanted hiPSC-ECs were gradually replaced by host ECs, indicating their role as a temporary immunomodulatory scaffold that facilitates host cell repopulation [210].

Scaffold design and printing precision likewise represent critical challenges to the clinical translation of TEVGs. Advances in artificial intelligence provide promising avenues to address these limitations: large language models (LLMs) and graph neural networks (GNNs) have been employed to predict the mechanical properties, degradation behavior, and immunogenic potential of candidate polymers such as PLGA and PCL; reinforcement learning (RL) algorithms enable dynamic optimization of key bioprinting parameters, including extrusion speed and layer thickness, thereby more accurately replicating the physiological architecture of native vessels [211]. Moreover, the integration of computer vision with machine learning allows real-time monitoring and correction of defects during the printing process [212].

4D printing is based on 3D printing and integrates responsive (smart) materials, enabling grafts to respond to external stimuli in a controlled manner [213]. Baruch *et al*. [214] introduced the use of dynamic vascular wall bioinks (ECM–PNIPAM hybrid hydrogels), which undergo selective shrinkage at physiological temperature, enabling pre-designed vessels within cardiac parenchyma to spontaneously contract to capillary dimensions. This strategy realizes programmable *in situ* "scaling down" of microstructures within organs [214]. This printing strategy can be integrated with shear stress conditioning in bioreactors and endothelial functional coatings (such as NO donors or anticoagulant peptides), holding promise for further improving the long-term patency of TEVGs.

6. Conclusion and Prospects

Research on ABVs demonstrates the broad prospects in this field. In terms of material selection, the strengths and limitations of different material options must first be fully evaluated. Natural biomaterials have excellent biocompatibility, but present challenges in terms of mechanical durability and controlled degradation. In contrast, synthetic materials such as PET and ePTFE, while mechanically strong, often induce thrombosis, inflammation, and intimal hyperplasia, limiting their wider application. Innovative manufacturing techniques, especially electrospinning, 3D printing, TIPS, and microfluidic spinning, can enable precise microstructural control, mechanical regulation, and enhanced biointegration. These approaches facilitate better integration of cells and bioactive factors to more closely mimic the natural vascular architecture and significantly improve the performance of graft materials.

TEVGs have shown great potential in small-diameter vascular reconstruction. They have tunable mechanical properties, enhanced endothelialization capacity, and low reliance on *in vitro* cell seeding. However, challenges remain in terms of suitable cell sources. Although autologous cells are ideal, their limited availability and expansion potential make it necessary to explore stem cells and their derivatives. However, significant obstacles remain in terms of differentiation efficiency, immunogenicity, and reproducibility.

Surface modification and targeted drug delivery are essential to enhance TEVG functionality, especially in terms of antithrombotic, antimicrobial, and anti-inflammatory properties. Careful selection of animal models can greatly influence the relevance of preclinical studies. While small animals are advantageous for early studies, large animals provide deeper physiological insights for long-term evaluations.

Although early clinical trials of TEGVs have demonstrated short-term safety and efficacy, further improvement is still needed in terms of long-term patency and graft-related complications. Future studies should prioritize the use of standardized cell sources, optimized materials, integrated structure-function design, and rigorous clinical data, which are the key steps towards routine clinical application.

Author Contributions

KJG conceived the study and wrote the manuscript. SXW and XYZ participated in data collection. WL proposed the research idea. All authors contributed to the editing and revision of the manuscript, and all authors read and approved the final version. All authors agree to be accountable for all aspects of the work, ensuring that any issues related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

References

[1] Lear SA, McKee M, Hystad P, Walker BB, Murphy A, Brauer M, *et al*. Social factors, health policy, and environment: implications for cardiovascular disease across the globe. European Heart Journal. 2025; 46: 2959–2973. https://doi.org/10.1093/eurheartj/ehaf212.

[2] West-Livingston L, Lim JW, Lee SJ. Translational tissue-engineered vascular grafts: From bench to bedside. Biomaterials. 2023; 302: 122322. https://doi.org/10.1016/j.biomaterials.2023.122322.

[3] Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, *et al*. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. Circulation. 2019; 139: e56–e528. https://doi.org/10.1161/CIR.0000000000000659.

[4] Wang Z, Liu L, Mithieux SM, Weiss AS. Fabricating Organized Elastin in Vascular Grafts. Trends in Biotechnology. 2021; 39: 505–518. https://doi.org/10.1016/j.tibtech.2020.09.003.

[5] Spadaccio C, Rainer A, Barbato R, Trombetta M, Chello M, Meyns B. The long-term follow-up of large-diameter Dacron® vascular grafts in surgical practice: a review. The Journal of Cardiovascular Surgery. 2019; 60: 501–513. https://doi.org/10.23736/S0021-9509.16.08061-7.

[6] Wilson John N, Dang C, Reddy N, Chao C, Ho KJ, Jiang B. Bioengineering Strategies for Treating Neointimal Hyperplasia in Peripheral Vasculature: Innovations and Challenges. Advanced Healthcare Materials. 2025; 14: e2401056. https://doi.org/10.1002/adhm.202401056.

[7] Zhang Y, Fang Q, Niu K, Gan Z, Yu Q, Gu T. Time-dependently slow-released multiple-drug eluting external sheath for efficient long-term inhibition of saphenous vein graft failure. Journal of Controlled Release: Official Journal of the Controlled Release Society. 2019; 293: 172–182. https://doi.org/10.1016/j.jconrel.2018.12.001.

[8] Gaudino M, Taggart D, Suma H, Puskas JD, Crea F, Massetti M. The Choice of Conduits in Coronary Artery Bypass Surgery. Journal of the American College of Cardiology. 2015; 66: 1729–1737. https://doi.org/10.1016/j.jacc.2015.08.395.

[9] Gaudino M, Benedetto U, Fremes S, Biondi-Zoccai G, Sedrakyan A, Puskas JD, *et al*. Radial-Artery or Saphenous-Vein Grafts in Coronary-Artery Bypass Surgery. The New England Journal of Medicine. 2018; 378: 2069–2077. https://doi.org/10.1056/NEJMoa1716026.

[10] Hillis LD, Smith PK, Anderson JL, Bittl JA, Bridges CR, Byrne JG, *et al*. 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011; 124: e652–e735. https://doi.org/10.1161/CIR.0b013e31823c074e.

[11] Aldea GS, Bakaeen FG, Pal J, Fremes S, Head SJ, Sabik J, *et al*. The Society of Thoracic Surgeons Clinical Practice Guidelines on Arterial Conduits for Coronary Artery Bypass Grafting. The Annals of Thoracic Surgery. 2016; 101: 801–809. https://doi.org/10.1016/j.athoracsur.2015.09.100.

[12] Caliskan E, de Souza DR, Böning A, Liakopoulos OJ, Choi YH, Pepper J, *et al*. Saphenous vein grafts in contemporary coronary artery bypass graft surgery. Nature Reviews. Cardiology. 2020; 17: 155–169. https://doi.org/10.1038/s41569-019-0249-3.

[13] de Vries MR, Simons KH, Jukema JW, Braun J, Quax PHA. Vein graft failure: from pathophysiology to clinical outcomes. Nature Reviews. Cardiology. 2016; 13: 451–470. https://doi.org/10.1038/nrcardio.2016.76.

[14] Harskamp RE, Lopes RD, Baisden CE, de Winter RJ, Alexander JH. Saphenous vein graft failure after coronary artery bypass surgery: pathophysiology, management, and future directions. Annals of Surgery. 2013; 257: 824–833. https://doi.org/10.1097/SLA.0b013e318288c38d.

[15] Laowpanitchakorn P, Zeng J, Piantino M, Uchida K, Katsuyama M, Matsusaki M. Biofabrication of engineered blood vessels for biomedical applications. Science and Technology of Advanced Materials. 2024; 25: 2330339. https://doi.org/10.1080/14686996.2024.2330339.

[16] Zhang Y, Lin L, Niu M, Bian F, Wang W, Zu Y. Artificial Human Blood Vessels for Tissue Engineering. ACS Materials Letters. 2025; 7: 1626–1645. https://doi.org/10.1021/acsmaterialslett.5c00038.

[17] Schriefl AJ, Zeindlinger G, Pierce DM, Regitnig P, Holzapfel GA. Determination of the layer-specific distributed collagen fibre orientations in human thoracic and abdominal aortas and common iliac arteries. Journal of the Royal Society, Interface. 2012; 9: 1275–1286. https://doi.org/10.1098/rsif.2011.0727.

[18] VOORHEES AB, Jr, JARETZKI A, 3rd, BLAKEMORE AH. The use of tubes constructed from vinyon "N" cloth in bridging arterial defects. Annals of Surgery. 1952; 135: 332–336. https://doi.org/10.1097/00000658-195203000-00006.

