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Research Article

Scaffold and Cell-Based Tissue Engineering Approaches as Alternative Therapy for Blood Vessel Disease

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Abstract

Cardiovascular diseases remain the leading cause of mortality worldwide. Although new therapies are actively being developed and used for cardiovascular pathologies, these attempts have not significantly decreased mortality rates. Regenerative medicine has made enormous progress and set promising approaches over the past half-century. However, since autologous (donor-derived) vascular grafts are lacking, an alternative prosthesis must be constructed for cardiovascular disease patients. In vascular tissue manufacturing and regenerative medicine, scientists seek to improve this significant clinical challenge using bio-fabrication techniques combining additive manufacturing, biomaterials science, and advanced cellular biology. In the last few decades, many improvements and changes in various approaches have helped develop bioengineered concepts that reflect native blood vessels' structure and function. However, numerous challenges must be overcome to clinically translate the next generation of tissue-engineered vascular transplants. This review provides an update on the cell sources, scaffold essential for cardiovascular tissue engineering, and tissue engineering approaches as prospective options for curative therapy for blood vessel disease.

Keywords: Scaffold; Cell Therapy; Tissue-Engineered Vascular Graft; Clinical Translation of Tissue-Engineered Vascular Grafts.

Statement of Significance

Synthetic grafts fail up to 75% within three years of implantation. This failure rate indicates that the current clinical strategies for managing cardiovascular disease utilizing small-diameter vessel-bypassing systems need improvement. In vascular tissue engineering and regenerative medicine, researchers intend to improve this critical clinical issue using bio-fabrication techniques that combine additive manufacturing and biomaterials science. However, several aspects of tissue-engineered vascular grafts (TEVGs) must be improved, such as cell availability, biocompatibility, mechanical properties, the safety of supplemented materials, and growth potential. Although recent advances in TEVG fabrication are promising, more research is needed to generate optimal TEVGs.

Introduction

According to the American Heart Association, cardiovascular disease (CVD) reported 18.6 million deaths in 2019, steadily rising as a foremost global reason for morbidity and mortality [1]. Yet, thousands die yearly due to vascular diseases, congestive heart failure, stroke, myocardial infarction, and valvular heart disease. Thus far, in the United States, millions of Americans live with coronary heart disease and vascular diseases necessitating surgical involvement via settling vascular grafts to repair vascular damage. CVD increases mortality and is predicted to increase to 23.3 million annually worldwide by 2030 [2-3]. The number of vascular bypass surgeries in the United States has increased the demand for vascular grafts, which has broadened its application prospects.

There are three types of vascular grafts: allogeneic, autologous, and synthetic. Autologous vascular grafts, such as the internal thoracic artery and saphenous vein, are the best choices for coronary artery bypass grafting patients because allogeneic vascular grafts often lead to immune rejection [4-5]. When patients do not have suitable blood vessels for transplantation, synthetic vascular grafts made of polylactic acid, polyglycolic acid, and expanded polytetrafluoroethylene can be used as alternatives to autologous vessels [6]. However, synthetic vascular grafts have biocompatibility and vascular compliance limitations due to their cytotoxicity and degradation rate [7].

Consequently, tissue engineering has emerged as a field capable of producing different vascular grafts to overcome these limitations. Thus, tissue engineering has gained interest in biomedical research, particularly in the cardiovascular field, to prepare vascular grafts with good biological activity and biocompatibility [8]. Tissue-engineered vascular grafts (TEVGs) are classified into three categories based on their diameter: large-diameter (>8 mm), medium-diameter (6–8 mm), and small-diameter (<6 mm) vascular grafts. Synthetic materials have successfully produced tissue-engineered vascular grafts (TEVGs) with large or medium diameters. However, in small-diameter vascular grafts, platelet attachment and thrombus formation increase due to a mismatch in mechanical properties between the graft and natural blood vessels. This leads to excessive proliferation of smooth muscle cells and new intima hyperplasia [7].