[19] BLAKEMORE AH, VOORHEES AB, Jr. The use of tubes constructed from vinyon N cloth in bridging arterial defects; experimental and clinical. Annals of Surgery. 1954; 140: 324–334. https://doi.org/10.1097/00000658-195409000-00008.

[20] Lang Z, Chen T, Zhu S, Wu X, Wu Y, Miao X, *et al*. Construction of vascular grafts based on tissue-engineered scaffolds. Materials Today. Bio. 2024; 29: 101336. https://doi.org/10.1016/j.mtbio.2024.101336.

[21] Qiu Y, Myers DR, Lam WA. The biophysics and mechanics of blood from a materials perspective. Nature Reviews. Materials. 2019; 4: 294–311. https://doi.org/10.1038/s41578-019-0099-y.

[22] Fleischer S, Tavakol DN, Vunjak-Novakovic G. From arteries to capillaries: approaches to engineering human vasculature. Advanced Functional Materials. 2020; 30: 1910811. https://doi.org/10.1002/adfm.201910811.

[23] Akentjew TL, Terraza C, Suazo C, Maksimcuka J, Wilkens CA, Vargas F, *et al*. Rapid fabrication of reinforced and cell-laden vascular grafts structurally inspired by human coronary arteries. Nature Communications. 2019; 10: 3098. https://doi.org/10.1038/s41467-019-11090-3.

[24] Giol ED, Van Vlierberghe S, Unger RE, Kersemans K, de Vos F, Kirkpatrick CJ, *et al*. Biomimetic strategy towards gelatin coatings on PET. Effect of protocol on coating stability and cell-interactive properties. Journal of Materials Chemistry. B. 2019; 7: 1258–1269. https://doi.org/10.1039/c8tb02676a.

[25] Wang F, Liang MD, Zhang B, Li WQ, Huang XC, Zhang XC, et al. Advances in artificial blood vessels: Exploring materials, preparation, and functionality. Journal of Materials Science & Technology. 2025; 219: 225–256. https://doi.org/10.1016/j.jmst.2024.09.029.

[26] Gao A, Hang R, Li W, Zhang W, Li P, Wang G, *et al*. Linker-free covalent immobilization of heparin, SDF-1α, and CD47 on

PTFE surface for antithrombogenicity, endothelialization and anti-inflammation. Biomaterials. 2017; 140: 201–211. https://doi.org/10.1016/j.biomaterials.2017.06.023.

[27] Pezzoli D, Cauli E, Chevallier P, Farè S, Mantovani D. Biomimetic coating of cross-linked gelatin to improve mechanical and biological properties of electrospun PET: A promising approach for small caliber vascular graft applications. Journal of Biomedical Materials Research. Part a. 2017; 105: 2405–2415. https://doi.org/10.1002/jbm.a.36098.

[28] Kang TY, Lee JH, Kim BJ, Kang JA, Hong JM, Kim BS, *et al*. In vivo endothelization of tubular vascular grafts through in situ recruitment of endothelial and endothelial progenitor cells by RGD-fused mussel adhesive proteins. Biofabrication. 2015; 7: 015007. https://doi.org/10.1088/1758-5090/7/1/015007.

[29] Nishikawa T, Iwakiri N, Kaneko Y, Taguchi A, Fukushima K, Mori H, *et al*. Nitric oxide release in human aortic endothelial cells mediated by delivery of amphiphilic polysiloxane nanoparticles to caveolae. Biomacromolecules. 2009; 10: 2074–2085. https://doi.org/10.1021/bm900128x.

[30] Yang C, Jeong S, Ku S, Lee K, Park MH. Use of gasotransmitters for the controlled release of polymer-based nitric oxide carriers in medical applications. Journal of Controlled Release: Official Journal of the Controlled Release Society. 2018; 279: 157–170. https://doi.org/10.1016/j.jconrel.2018.04.025.

[31] Henry JJD, Yu J, Wang A, Lee R, Fang J, Li S. Engineering the mechanical and biological properties of nanofibrous vascular grafts for in situ vascular tissue engineering. Biofabrication. 2017; 9: 035007. https://doi.org/10.1088/1758-5090/aa834b.

[32] Chong DST, Turner LA, Gadegaard N, Seifalian AM, Dalby MJ, Hamilton G. Nanotopography and plasma treatment: redesigning the surface for vascular graft endothelialisation. European Journal of Vascular and Endovascular Surgery: the Official Journal of the European Society for Vascular Surgery. 2015; 49: 335–343. https://doi.org/10.1016/j.ejvs.2014.12.008.

[33] Zhang W, Tian X, Xu S, Wu B, Jiang T. Supramolecular Prodrug Hydrogel for One-Week Protection Against Thrombosis. Small (Weinheim an Der Bergstrasse, Germany). 2025; e2500193. https://doi.org/10.1002/smll.202500193. (online ahead of print)

[34] Xing Z, Wu S, Zhao C, Bai Y, Jin D, Yin M, *et al*. Vascular transplantation with dual-biofunctional ePTFE vascular grafts in a porcine model. Journal of Materials Chemistry. B. 2021; 9: 7409–7422. https://doi.org/10.1039/d1tb01398j.

[35] Wang D, Xu Y, Lin YJ, Yilmaz G, Zhang J, Schmidt G, *et al*. Biologically Functionalized Expanded Polytetrafluoroethylene Blood Vessel Grafts. Biomacromolecules. 2020; 21: 3807–3816. https://doi.org/10.1021/acs.biomac.0c00897.

[36] Zhao Z, Xu M, Zhang Z, Yin X, Pu X, Wang J, *et al*. Osteoinductive IL-8/tDM/PLGA scaffolds based on autologous BMSC recruitment and endogenous growth factor regulation. Biomaterials Science. 2025; 13: 3972–3991. https://doi.org/10.1039/d5bm00469a.

[37] Han Y, Jia X, Yang Y, Guo P, Li C, Zhang Y, *et al*. Study of bioactive 3D-printed scaffolds incorporating zinc-based MOF for bone defect repair and anti-inflammatory applications. Materials Today. Bio. 2025; 32: 101884. https://doi.org/10.1016/j.mtbio.2025.101884.

[38] Jin S, Cai Y, Li Y, Wen J, Fu X, Song P, *et al*. A sandwich-like nanofibrous scaffold with macrophage phenotype transformation and myogenic differentiation for skeletal muscle regeneration. Bioactive Materials. 2025; 51: 211–230. https://doi.org/10.1016/j.bioactmat.2025.05.008.

[39] Bahnick AJ, Ruppert D, Krisanic GA, Everitt JI, Fowler VG, Jr, Levinson H, *et al*. Bioresorbable Suture Anchor Clips for Soft Tissue Wound Repair. Biomacromolecules. 2025; 26: 1709–1724. https://doi.org/10.1021/acs.biomac.4c01491.

[40] Wu Y, Zhang W, Huang L, Xu X, He S, Wang Z, *et al*. Microenvironment-Regulated Hydrogels Prepared with a Brand-New Small Molecule Cross-Linker for Stepwise Treatment of Myocardial Infarction. Advanced Healthcare Materials. 2025; 14: e2500804. https://doi.org/10.1002/adhm.202500804.

[41] Guo M, Ruan M, Wu J, Ye J, Wang C, Guo Z, *et al*. Polytannic acid coated PLGA nanoparticle decorated with antimicrobial peptide for synergistic bacteria treatment and infectious wound healing promotion. Colloids and Surfaces. B, Biointerfaces. 2025; 245: 114217. https://doi.org/10.1016/j.colsurfb.2024.114217.

[42] Zeng R, Lv B, Lin Z, Chu X, Xiong Y, Knoedler S, *et al*. Neddylation suppression by a macrophage membrane-coated nanoparticle promotes dual immunomodulatory repair of diabetic wounds. Bioactive Materials. 2024; 34: 366–380. https://doi.org/10.1016/j.bioactmat.2023.12.025.

[43] Peng Y, Shang Y, Che J, Yu Y, Zhao Y, Gu X. Multifunctional Analgesic Sutures from Microfluidic Spinning Technology. Advanced Healthcare Materials. 2025; 14: e2402420. https://doi.org/10.1002/adhm.202402420.

[44] Li Y, Yan D, Fu F, Liu Y, Zhang B, Wang J, *et al*. Composite core-shell microparticles from microfluidics for synergistic drug delivery. Science China-Materials. 2017; 60: 543–553. https://doi.org/10.1007/s40843-016-5151-6.

[45] Makadia HK, Siegel SJ. Poly Lactic-co-Glycolic Acid (PLGA) as Biodegradable Controlled Drug Delivery Carrier. Polymers. 2011; 3: 1377–1397. https://doi.org/10.3390/polym3031377.

[46] Fu J, Wang M, De Vlaminck I, Wang Y. Thick PCL Fibers Improving Host Remodeling of PGS-PCL Composite Grafts Implanted in Rat Common Carotid Arteries. Small (Weinheim an Der Bergstrasse, Germany). 2020; 16: e2004133. https://doi.org/10.1002/smll.202004133.

[47] Sell SA, Wolfe PS, Garg K, McCool JM, Rodriguez IA, Bowlin GL. The Use of Natural Polymers in Tissue Engineering: A Focus on Electrospun Extracellular Matrix Analogues. Polymers. 2010; 2: 522–553. https://doi.org/10.3390/polym2040522.

[48] Vishvaja S, Priyadharshini D, Sabarees G, Tamilarasi GP, Gouthaman S, Solomon VR. Optimizing processes and unveiling the therapeutic potential of electrospun gelatin nanofibers for biomedical applications. Journal of Materials Chemistry. B. 2025; 13: 5202–5225. https://doi.org/10.1039/d4tb02769h.

[49] Niklason LE, Lawson JH. Bioengineered human blood vessels. Science (New York, N.Y.). 2020; 370: eaaw8682. https://doi.org/10.1126/science.aaw8682.

[50] Niu Y, Galluzzi M. Hyaluronic Acid/Collagen Nanofiber Tubular Scaffolds Support Endothelial Cell Proliferation, Phenotypic Shape and Endothelialization. Nanomaterials (Basel, Switzerland). 2021; 11: 2334. https://doi.org/10.3390/nano11092334.

[51] Zhang F, Bambharoliya T, Xie Y, Liu L, Celik H, Wang L, *et al*. A hybrid vascular graft harnessing the superior mechanical properties of synthetic fibers and the biological performance of collagen filaments. Materials Science & Engineering. C, Materials for Biological Applications. 2021; 118: 111418. https://doi.org/10.1016/j.msec.2020.111418.

[52] Fan Q, Zheng Y, Wang X, Xie R, Ding Y, Wang B, *et al*. Dynamically Re-Organized Collagen Fiber Bundles Transmit Mechanical Signals and Induce Strongly Correlated Cell Migration and Self-Organization. Angewandte Chemie (International Ed. in English). 2021; 60: 11858–11867. https://doi.org/10.1002/anie.202016084.

[53] Zhang F, Xie Y, Celik H, Akkus O, Bernacki SH, King MW. Engineering small-caliber vascular grafts from collagen filaments and nanofibers with comparable mechanical properties to native vessels. Biofabrication. 2019; 11: 035020. https://doi.org/10.1088/1758-5090/ab15ce.

[54] Liu S, Chen G, Chen Z, Wang F, Lv Y. Research progress on stiffness controllable scaffolds based on gelatin methacry-

loyl hydrogels for tissue repair and reconstruction. International Journal of Biological Macromolecules. 2025; 321: 146485. https://doi.org/10.1016/j.ijbiomac.2025.146485.

[55] Lv S, Zhang S, Zuo J, Liang S, Yang J, Wang J, *et al*. Progress in preparation and properties of chitosan-based hydrogels. International Journal of Biological Macromolecules. 2023; 242: 124915. https://doi.org/10.1016/j.ijbiomac.2023.124915.

[56] Rodrigues LC, Fernandes EM, Ribeiro AR, Ribeiro AP, Silva SS, Reis RL. Physicochemical features assessment of acemannan-based ternary blended films for biomedical purposes. Carbohydrate Polymers. 2021; 257: 117601. https://doi.org/10.1016/j.carbpol.2020.117601.

[57] Rodrigues LC, Gomes JM, da Costa DS, Fernandes EM, Costa RR, Rodriguez-Cabello JC, *et al*. 3D tubular constructs based on natural polysaccharides and recombinant polypeptide synergistic blends as potential candidates for blood vessel solutions. International Journal of Biological Macromolecules. 2025; 310: 143084. https://doi.org/10.1016/j.ijbiomac.2025.143084.

[58] Bao L, Hong FF, Li G, Hu G, Chen L. Improved Performance of Bacterial Nanocellulose Conduits by the Introduction of Silk Fibroin Nanoparticles and Heparin for Small-Caliber Vascular Graft Applications. Biomacromolecules. 2021; 22: 353–364. https://doi.org/10.1021/acs.biomac.0c01211.

[59] Zhang S, Wang J, Zheng Z, Yan J, Zhang L, Li Y, *et al*. Porous nerve guidance conduits reinforced with braided composite structures of silk/magnesium filaments for peripheral nerve repair. Acta Biomaterialia. 2021; 134: 116–130. https://doi.org/10.1016/j.actbio.2021.07.028.

[60] Wu P, Liu Q, Li R, Wang J, Zhen X, Yue G, *et al*. Facile preparation of paclitaxel loaded silk fibroin nanoparticles for enhanced antitumor efficacy by locoregional drug delivery. ACS Applied Materials & Interfaces. 2013; 5: 12638–12645. https://doi.org/10.1021/am403992b.

[61] Scherner M, Reutter S, Klemm D, Sterner-Kock A, Guschlbauer M, Richter T, *et al*. In vivo application of tissue-engineered blood vessels of bacterial cellulose as small arterial substitutes: proof of concept? The Journal of Surgical Research. 2014; 189: 340–347. https://doi.org/10.1016/j.jss.2014.02.011.

[62] Ryan AJ, Ryan EJ, Cameron AR, O'Brien FJ. Hierarchical biofabrication of biomimetic collagen-elastin vascular grafts with controllable properties via lyophilisation. Acta Biomaterialia. 2020; 112: 52–61. https://doi.org/10.1016/j.actbio.2020.06.002.

[63] Stella JA, D'Amore A, Wagner WR, Sacks MS. On the biomechanical function of scaffolds for engineering load-bearing soft tissues. Acta Biomaterialia. 2010; 6: 2365–2381. https://doi.org/10.1016/j.actbio.2010.01.001.

[64] Moore MJ, Tan RP, Yang N, Rnjak-Kovacina J, Wise SG. Bioengineering artificial blood vessels from natural materials. Trends in Biotechnology. 2022; 40: 693–707. https://doi.org/10.1016/j.tibtech.2021.11.003.

[65] Ahn M, Cho WW, Lee H, Park W, Lee SH, Back JW, *et al*. Engineering of Uniform Epidermal Layers via Sacrificial Gelatin Bioink-Assisted 3D Extrusion Bioprinting of Skin. Advanced Healthcare Materials. 2023; 12: e2301015. https://doi.org/10.1002/adhm.202301015.

[66] Qiu K, Haghiashtiani G, McAlpine MC. 3D Printed Organ Models for Surgical Applications. Annual Review of Analytical Chemistry (Palo Alto, Calif.). 2018; 11: 287–306. https://doi.org/10.1146/annurev-anchem-061417-125935.

[67] Segaran N, Saini G, Mayer JL, Naidu S, Patel I, Alzubaidi S, *et al*. Application of 3D Printing in Preoperative Planning. Journal of Clinical Medicine. 2021; 10: 917. https://doi.org/10.3390/jcm10050917.

[68] Choi J, Lee EJ, Jang WB, Kwon SM. Development of Biocompatible 3D-Printed Artificial Blood Vessels through Multidimensional Approaches. Journal of Functional Biomaterials. 2023; 14: 497. https://doi.org/10.3390/jfb14100497.

[69] Bazgir M, Saeinasab M, Zhang W, Zhang X, Min Tsui K, Maasoumi Sarvestani A, *et al*. Investigation of Cell Adhesion and Cell Viability of the Endothelial and Fibroblast Cells on Electrospun PCL, PLGA and Coaxial Scaffolds for Production of Tissue Engineered Blood Vessel. Journal of Functional Biomaterials. 2022; 13: 282. https://doi.org/10.3390/jfb13040282.

[70] Pati F, Jang J, Ha DH, Won Kim S, Rhie JW, Shim JH, *et al*. Printing three-dimensional tissue analogues with decellularized extracellular matrix bioink. Nature Communications. 2014; 5: 3935. https://doi.org/10.1038/ncomms4935.

[71] Nam SY, Park SH. ECM Based Bioink for Tissue Mimetic 3D Bioprinting. Advances in Experimental Medicine and Biology. 2018; 1064: 335–353. https://doi.org/10.1007/978-981-13-0445-3_20.

[72] Salg GA, Blaeser A, Gerhardus JS, Hackert T, Kenngott HG. Vascularization in Bioartificial Parenchymal Tissue: Bioink and Bioprinting Strategies. International Journal of Molecular Sciences. 2022; 23: 8589. https://doi.org/10.3390/ijms23158589.

[73] Smoak MM, Han A, Watson E, Kishan A, Grande-Allen KJ, Cosgriff-Hernandez E, *et al*. Fabrication and Characterization of Electrospun Decellularized Muscle-Derived Scaffolds. Tissue Engineering. Part C, Methods. 2019; 25: 276–287. https://doi.org/10.1089/ten.TEC.2018.0339.