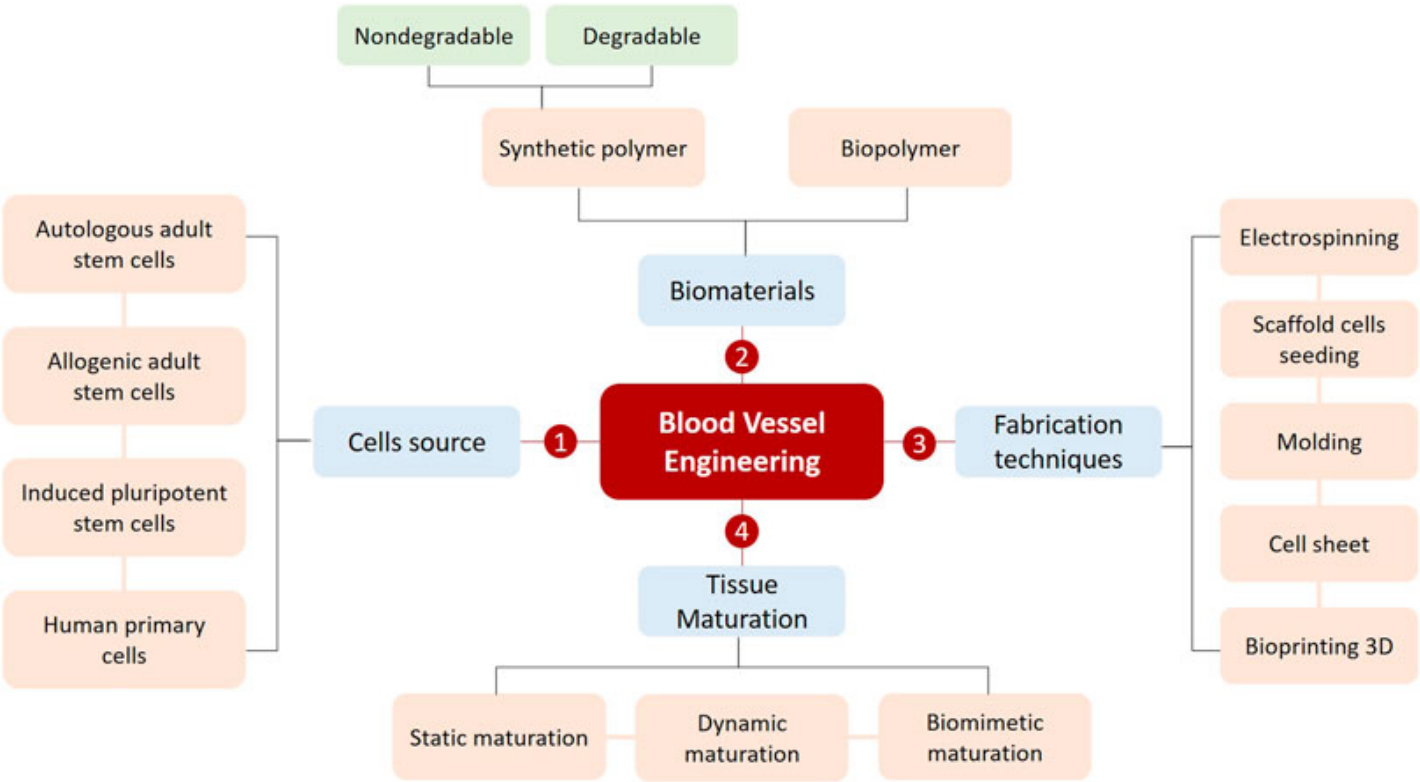

Figure 1: The basic strategies for productively designing a blood vessel. Reprinted from ref. [9].