[74] Dabaghi M, Saraei N, Carpio MB, Nanduri V, Ungureanu J, Babi M, *et al*. A Robust Protocol for Decellularized Human Lung Bioink Generation Amenable to 2D and 3D Lung Cell Culture. Cells. 2021; 10: 1538. https://doi.org/10.3390/cells10061538.

[75] Jin H, Kang Y, Gao H, Lin Z, Huang D, Zheng Z, *et al*. Decellularization-Based Modification Strategy for Bioactive Xenografts Promoting Tendon Repair. Advanced Healthcare Materials. 2024; 13: e2302660. https://doi.org/10.1002/adhm.202302660.

[76] Li S, Deng R, Forouzanfar T, Wu G, Quan D, Zhou M. Decellularized Periosteum-Derived Hydrogels Promote the Proliferation, Migration and Osteogenic Differentiation of Human Umbilical Cord Mesenchymal Stem Cells. Gels (Basel, Switzerland). 2022; 8: 294. https://doi.org/10.3390/gels8050294.

[77] Jang J, Park HJ, Kim SW, Kim H, Park JY, Na SJ, *et al*. 3D printed complex tissue construct using stem cell-laden decellularized extracellular matrix bioinks for cardiac repair. Biomaterials. 2017; 112: 264–274. https://doi.org/10.1016/j.biomaterials.2016.10.026.

[78] Ben Omondi O, Arroyan YN, Onyango B, Kong LW, Wang GX, Ye ZY. Revolutionizing healthcare: Emerging frontiers in 3D bioprinting of tissues and organs. European Polymer Journal. 2024; 217: 113210. https://doi.org/10.1016/j.eurpolymj.2024.113210.

[79] Cui H, Miao S, Esworthy T, Zhou X, Lee SJ, Liu C, *et al*. 3D bioprinting for cardiovascular regeneration and pharmacology. Advanced Drug Delivery Reviews. 2018; 132: 252–269. https://doi.org/10.1016/j.addr.2018.07.014.

[80] Siepe M, Akhyari P, Lichtenberg A, Schlensak C, Beyersdorf F. Stem cells used for cardiovascular tissue engineering. European Journal of Cardio-thoracic Surgery: Official Journal of the European Association for Cardio-thoracic Surgery. 2008; 34: 242–247. https://doi.org/10.1016/j.ejcts.2008.03.067.

[81] Agarwal T, Fortunato GM, Hann SY, Ayan B, Vajanthri KY, Presutti D, *et al*. Recent advances in bioprinting technologies for engineering cardiac tissue. Materials Science & Engineering. C, Materials for Biological Applications. 2021; 124: 112057. https://doi.org/10.1016/j.msec.2021.112057.

[82] Murphy AR, Franco RA, Allenby MC. Fabricating Microfluidic Co-Cultures of Immortalized Cell Lines Uncovers Robust Design Principles for the Simultaneous Formation of Patterned,

Vascularized, and Stem Cell-Derived Adipose Tissue. Small (Weinheim an Der Bergstrasse, Germany). 2025; 21: e2501834. https://doi.org/10.1002/smll.202501834.

[83] Matai I, Kaur G, Seyedsalehi A, McClinton A, Laurencin CT. Progress in 3D bioprinting technology for tissue/organ regenerative engineering. Biomaterials. 2020; 226: 119536. https://doi.org/10.1016/j.biomaterials.2019.119536.

[84] Kong Z, Wang X. Bioprinting Technologies and Bioinks for Vascular Model Establishment. International Journal of Molecular Sciences. 2023; 24: 891. https://doi.org/10.3390/ijms24010891.

[85] Zhou X, Nowicki M, Sun H, Hann SY, Cui H, Esworthy T, et al. 3D Bioprinting-Tunable Small-Diameter Blood Vessels with Biomimetic Biphasic Cell Layers. ACS Applied Materials & Interfaces. 2020; 12: 45904–45915. https://doi.org/10.1021/acsami.0c14871.

[86] Bosch-Rué E, Delgado LM, Gil FJ, Perez RA. Direct extrusion of individually encapsulated endothelial and smooth muscle cells mimicking blood vessel structures and vascular native cell alignment. Biofabrication. 2020; 13: 015003. https://doi.org/10.1088/1758-5090/abbd27.

[87] Bosch-Rué È, Díez-Tercero L, Delgado LM, Pérez RA. Biofabrication of Collagen Tissue-Engineered Blood Vessels with Direct Co-Axial Extrusion. International Journal of Molecular Sciences. 2022; 23: 5618. https://doi.org/10.3390/ijms23105618.

[88] Qu H, Gao C, Liu K, Fu H, Liu Z, Kouwer PHJ, *et al*. Gradient matters via filament diameter-adjustable 3D printing. Nature Communications. 2024; 15: 2930. https://doi.org/10.1038/s41467-024-47360-y.

[89] Sadée C, Testa S, Barba T, Hartmann K, Schuessler M, Thieme A, *et al*. Medical digital twins: enabling precision medicine and medical artificial intelligence. The Lancet. Digital Health. 2025; 7: 100864. https://doi.org/10.1016/j.landig.2025.02.004.

[90] Schouten D, Nicoletti G, Dille B, Chia C, Vendittelli P, Schuurmans M, *et al*. Navigating the landscape of multimodal AI in medicine: A scoping review on technical challenges and clinical applications. Medical Image Analysis. 2025; 105: 103621. https://doi.org/10.1016/j.media.2025.103621.

[91] Lee H. Engineering In vitro Models: Bioprinting of Organoids with Artificial Intelligence. Cyborg and Bionic Systems (Washington, D.C.). 2023; 4: 0018. https://doi.org/10.34133/cbsystems.0018.

[92] Li L, Cheng S, Li J, Yang J, Wang H, Dong B, *et al*. Randomized comparison of AI enhanced 3D printing and traditional simulations in hepatobiliary surgery. NPJ Digital Medicine. 2025; 8: 293. https://doi.org/10.1038/s41746-025-01571-9.

[93] Corrado F, Di Maio L, Palmero P, Coppola B, Abbas Z, La Gatta A, *et al*. Vat photo-polymerization 3D printing of gradient scaffolds for osteochondral tissue regeneration. Acta Biomaterialia. 2025; 200: 67–86. https://doi.org/10.1016/j.actbio.2025.05.042.

[94] Wang X, Chan V, Corridon PR. Decellularized blood vessel development: Current state-of-the-art and future directions. Frontiers in Bioengineering and Biotechnology. 2022; 10: 951644. https://doi.org/10.3389/fbioe.2022.951644.

[95] Zou Y, Zhang Y. Mechanical evaluation of decellularized porcine thoracic aorta. The Journal of Surgical Research. 2012; 175: 359–368. https://doi.org/10.1016/j.jss.2011.03.070.

[96] Gong W, Lei D, Li S, Huang P, Qi Q, Sun Y, *et al*. Hybrid small-diameter vascular grafts: Anti-expansion effect of electrospun poly ε-caprolactone on heparin-coated decellularized matrices. Biomaterials. 2016; 76: 359–370. https://doi.org/10.1016/j.biomaterials.2015.10.066.

[97] Luo H, Cha R, Li J, Hao W, Zhang Y, Zhou F. Advances in tissue engineering of nanocellulose-based scaffolds: A review. Carbohydrate Polymers. 2019; 224: 115144. https://doi.org/10.1016/j.carbpol.2019.115144.

[98] Kontturi E, Laaksonen P, Linder MB, Nonappa, Gröschel AH, Rojas OJ, *et al*. Advanced Materials through Assembly of Nanocelluloses. Advanced Materials (Deerfield Beach, Fla.). 2018; 30: e1703779. https://doi.org/10.1002/adma.201703779.

[99] Do TM, Yang Y, Deng A. Porous Bilayer Vascular Grafts Fabricated from Electrospinning of the Recombinant Human Collagen (RHC) Peptide-Based Blend. Polymers. 2021; 13: 4042. https://doi.org/10.3390/polym13224042.

[100] Tondnevis F, Keshvari H, Mohandesi JA. Fabrication, characterization, and in vitro evaluation of electrospun polyurethane-gelatin-carbon nanotube scaffolds for cardiovascular tissue engineering applications. Journal of Biomedical Materials Research. Part B, Applied Biomaterials. 2020; 108: 2276–2293. https://doi.org/10.1002/jbm.b.34564.

[101] Yang Y, Lei D, Zou H, Huang S, Yang Q, Li S, *et al*. Hybrid electrospun rapamycin-loaded small-diameter decellularized vascular grafts effectively inhibit intimal hyperplasia. Acta Biomaterialia. 2019; 97: 321–332. https://doi.org/10.1016/j.actbio.2019.06.037.

[102] Braghirolli DI, Helfer VE, Chagastelles PC, Dalberto TP, Gamba D, Pranke P. Electrospun scaffolds functionalized with heparin and vascular endothelial growth factor increase the proliferation of endothelial progenitor cells. Biomedical Materials. 2017; 12: 025003. https://doi.org/10.1088/1748-605X/aa5bbc.

[103] Cuenca JP, Kang HJ, Fahad MAA, Park M, Choi M, Lee HY, *et al*. Physico-mechanical and biological evaluation of heparin/VEGF-loaded electrospun polycaprolactone/decellularized rat aorta extracellular matrix for small-diameter vascular grafts. Journal of Biomaterials Science. Polymer Edition. 2022; 33: 1664–1684. https://doi.org/10.1080/09205063.2022.2069398.

[104] Kuang H, Wang Y, Shi Y, Yao W, He X, Liu X, *et al*. Construction and performance evaluation of Hep/silk-PLCL composite nanofiber small-caliber artificial blood vessel graft. Biomaterials. 2020; 259: 120288. https://doi.org/10.1016/j.biomaterials.2020.120288.

[105] Tejeda-Alejandre R, Lammel-Lindemann JA, Lara-Padilla H, Dean D, Rodriguez CA. Influence of Electrical Field Collector Positioning and Motion Scheme on Electrospun Bifurcated Vascular Graft Membranes. Materials (Basel, Switzerland). 2019; 12: 2123. https://doi.org/10.3390/ma12132123.

[106] Singh C, Wong CS, Wang X. Medical Textiles as Vascular Implants and Their Success to Mimic Natural Arteries. Journal of Functional Biomaterials. 2015; 6: 500–525. https://doi.org/10.3390/jfb6030500.

[107] Yan S, Napiwocki B, Xu Y, Zhang J, Zhang X, Wang X, *et al*. Wavy small-diameter vascular graft made of eggshell membrane and thermoplastic polyurethane. Materials Science & Engineering. C, Materials for Biological Applications. 2020; 107: 110311. https://doi.org/10.1016/j.msec.2019.110311.

[108] Lian S, Lamprou D, Zhao M. Electrospinning technologies for the delivery of Biopharmaceuticals: Current status and future trends. International Journal of Pharmaceutics. 2024; 651: 123641. https://doi.org/10.1016/j.ijpharm.2023.123641.

[109] Luraghi A, Peri F, Moroni L. Electrospinning for drug delivery applications: A review. Journal of Controlled Release: Official Journal of the Controlled Release Society. 2021; 334: 463–484. https://doi.org/10.1016/j.jconrel.2021.03.033.

[110] Uhljar LÉ, Ambrus R. Electrospinning of Potential Medical Devices (Wound Dressings, Tissue Engineering Scaffolds, Face Masks) and Their Regulatory Approach. Pharmaceutics. 2023; 15: 417. https://doi.org/10.3390/pharmaceutics15020417.

[111] Shang L, Yu Y, Liu Y, Chen Z, Kong T, Zhao Y. Spinning and Applications of Bioinspired Fiber Systems. ACS Nano. 2019; 13: 2749–2772. https://doi.org/10.1021/acsnano.8b09651.

[112] Wang Y, Guo J, Luo Z, Shen Y, Wang J, Yu Y, *et al*. Biopolymer-Assembled Porous Hydrogel Microfibers from Mi-

crofluidic Spinning for Wound Healing. Advanced Healthcare Materials. 2024; 13: e2302170. https://doi.org/10.1002/adhm.202302170.

[113] Wang Q, Wang C, Yang X, Wang J, Zhang Z, Shang L. Microfluidic preparation of optical sensors for biomedical applications. Smart Medicine. 2023; 2: e20220027. https://doi.org/10.1002/SMMD.20220027.

[114] Jia L, Han F, Yang H, Turnbull G, Wang J, Clarke J, *et al*. Microfluidic Fabrication of Biomimetic Helical Hydrogel Microfibers for Blood-Vessel-on-a-Chip Applications. Advanced Healthcare Materials. 2019; 8: e1900435. https://doi.org/10.1002/adhm.201900435.

[115] Jung JT, Kim JF, Wang HH, di Nicolo E, Drioli E, Lee YM. Understanding the non-solvent induced phase separation (NIPS) effect during the fabrication of microporous PVDF membranes via thermally induced phase separation (TIPS). Journal of Membrane Science. 2016; 514: 250–263. https://doi.org/10.1016/j.memsci.2016.04.069.

[116] Ma W, Liu Z, Zhu T, Wang L, Du J, Wang K, *et al*. Fabric-Enhanced Vascular Graft with Hierarchical Structure for Promoting the Regeneration of Vascular Tissue. Advanced Healthcare Materials. 2024; 13: e2302676. https://doi.org/10.1002/adhm.202302676.

[117] Gupta P, Mandal BB. Tissue-Engineered Vascular Grafts: Emerging Trends and Technologies. Advanced Functional Materials. 2021; 31: 2100027. https://doi.org/10.1002/adfm.202100027.

[118] Weinberg CB, Bell E. A blood vessel model constructed from collagen and cultured vascular cells. Science (New York, N.Y.). 1986; 231: 397–400. https://doi.org/10.1126/science.2934816.

[119] Shin'oka T, Imai Y, Ikada Y. Transplantation of a tissue-engineered pulmonary artery. The New England Journal of Medicine. 2001; 344: 532–533. https://doi.org/10.1056/NEJM200102153440717.

[120] Matsuzaki Y, John K, Shoji T, Shinoka T. The Evolution of Tissue Engineered Vascular Graft Technologies: From Preclinical Trials to Advancing Patient Care. Applied Sciences (Basel, Switzerland). 2019; 9: 1274. https://doi.org/10.3390/app9071274.

[121] Chandra P, Atala A. Engineering blood vessels and vascularized tissues: technology trends and potential clinical applications. Clinical Science (London, England: 1979). 2019; 133: 1115–1135. https://doi.org/10.1042/CS20180155.

[122] Kirkton RD, Santiago-Maysonet M, Lawson JH, Tente WE, Dahl SLM, Niklason LE, *et al*. Bioengineered human acellular vessels recellularize and evolve into living blood vessels after human implantation. Science Translational Medicine. 2019; 11: eaau6934. https://doi.org/10.1126/scitranslmed.aau6934.

[123] Mahara A, Shirai M, Soni R, Le HT, Shimizu K, Hirano Y, *et al*. Vascular tissue reconstruction by monocyte subpopulations on small-diameter acellular grafts via integrin activation. Materials Today. Bio. 2023; 23: 100847. https://doi.org/10.1016/j.mtbio.2023.100847.

[124] Saito J, Kaneko M, Ishikawa Y, Yokoyama U. Challenges and Possibilities of Cell-Based Tissue-Engineered Vascular Grafts. Cyborg and Bionic Systems (Washington, D.C.). 2021; 2021: 1532103. https://doi.org/10.34133/2021/1532103.

[125] Generali M, Casanova EA, Kehl D, Wanner D, Hoerstrup SP, Cinelli P, *et al*. Autologous endothelialized small-caliber vascular grafts engineered from blood-derived induced pluripotent stem cells. Acta Biomaterialia. 2019; 97: 333–343. https://doi.org/10.1016/j.actbio.2019.07.032.

[126] West-Livingston L, Ju YM, Lee H, Geary RL, Atala A, Lee SJ. Antibody-Conjugated Electrospun Vascular Scaffolds to Enhance *In Situ* Endothelialization. ACS Applied Bio Materials. 2020; 3: 4486–4494. https://doi.org/10.1021/acsabm.0c00449.

[127] Ju YM, Ahn H, Arenas-Herrera J, Kim C, Abolbashari M, Atala A, *et al*. Electrospun vascular scaffold for cellularized small diameter blood vessels: A preclinical large animal study. Acta Biomaterialia. 2017; 59: 58–67. https://doi.org/10.1016/j.actbio.2017.06.027.

[128] Shi X, He L, Zhang SM, Luo J. Human iPS Cell-derived Tissue Engineered Vascular Graft: Recent Advances and Future Directions. Stem Cell Reviews and Reports. 2021; 17: 862–877. https://doi.org/10.1007/s12015-020-10091-w.

[129] Orlova VV, van den Hil FE, Petrus-Reurer S, Drabsch Y, Ten Dijke P, Mummery CL. Generation, expansion and functional analysis of endothelial cells and pericytes derived from human pluripotent stem cells. Nature Protocols. 2014; 9: 1514–1531. https://doi.org/10.1038/nprot.2014.102.

[130] Shi Y, Li D, Yi B, Tang H, Xu T, Zhang Y. Physiological cyclic stretching potentiates the cell-cell junctions in vascular endothelial layer formed on aligned fiber substrate. Biomaterials Advances. 2024; 157: 213751. https://doi.org/10.1016/j.bioadv.2023.213751.