Accordingly, modern tissue-engineering methods, such as the decellularization procedure and 3D additive bioprinting methods, have been proposed to increase the availability of bioengineered vascular grafts to manage CVD better. Vascular grafting has many applications in CVD. For example, many experiments have focused on the scaffold and cell base for treating CVDs (Figure 1). Specifically, small-diameter vascular grafts are in high demand for coronary artery bypass grafting, often necessary due to coronary artery obstruction. In addition, recent advancements in engineering cardiac tissue have improved techniques such as stem cell isolation and culture in bioreactors [10]. The primary principle is to produce living cells through cellularized grafts that can grow and replace damaged cells using a combination of cells, scaffolds, and growth factors [11].

Structures of Blood Vessels

The arterial wall is composed of three distinct layers, i.e., the tunica, a membranous covering of a separate layer of the wall of a blood vessel (Figure 2).

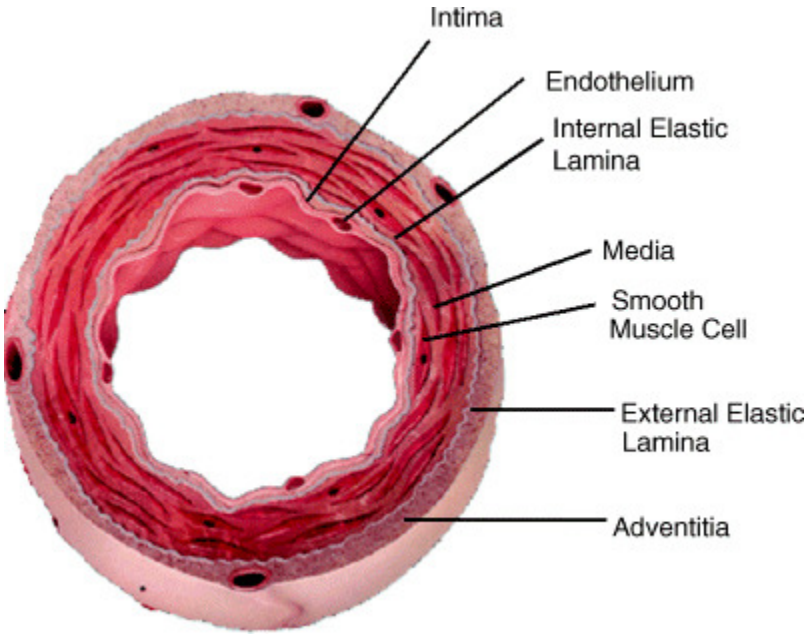

Figure 2: The point of view of the arterial wall comprises three main layers of the Tunica: intima, media, and adventitia. A single layer of endothelial cells covers the lumen, while smooth muscle cells and fibroblast cells comprise the outer layers. Reprinted from ref [12].

Tunica Intima

The tunica intima is the innermost, thinnest layer and comprises endothelial cells (ECs) maintained by the subepithelial layer of connective tissue and supportive cells. ECs regulate biological processes, such as blood flow regulation and extracellular matrix (ECM) component synthesis. In addition, ECs allow material in and out of the bloodstream and white blood cells. A thin membrane of elastic fibers parallel to the blood vessels encloses the Tunica Intima [13].

Tunica Media

The tunica media includes smooth muscle, elastin fibers, and connective tissue organized in concentric layers. The smooth muscle function has contractile phenotypes that open and close blood vessels. In addition, it works independently and involuntarily. The thicker area, essential for maintaining blood pressure, consists of more elastic fibers in the arteries than in the veins [14].

Tunica Adventitia

The tunica adventitia is the outer layer of blood vessels that comprises connective tissue and fibroblasts embedded in a loose collagen matrix. Additionally, most collagen types are type I and II, providing blood vessel strength or resistance to dilation due to excessive blood pressure [13].