[131] Luo J, Shi X, Lin Y, Yuan Y, Kural MH, Wang J, *et al*. Efficient Differentiation of Human Induced Pluripotent Stem Cells into Endothelial Cells under Xenogeneic-free Conditions for Vascular Tissue Engineering. Acta Biomaterialia. 2021; 119: 184–196. https://doi.org/10.1016/j.actbio.2020.11.007.

[132] Luo J, Qin L, Zhao L, Gui L, Ellis MW, Huang Y, *et al*. Tissue-Engineered Vascular Grafts with Advanced Mechanical Strength from Human iPSCs. Cell Stem Cell. 2020; 26: 251–261.e8. https://doi.org/10.1016/j.stem.2019.12.012.

[133] Avci-Adali M, Stoll H, Wilhelm N, Perle N, Schlensak C, Wendel HP. In vivo tissue engineering: mimicry of homing factors for self-endothelialization of blood-contacting materials. Pathobiology: Journal of Immunopathology, Molecular and Cellular Biology. 2013; 80: 176–181. https://doi.org/10.1159/000347222.

[134] Melchiorri AJ, Hibino N, Yi T, Lee YU, Sugiura T, Tara S, *et al*. Contrasting biofunctionalization strategies for the enhanced endothelialization of biodegradable vascular grafts. Biomacromolecules. 2015; 16: 437–446. https://doi.org/10.1021/bm501853s.

[135] Yan H, Cheng Q, Si J, Wang S, Wan Y, Kong X, *et al*. Functionalization of *in vivo* tissue-engineered living biotubes enhance patency and endothelization without the requirement of systemic anticoagulant administration. Bioactive Materials. 2023; 26: 292–305. https://doi.org/10.1016/j.bioactmat.2023.03.003.

[136] Zhao J, Bai L, Ren XK, Guo J, Xia S, Zhang W, *et al*. Co-immobilization of ACH_{11} antithrombotic peptide and CAG cell-adhesive peptide onto vascular grafts for improved hemocompatibility and endothelialization. Acta Biomaterialia. 2019; 97: 344–359. https://doi.org/10.1016/j.actbio.2019.07.057.

[137] Shen YH, Shoichet MS, Radisic M. Vascular endothelial growth factor immobilized in collagen scaffold promotes penetration and proliferation of endothelial cells. Acta Biomaterialia. 2008; 4: 477–489. https://doi.org/10.1016/j.actbio.2007.12.011.

[138] Pineda-Castillo SA, Acar H, Detamore MS, Holzapfel GA, Lee CH. Modulation of Smooth Muscle Cell Phenotype for Translation of Tissue-Engineered Vascular Grafts. Tissue Engineering. Part B, Reviews. 2023; 29: 574–588. https://doi.org/10.1089/ten.TEB.2023.0006.

[139] Marzi J, Brauchle EM, Schenke-Layland K, Rolle MW. Non-invasive functional molecular phenotyping of human smooth muscle cells utilized in cardiovascular tissue engineering. Acta Biomaterialia. 2019; 89: 193–205. https://doi.org/10.1016/j.actbio.2019.03.026.

[140] Vatankhah E, Prabhakaran MP, Ramakrishna S. Impact of electrospun Tecophilic/gelatin scaffold biofunctionalization on proliferation of vascular smooth muscle cells. Scientia Iranica.

2017; 24: 3458–3465. https://doi.org/10.24200/sci.2017.4420.
[141] Wang Y, Hu J, Jiao J, Liu Z, Zhou Z, Zhao C, *et al*. Engineering vascular tissue with functional smooth muscle cells derived from human iPS cells and nanofibrous scaffolds. Biomaterials. 2014; 35: 8960–8969. https://doi.org/10.1016/j.biomaterials.2014.07.011.
[142] Lee J, Yoo JJ, Atala A, Lee SJ. The effect of controlled release of PDGF-BB from heparin-conjugated electrospun PCL/gelatin scaffolds on cellular bioactivity and infiltration. Biomaterials. 2012; 33: 6709–6720. https://doi.org/10.1016/j.biomaterials.2012.06.017.
[143] Yu J, Wang A, Tang Z, Henry J, Li-Ping Lee B, Zhu Y, *et al*. The effect of stromal cell-derived factor-1α/heparin coating of biodegradable vascular grafts on the recruitment of both endothelial and smooth muscle progenitor cells for accelerated regeneration. Biomaterials. 2012; 33: 8062–8074. https://doi.org/10.1016/j.biomaterials.2012.07.042.
[144] Ardila DC, Tamimi E, Doetschman T, Wagner WR, Vande Geest JP. Modulating smooth muscle cell response by the release of TGFβ2 from tubular scaffolds for vascular tissue engineering. Journal of Controlled Release: Official Journal of the Controlled Release Society. 2019; 299: 44–52. https://doi.org/10.1016/j.jconrel.2019.02.024.
[145] Hishikawa K, Nakaki T, Marumo T, Hayashi M, Suzuki H, Kato R, *et al*. Pressure promotes DNA synthesis in rat cultured vascular smooth muscle cells. The Journal of Clinical Investigation. 1994; 93: 1975–1980. https://doi.org/10.1172/JCI117189.
[146] Owens GK, Kumar MS, Wamhoff BR. Molecular regulation of vascular smooth muscle cell differentiation in development and disease. Physiological Reviews. 2004; 84: 767–801. https://doi.org/10.1152/physrev.00041.2003.
[147] Ran K, Yang Z, Zhao Y, Wang X. Transmural pressure drives proliferation of human arterial smooth muscle cells via mechanism associated with NADPH oxidase and Survivin. Microvascular Research. 2019; 126: 103905. https://doi.org/10.1016/j.mvr.2019.103905.
[148] Frismantiene A, Philippova M, Erne P, Resink TJ. Smooth muscle cell-driven vascular diseases and molecular mechanisms of VSMC plasticity. Cellular Signalling. 2018; 52: 48–64. https://doi.org/10.1016/j.cellsig.2018.08.019.
[149] Humphrey JD, Dufresne ER, Schwartz MA. Mechanotransduction and extracellular matrix homeostasis. Nature Reviews. Molecular Cell Biology. 2014; 15: 802–812. https://doi.org/10.1038/nrm3896.
[150] Omraninava M, Rezapour-Nasrabad R, Hosseini M, Kasiri MA, Shahzamani S, Bahrami M, *et al*. Promotion of skin regeneration in diabetic rats by collagen-based hydrogel incorporated with basic fibroblast growth factor: A histological, molecular, and tensiometrical study. Tissue & Cell. 2025; 96: 102983. https://doi.org/10.1016/j.tice.2025.102983.
[151] Hinz B, Phan SH, Thannickal VJ, Prunotto M, Desmoulière A, Varga J, *et al*. Recent developments in myofibroblast biology: paradigms for connective tissue remodeling. The American Journal of Pathology. 2012; 180: 1340–1355. https://doi.org/10.1016/j.ajpath.2012.02.004.
[152] Sun X, Zhang N, Chen L, Lai Y, Yang S, Li Q, *et al*. Collagen/polyvinyl alcohol scaffolds combined with platelet-rich plasma to enhance anterior cruciate ligament repair. Biomaterials Advances. 2025; 169: 214164. https://doi.org/10.1016/j.bioadv.2024.214164.
[153] Torres Y, Gluais M, Da Silva N, Rey S, Grémare A, Magnan L, *et al*. Cell-assembled extracellular matrix (CAM) sheet production: Translation from using human to large animal cells. Journal of Tissue Engineering. 2021; 12: 2041731420978327. https://doi.org/10.1177/2041731420978327.
[154] Song HHG, Rumma RT, Ozaki CK, Edelman ER, Chen CS. Vascular Tissue Engineering: Progress, Challenges, and Clinical Promise. Cell Stem Cell. 2018; 22: 340–354. https://doi.org/10.1016/j.stem.2018.02.009.
[155] Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, *et al*. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell. 2007; 131: 861–872. https://doi.org/10.1016/j.cell.2007.11.019.
[156] Patsch C, Challet-Meylan L, Thoma EC, Urich E, Heckel T, O'Sullivan JF, *et al*. Generation of vascular endothelial and smooth muscle cells from human pluripotent stem cells. Nature Cell Biology. 2015; 17: 994–1003. https://doi.org/10.1038/ncb3205.
[157] Cheung C, Bernardo AS, Trotter MWB, Pedersen RA, Sinha S. Generation of human vascular smooth muscle subtypes provides insight into embryological origin-dependent disease susceptibility. Nature Biotechnology. 2012; 30: 165–173. https://doi.org/10.1038/nbt.2107.
[158] Atchison L, Zhang H, Cao K, Truskey GA. A Tissue Engineered Blood Vessel Model of Hutchinson-Gilford Progeria Syndrome Using Human iPSC-derived Smooth Muscle Cells. Scientific Reports. 2017; 7: 8168. https://doi.org/10.1038/s41598-017-08632-4.
[159] Gui L, Dash BC, Luo J, Qin L, Zhao L, Yamamoto K, *et al*. Implantable tissue-engineered blood vessels from human induced pluripotent stem cells. Biomaterials. 2016; 102: 120–129. https://doi.org/10.1016/j.biomaterials.2016.06.010.
[160] Sundaram S, One J, Siewert J, Teodosescu S, Zhao L, Dimitrievska S, *et al*. Tissue-engineered vascular grafts created from human induced pluripotent stem cells. Stem Cells Translational Medicine. 2014; 3: 1535–1543. https://doi.org/10.5966/sctm.2014-0065.
[161] Goushki MA, Kharat Z, Kehtari M, Sohi AN, Ahvaz HH, Rad I, *et al*. Applications of extraembryonic tissue-derived cells in vascular tissue regeneration. Stem Cell Research & Therapy. 2024; 15: 205. https://doi.org/10.1186/s13287-024-03784-3.
[162] Jouda H, Larrea Murillo L, Wang T. Current Progress in Vascular Engineering and Its Clinical Applications. Cells. 2022; 11: 493. https://doi.org/10.3390/cells11030493.
[163] Dash BC, Jiang Z, Suh C, Qyang Y. Induced pluripotent stem cell-derived vascular smooth muscle cells: methods and application. The Biochemical Journal. 2015; 465: 185–194. https://doi.org/10.1042/BJ20141078.
[164] Ayoubi S, Sheikh SP, Eskildsen TV. Human induced pluripotent stem cell-derived vascular smooth muscle cells: differentiation and therapeutic potential. Cardiovascular Research. 2017; 113: 1282–1293. https://doi.org/10.1093/cvr/cvx125.
[165] Xiao D, Mi X, Wang Q, Chen S, Chen R, Zhao Y, *et al*. Advancements in manufacturing technologies in the small-diameter artificial blood vessels field. Biomedical Materials (Bristol, England). 2025; 20: 10.1088/1748–605X/adca7b. https://doi.org/10.1088/1748-605X/adca7b.
[166] Hu K, Li Y, Ke Z, Yang H, Lu C, Li Y, *et al*. History, progress and future challenges of artificial blood vessels: a narrative review. Biomaterials Translational. 2022; 3: 81–98. https://doi.org/10.12336/biomatertransl.2022.01.008.
[167] Arepally GM, Cines DB. Pathogenesis of heparin-induced thrombocytopenia. Translational Research: the Journal of Laboratory and Clinical Medicine. 2020; 225: 131–140. https://doi.org/10.1016/j.trsl.2020.04.014.
[168] Choi WS, Joung YK, Lee Y, Bae JW, Park HK, Park YH, *et al*. Enhanced Patency and Endothelialization of Small-Caliber Vascular Grafts Fabricated by Coimmobilization of Heparin and Cell-Adhesive Peptides. ACS Applied Materials & Interfaces. 2016; 8: 4336–4346. https://doi.org/10.1021/acsami.5b12052.
[169] Cokić VP, Schechter AN. Effects of nitric oxide on red blood cell development and phenotype. Current Topics in Develop-

mental Biology. 2008; 82: 169–215. https://doi.org/10.1016/S0070-2153(07)00007-5.

[170] Yang D, Li Y, Tan J, Li W, Xu Z, Xu J, *et al*. Biomimetic Antithrombotic Tissue-Engineered Vascular Grafts for Converting Cholesterol and Free Radicals into Nitric Oxide. Advanced Healthcare Materials. 2023; 12: e2300340. https://doi.org/10.1002/adhm.202300340.

[171] Sánchez PF, Brey EM, Briceño JC. Endothelialization mechanisms in vascular grafts. Journal of Tissue Engineering and Regenerative Medicine. 2018; 12: 2164–2178. https://doi.org/10.1002/term.2747.

[172] Zhuang Y, Zhang C, Cheng M, Huang J, Liu Q, Yuan G, *et al*. Challenges and strategies for *in situ* endothelialization and long-term lumen patency of vascular grafts. Bioactive Materials. 2021; 6: 1791–1809. https://doi.org/10.1016/j.bioactmat.2020.11.028.

[173] Jalowiec JM, D'Este M, Bara JJ, Denom J, Menzel U, Alini M, *et al*. An In Vitro Investigation of Platelet-Rich Plasma-Gel as a Cell and Growth Factor Delivery Vehicle for Tissue Engineering. Tissue Engineering. Part C, Methods. 2016; 22: 49–58. https://doi.org/10.1089/ten.TEC.2015.0223.

[174] Amable PR, Carias RBV, Teixeira MVT, da Cruz Pacheco I, Corrêa do Amaral RJF, Granjeiro JM, *et al*. Platelet-rich plasma preparation for regenerative medicine: optimization and quantification of cytokines and growth factors. Stem Cell Research & Therapy. 2013; 4: 67. https://doi.org/10.1186/scrt218.

[175] Li G, Yang T, Liu Y, Su H, Liu W, Fang D, *et al*. The proteins derived from platelet-rich plasma improve the endothelialization and vascularization of small diameter vascular grafts. International Journal of Biological Macromolecules. 2023; 225: 574–587. https://doi.org/10.1016/j.ijbiomac.2022.11.116.

[176] Li J, Zhai D, Lv F, Yu Q, Ma H, Yin J, *et al*. Preparation of copper-containing bioactive glass/eggshell membrane nanocomposites for improving angiogenesis, antibacterial activity and wound healing. Acta Biomaterialia. 2016; 36: 254–266. https://doi.org/10.1016/j.actbio.2016.03.011.

[177] Liu M, Wang R, Liu J, Zhang W, Liu Z, Lou X, *et al*. Incorporation of magnesium oxide nanoparticles into electrospun membranes improves pro-angiogenic activity and promotes diabetic wound healing. Biomaterials Advances. 2022; 133: 112609. https://doi.org/10.1016/j.msec.2021.112609.

[178] Kargozar S, Baino F, Hamzehlou S, Hill RG, Mozafari M. Bioactive Glasses: Sprouting Angiogenesis in Tissue Engineering. Trends in Biotechnology. 2018; 36: 430–444. https://doi.org/10.1016/j.tibtech.2017.12.003.

[179] Ege D, Zheng K, Boccaccini AR. Borate Bioactive Glasses (BBG): Bone Regeneration, Wound Healing Applications, and Future Directions. ACS Applied Bio Materials. 2022; 5: 3608–3622. https://doi.org/10.1021/acsabm.2c00384.

[180] Sundaram MN, Amirthalingam S, Mony U, Varma PK, Jayakumar R. Injectable chitosan-nano bioglass composite hemostatic hydrogel for effective bleeding control. International Journal of Biological Macromolecules. 2019; 129: 936–943. https://doi.org/10.1016/j.ijbiomac.2019.01.220.

[181] Alasvand N, Behnamghader A, Milan PB, Simorgh S, Mobasheri A, Mozafari M. Tissue-engineered small-diameter vascular grafts containing novel copper-doped bioactive glass biomaterials to promote angiogenic activity and endothelial regeneration. Materials Today. Bio. 2023; 20: 100647. https://doi.org/10.1016/j.mtbio.2023.100647.

[182] Durham AL, Speer MY, Scatena M, Giachelli CM, Shanahan CM. Role of smooth muscle cells in vascular calcification: implications in atherosclerosis and arterial stiffness. Cardiovascular Research. 2018; 114: 590–600. https://doi.org/10.1093/cvr/cvy010.

[183] Bennett MR, Sinha S, Owens GK. Vascular Smooth Muscle Cells in Atherosclerosis. Circulation Research. 2016; 118: 692–702. https://doi.org/10.1161/CIRCRESAHA.115.306361.

[184] Wen Y, Li Y, Yang R, Chen Y, Shen Y, Liu Y, *et al*. Biofunctional coatings and drug-coated stents for restenosis therapy. Materials Today. Bio. 2024; 29: 101259. https://doi.org/10.1016/j.mtbio.2024.101259.

[185] Evans BC, Hocking KM, Osgood MJ, Voskresensky I, Dmowska J, Kilchrist KV, *et al*. MK2 inhibitory peptide delivered in nanopolyplexes prevents vascular graft intimal hyperplasia. Science Translational Medicine. 2015; 7: 291ra95. https://doi.org/10.1126/scitranslmed.aaa4549.

[186] Wang Z, Lu Y, Qin K, Wu Y, Tian Y, Wang J, *et al*. Enzyme-functionalized vascular grafts catalyze in-situ release of nitric oxide from exogenous NO prodrug. Journal of Controlled Release: Official Journal of the Controlled Release Society. 2015; 210: 179–188. https://doi.org/10.1016/j.jconrel.2015.05.283.