Scaffold Types and Approaches

Many researchers have been dedicated to scaffold-guided vascular reconstruction, which means understanding how to use "scaffolds" to help rebuild blood vessel tissue. Scaffolds are 3D structures that help support attaching cells and growing tissue. The ideal scaffold should break down naturally after the tissue has formed, so there is no need to remove it, and the breakdown products should not be harmful to the cells. Scaffolds can be made from either synthetic or natural materials [15]. Scaffolds for tissue engineering should be non-immunogenic, non-toxic, and flexible, with a good surface for cell attachment and proliferation and 3D structures for extracellular matrix (ECM). Tissue-engineered vascular grafts (TEVGs) can be fabricated using different methods, including biodegradable polymer-based, decellularized ECM-based, cell sheet-based, and 3D bioprinting approaches. The first two methods are scaffold-guided, while the cell sheet-based approach is self-assembled without synthesized materials. 3D bioprinting, including the spheroid-based technique, is a promising approach for TEVG fabrication with diverse potential applications [16-18]. Table 1 shows the several types of scaffolds [19].

Scaffold	Sources	Advantages	Disadvantages
Hydrogels	Natural, synthetic and mixed	In-situ injection of cells Eliminates immune response	Vulnerable to breakage before tissue formation
Decullarised	Natural	Vascularization Reduced immune response	Decreased rate of cell division
Prefabricated	Natural and synthetic	Easy to engineer and manipulate 3D forms	Incompatibility with cellular application Optimal porosity should be maintained
Cell sheets	Natural	Easy to scale up in 3D form Easy to manipulate Conduction of action potential	Fragile and difficult to handle Limited thickness

Table 1: Types of Scaffolds.

Biodegradable Polymers

TEVGs are engineered grafts used for surgical procedures and must withstand the blood pressure in the body. Biodegradable polymers, such as polyglycolic acid (PGA), polylactic acid (PLA), and poly(ε-caprolactone) (PCL), are commonly used as temporary scaffolds to support seeded vascular cells in the fabrication of tissue-engineered vascular grafts (TEVGs) [20]. These materials degrade over time and provide mechanical support until the implanted cells secrete and organize their own extracellular matrices (ECMs). The degradation rate of the polymer-based scaffolds can be manipulated by changing their size, surface area, and composition, which affects their mechanical properties and ability to withstand blood pressure. However, an imbalance between material degradation and neo-tissue formation can lead to mechanical mismatch and subsequent graft failure [21]. The process of creating implantable TEVGs can take weeks or months, making them more appropriate for planned or elective surgeries rather than emergency situations. However, decellularized materials may be a more readily available option for emergency situations, as they can be cryopreserved until needed.

In 1988, researchers seeded rat vascular smooth muscle cells (SMCs) on biodegradable polyurethane-based scaffolds and implanted them in the rat aorta. After two days, multilayered SMCs were observed, which had become thicker by one week after implantation. In addition, the new tissues showed endothelial cell-like cells on the luminal side, indicating the successful integration of the seeded cells and the formation of new tissue [22].

Researchers have explored using biodegradable polymer-based tissue-engineered vascular grafts (TEVGs) for patient implantation. One such approach involves a bilayered scaffold developed by Vorp's research group in 2009, which consists of a highly porous inner layer for cell integration and growth and an external reinforcing fibrous layer [23]. Human skeletal muscle-

derived stem cells were seeded on the inner surface of the scaffold using a rotational vacuum seeding system, which may have the potential for use in regenerative medicine [24].

Hoerstrup's research group implanted biodegradable polymer-based tissue-engineered vascular grafts seeded with autologous myofibroblasts and endothelial cells (ECs) into growing lambs, which showed potential for growth and remodelling. The TEVGs were incubated in a pulsatile bioreactor for 21 days before implantation as main pulmonary artery replacements and followed up for two years after implantation. The implanted grafts showed increased diameter and length, and imaging tests revealed no evidence of complications [25-26].

Electrospinning is a technique that can create a nanofibrous scaffold – a fragile and lightweight structure [27-29]. This kind of scaffold interacts with cells differently from standard synthetic grafts, with beneficial uses in medical applications [30]. The electrospinning technique exposes the polymers to a high electric current, causing those polymers to form fibers, eventually creating a scaffold. Changing various microstructural parameters, such as the fiber size, porosity, and alignment, can control the scaffolds' mechanical properties. Additionally, manipulating the scaffolds' mechanical properties can regulate cell survival, migration, and proliferation when forming tissue. For example, Ju et al. (2010) used a particular technique to produce a PCL/collagen bilayer scaffold with an outer layer that allowed for easier smooth muscle cell infiltration and an inner layer for easier endothelial cell attachment (Figure 3A–G) [31].