[187] Xie C, Guo T, Wang W, Li G, Cai Z, Chen S, *et al*. Scaffold Engineering with Flavone-Modified Biomimetic Architecture for Vascular Tissue Engineering Applications. Tissue Engineering and Regenerative Medicine. 2022; 19: 755–767. https://doi.org/10.1007/s13770-022-00448-2.

[188] Lee KW, Gade PS, Dong L, Zhang Z, Aral AM, Gao J, *et al*. A biodegradable synthetic graft for small arteries matches the performance of autologous vein in rat carotid arteries. Biomaterials. 2018; 181: 67–80. https://doi.org/10.1016/j.biomaterials.2018.07.037.

[189] Byrom MJ, Bannon PG, White GH, Ng MKC. Animal models for the assessment of novel vascular conduits. Journal of Vascular Surgery. 2010; 52: 176–195. https://doi.org/10.1016/j.jvs.2009.10.080.

[190] Yevtushenko P, Kuehne T, Bruening J, Goubergrits L. A Simulation-Based Comparison of Human, Porcine and Ovine Pulmonary Artery Hemodynamics. Evaluating the Suitability of Large Animal Models for Endopulmonary Device Evaluation from a Hemodynamics Point of View. Cardiovascular Engineering and Technology. 2025. https://doi.org/10.1007/s13239-025-00803-z. (online ahead of print)

[191] Ueberrueck T, Tautenhahn J, Meyer L, Kaufmann O, Lippert H, Gastinger I, *et al*. Comparison of the ovine and porcine animal models for biocompatibility testing of vascular prostheses. The Journal of Surgical Research. 2005; 124: 305–311. https://doi.org/10.1016/j.jss.2004.10.021.

[192] Chen C, Lumsden AB, Hanson SR. Local infusion of heparin reduces anastomotic neointimal hyperplasia in aortoiliac expanded polytetrafluoroethylene bypass grafts in baboons. Journal of Vascular Surgery. 2000; 31: 354–363. https://doi.org/10.1016/s0741-5214(00)90165-4.

[193] Feingold HM, Pivacek LE, Melaragno AJ, Valeri CR. Coagulation assays and platelet aggregation patterns in human, baboon, and canine blood. American Journal of Veterinary Research. 1986; 47: 2197–2199.

[194] Trantina-Yates A, Weissenstein C, Human P, Zilla P. Stentless bioprosthetic heart valve research: sheep versus primate model. The Annals of Thoracic Surgery. 2001; 71: S422–S27. https://doi.org/10.1016/s0003-4975(01)02502-4.

[195] Shin'oka T, Matsumura G, Hibino N, Naito Y, Watanabe M, Konuma T, *et al*. Midterm clinical result of tissue-engineered vascular autografts seeded with autologous bone marrow cells. The Journal of Thoracic and Cardiovascular Surgery. 2005; 129: 1330–1338. https://doi.org/10.1016/j.jtcvs.2004.12.047.

[196] Hibino N, McGillicuddy E, Matsumura G, Ichihara Y, Naito Y, Breuer C, *et al*. Late-term results of tissue-engineered vascular grafts in humans. The Journal of Thoracic and Cardiovascular Surgery. 2010; 139: 431–436, 436.e1–2. https://doi.org/10.1016/j.jtcvs.2009.09.057.

[197] Bockeria LA, Svanidze O, Kim A, Shatalov K, Makarenko V,

Cox M, *et al*. Total cavopulmonary connection with a new bioabsorbable vascular graft: First clinical experience. The Journal of Thoracic and Cardiovascular Surgery. 2017; 153: 1542–1550. https://doi.org/10.1016/j.jtcvs.2016.11.071.

[198] Gutowski P, Gage SM, Guziewicz M, Ilzecki M, Kazimierczak A, Kirkton RD, *et al*. Arterial reconstruction with human bioengineered acellular blood vessels in patients with peripheral arterial disease. Journal of Vascular Surgery. 2020; 72: 1247–1258. https://doi.org/10.1016/j.jvs.2019.11.056.

[199] Rodriguez-Soto MA, Suarez Vargas N, Riveros A, Camargo CM, Cruz JC, Sandoval N, *et al*. Failure Analysis of TEVG's I: Overcoming the Initial Stages of Blood Material Interaction and Stabilization of the Immune Response. Cells. 2021; 10: 3140. https://doi.org/10.3390/cells10113140.

[200] Hedin U. Long-term results of PTFE grafts. The Journal of Vascular Access. 2015; 16 Suppl 9: S87–S92. https://doi.org/10.5301/jva.5000350.

[201] Horbett TA. Fibrinogen adsorption to biomaterials. Journal of Biomedical Materials Research. Part a. 2018; 106: 2777–2788. https://doi.org/10.1002/jbm.a.36460.

[202] Herten M, Bisdas T, Knaack D, Becker K, Osada N, Torsello GB, *et al*. Rapid *in Vitro* Quantification of *S. aureus* Biofilms on Vascular Graft Surfaces. Frontiers in Microbiology. 2017; 8: 2333. https://doi.org/10.3389/fmicb.2017.02333.

[203] Rodriguez-Soto MA, Riveros A, Suarez Vargas N, Garcia-Brand AJ, Camargo CM, Cruz JC, *et al*. Failure Analysis of TEVG's II: Late Failure and Entering the Regeneration Pathway. Cells. 2022; 11: 939. https://doi.org/10.3390/cells11060939.

[204] Camasão DB, Mantovani D. The mechanical characterization of blood vessels and their substitutes in the continuous quest for physiological-relevant performances. A critical review. Materials Today. Bio. 2021; 10: 100106. https://doi.org/10.1016/j.mtbio.2021.100106.

[205] Bouchet M, Gauthier M, Maire M, Ajji A, Lerouge S. Towards compliant small-diameter vascular grafts: Predictive analytical model and experiments. Materials Science & Engineering. C, Materials for Biological Applications. 2019; 100: 715–723. https://doi.org/10.1016/j.msec.2019.03.023.

[206] Jeong Y, Yao Y, Yim EKF. Current understanding of intimal hyperplasia and effect of compliance in synthetic small diameter vascular grafts. Biomaterials Science. 2020; 8: 4383–4395. https://doi.org/10.1039/d0bm00226g.

[207] Post A, Diaz-Rodriguez P, Balouch B, Paulsen S, Wu S, Miller J, *et al*. Elucidating the role of graft compliance mismatch on intimal hyperplasia using an ex vivo organ culture model. Acta Biomaterialia. 2019; 89: 84–94. https://doi.org/10.1016/j.actbio.2019.03.025.

[208] Pashneh-Tala S, MacNeil S, Claeyssens F. The Tissue-Engineered Vascular Graft-Past, Present, and Future. Tissue Engineering. Part B, Reviews. 2016; 22: 68–100. https://doi.org/10.1089/ten.teb.2015.0100.

[209] Wilcox EC, Edelman ER. Substratum interactions determine immune response to allogeneic transplants of endothelial cells. Frontiers in Immunology. 2022; 13: 946794. https://doi.org/10.3389/fimmu.2022.946794.

[210] Park J, Riaz M, Qin L, Zhang W, Batty L, Fooladi S, *et al*. Fully biologic endothelialized-tissue-engineered vascular conduits provide antithrombotic function and graft patency. Cell Stem Cell. 2025; 32: 137–143.e6. https://doi.org/10.1016/j.stem.2024.11.006.

[211] Ramachandran A. Revolutionizing Tissue Engineering AI-Driven Innovations in Scaffold Design, Regenerative Medicine, and Industrial Scale Manufacturing. 2025. Available at: https://www.researchgate.net/publication/388527817_Revolutionizing_Tissue_Engineering_AI-Driven_Innovations_in_Scaffold_Design_Regenerative_Medicine_and_Industrial_Scale_Manufacturing (Accessed: 16 September 2025).

[212] Danilov VV, Laptev VV, Klyshnikov KY, Stepanov AD, Bogdanov LA, Antonova LV, *et al*. ML-driven segmentation of microvascular features during histological examination of tissue-engineered vascular grafts. Frontiers in Bioengineering and Biotechnology. 2024; 12: 1411680. https://doi.org/10.3389/fbioe.2024.1411680.

[213] Rana D, Rangel VR, Padmanaban P, Trikalitis VD, Kandar A, Kim HW, *et al*. Bioprinting of Aptamer-Based Programmable Bioinks to Modulate Multiscale Microvascular Morphogenesis in 4D. Advanced Healthcare Materials. 2025; 14: e2402302. https://doi.org/10.1002/adhm.202402302.

[214] Baruch ES, Cohen R, Silberman E, Namestnikov M, Cabilly I, Shapira A, *et al*. One-Step Coordinated Multi-Kinetic 4D Printing of Human Vascularized Cardiac Tissues with Selective Fast-Shrinking Capillaries. Advanced Materials (Deerfield Beach, Fla.). 2025; e12879. https://doi.org/10.1002/adma.202512879.