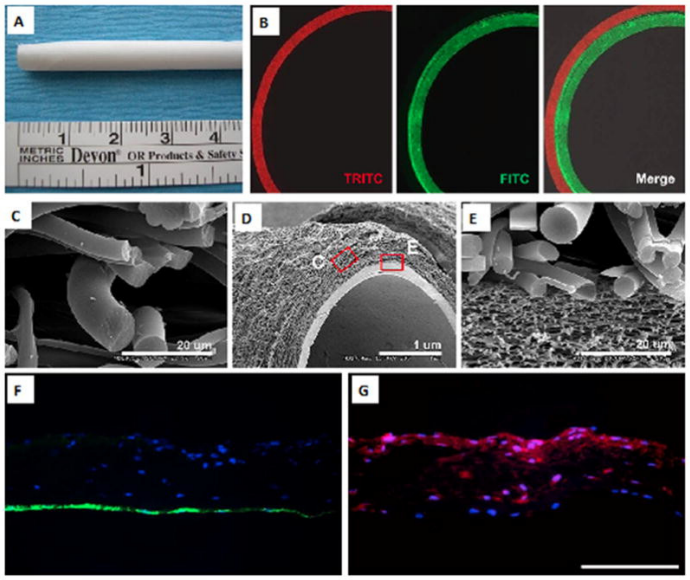

Figure 3: An electrospun scaffold. (A) scaffold; (B) fluorescent pictures of the scaffold; (C–E) scanning electron microscope revealed layers of the scaffold, (C) external layer, (D) bilayer structure, and (E) both the inner and outer layers; (F–G) fluorescent images of endothelial cell (EC) and smooth muscle cells (SMC) seeded scaffold (F) EC seeded inner layer (G) SMC seeded outer layer. Reprinted from ref. [31].

Electrospinning can use either degradable (e.g., PLA, PGA, and polyurethane/silk fibroin) or natural materials to create scaffolds and tubular conduits, such as vascular grafts [32]. For example, combining poly (lactic-co-glycolic acid) with collagen type I and elastin can improve scaffolds' mechanical properties for creating electrospun blood vessels [33-34]. Alternatively, naturally derived materials like collagen, gelatin, and fibronectin can enhance cellular functions like adhesion, growth, and differentiation by providing more Arginylglycylaspartic acid binding sites [31]. For example, scientists create artificial blood vessels using electrospun tubular scaffolds with controlled release of vascular endothelial growth factor [35-36]. This approach can improve cell adhesion and proliferation in the vessel wall, leading to better anti-thrombogenic properties and avoiding common problems post-implantation [37]. However, using native tissue as a scaffold is sometimes very limiting because getting the right size, caliber, and length is challenging. Therefore, scientists developed a synthetic biomaterial with a naturally derived substance to make it more consistent with fabricating [38].

Decellularized Scaffolds

Decellularization is a process used to treat tissues, using physical, chemical, and enzymatic methods to remove the cells while keeping the tissue architecture intact [39]. The decellularized vascular matrix is the non-cellular part of the blood vessel wall, which is more than a supporting structure, but a vital microenvironment for cell life. These sources are constantly being updated through experimental techniques. Decellularized ECM-based approach involves using grafts from different animal and human sources that have been stripped of their cells to reduce the risk of rejection. It consists of three main components: structural proteins (collagen and elastin), linked/adhesive proteins (integrin, fibronectin, and laminin), and invisible gelatinous structures (proteoglycan and hyaluronic acid). The content of these components can vary depending on the developmental stages of blood vessels and their functions. The first decellularized vascular grafts were derived from bovine blood vessels and ureters. Since then, tissue engineering technology has evolved, producing vascular grafts such as Artecraft®, Solcograft®, and ProCol® using these decellularized materials [40]. Scientists showed that these types of grafts are effective for haemodialysis access with similar success rates as traditional ePTFE grafts but with lower complication rates such as infection and thrombosis. Chemla and Morsy conducted a study on SynerGraft® for hemodialysis grafts. They found that decellularized grafts had similar success rates to conventional prosthetic grafts regarding patency and freedom

from infection after 12 months [41].

In 1966, Rosenberg et al. tried decellularization with bovine carotid artery but faced occlusion of vascular graft postoperatively [42]. In 1995, Sandusky et al. implanted porcine small intestine submucosa (SIS) as a carotid artery interposition graft in dogs with equal patency rate in both the vascular graft and autogenous saphenous vein [43].

In 2003, Dahl and colleagues evaluated three different methods to remove cells from pig carotid arteries. The methods utilized were as follows: in Treatment A, which involves submerging vessels in a nonionic detergent solution with a chelator to inhibit enzymes and deoxynuclease for 24 hours; in Treatment B, involves submerging vessels in a hypotonic solution for 11 hours followed by transfer to a hypertonic solution for 11 hours; in Treatment C, vessels were submerged in a zwitterionic detergent solution. Among these methods, they found that treatment C was the most effective in eliminating cell nuclei while maintaining mechanical properties similar to native vessels [44].

In 2011, Dahl et al. created tissue-engineered vascular grafts (TEVGs) using a bio-degradable scaffold-based decellularization approach. They seeded the scaffolds with cells from an aorta and allowed them to grow for several weeks in a machine that stretched them. Then they removed all the cells so that only the scaffold remained, which had high-pressure resistance even after being stored at low temperatures for up to one year. Also, the resulting TEVGs were seeded with autologous ECs (endothelial cells) shortly before implantation into baboons as arteriovenous conduits. These implanted TEVGs maintained 88% patency without aneurysmal formation for up to six months in the baboon models.[45].

Daugs et al. used a decellularization technique successfully applied to bovine carotid arteries using different chemical solutions. The histological analysis showed good preservation of the extracellular matrix structure, and mechanical tests proved that the decellularized arteries have appropriate biomechanical properties [46]. The decellularized vascular matrix has unique advantages for small-diameter tissue-engineered vascular grafts, including complete retention of the extracellular matrix, superior biocompatibility, and non-immunogenicity. These advantages could replace the patient's vessels in coronary artery bypass grafting.

In a clinical trial, decellularized TEVGs were seeded with autologous ECs and implanted as arteriovenous dialysis shunts in 60 patients with end-stage renal disease. The primary patency was 28% at 12 months after implantation, and small graft segments obtained from eight patients showed luminal endothelialisation and repopulation of vascular SMCs in the implanted graft walls. Two additional phases 3 clinical trials comparing these TEVGs to ePTFE and arteriovenous fistulas are currently ongoing [47].

Natural Scaffolds

In the field of bioengineering, collagen is a material that is often used in tissue engineering. Collagen is the main structural protein in blood vessels and is produced by cells as precursor procollagens. Procollagens are turned into collagens using procollagen proteinases, forming collagen fibers [48]. Collagen is the main component of the extracellular matrix (ECM), which plays a role in signaling and maintaining blood pressure and smooth muscle cell function. It also promotes cell adhesion and proliferation and has low antigenicity, making it biocompatible [49-50]. When using collagen in TEVGs, it is essential to consider how platelets and coagulation proteins can attach to the integrin binding sites, leading to thrombus formation [51]. To address this issue, researchers have used a collagen-rich construct derived from small intestine submucosa and type I bovine collagen that was cross-linked with 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride and treated with heparin-benzalkonium chloride complex to reduce its tendency for thrombosis [52]. Researchers suggest that using collagens in tissue-engineered blood vessels (TEVGs) makes them stronger and helps attract endothelial cells, but it can also make the TEVG more likely to cause blood clots. Therefore, controlling this risk is essential before implanting the TEVG [53].

Elastin is essential for regulating the thickness of blood vessel walls by preventing excessive growth of smooth muscle cells (SMCs). Mutations in the elastin gene can cause SMCs to grow too much, leading to blockages in arteries. Elastin also affects cell functions such as adhesion and chemotaxis [54]. Elastin also contributes to ECM signalling and helps maintain elasticity and stiffness. Elastin is a material used in the body to maintain the elasticity of blood vessels, allowing blood pressure to withstand. It does this by having cell adhesion sites and allowing for flexibility. This contributes to the mechanical properties of arteries [55-56].

Silk fibroin is a biocompatible and biodegradable material commonly used in medical applications [57-58]. It is less likely to cause an immune response in humans and can promote tissue growth. Due to its thermal stability can be used in various forms, such as non-woven fabrics, sponges, or coatings. In a study, a bilayer vascular graft with sponge-coated and woven silk fibroin was used to evaluate a common carotid artery bypass in a canine. The sponge layer of the graft was mainly degraded and replaced by fibrous tissue after one year [59].

Chitosan is a material recently studied for use as a tissue-engineered vascular graft due to its antibacterial and high haemostatic effects [60]. However, it has a low molecular weight and degrades rapidly in vitro and in vivo, making it challenging to use as a single material for cardiovascular tissue [61]. Instead, it is

often combined with other materials to facilitate cellular infiltration and vascular formation [62]. Chitosan is a widely used polymer in regenerative and tissue engineering applications due to its excellent biocompatibility and biodegradability. It is particularly useful in skin tissue engineering because of its structural similarity to skin tissue. Cardoso et al. developed chitosan hydrogels containing Nano encapsulated Phenytoin for cutaneous wound healing [63]. Huang et al. developed a type of hydrogel from a combination of Cellulose nanocrystals and Carboxymethyl chitosan that can promote painless and scarless tissue regeneration for burn wound healing. This hydrogel has self-healing abilities and can dissolve easily. The hydrogel's high equilibrium swelling ratio (350%) is due to the dialdehyde-modified cellulose nanocrystal [64].

Hydrogels Scaffolds

Hydrogels are a scaffold used in cardiac tissue engineering [65]. They capture cells within a gel matrix formed by cross-linking water-soluble polymers, which can be natural or synthetic materials. Anchoring materials like RGD (arginine–glycine–aspartic acid) peptides help the cells adhere to the scaffold and multiply. As cells grow, scaffolds lose water and become compressed. Initially used for cell multiplication outside the body, hydrogels can now be injected into patients to deliver cells directly where needed [66]. Injectable hydrogels are a type of material that can be delivered to the body using catheters. They are made by mixing liquid hydrogels and do not require surgery or drugs for delivery, making them an attractive option in tissue engineering [67]. Some types of hydrogels, like chitosan and alginate-based ones, show desirable biocompatibility properties, making them precisely useful for tissue engineering purposes [68-69]. Hydrogels can be used in tissue engineering as scaffolds that mimic natural tissues. They provide bulk and mechanical structures for cells to adhere to or suspend within. Incorporating appropriate peptide moieties, such as RGD adhesion peptides, can significantly increase cellular attachment and improve cellular migration, proliferation, growth, and organization in tissue regeneration applications. Many different types of cells have been shown to bind favourably to these modified hydrogel scaffolds, including endothelial cells (ECs), fibroblasts, and smooth muscle cells [70-71]. Hydrogels have become popular as scaffold materials because they are like natural tissues and provide a good environment for cell growth. Scientists have found ways to control the shape, size, and other properties of hydrogel scaffolds so they can be used more effectively in tissue engineering applications, like creating blood vessels or complex tissues made up of multiple types of cells. Hydrogels have properties that make them suitable for use as supporting matrices in cardiac tissue engineering because they are soft, viscoelastic, and like natural tissues. Hydrogels are used to support and deliver cells into damaged heart tissue. They help maintain cell survival, functioning, and restore the wall stress of the heart [72-73]. Scientists have recently developed many types of hydrogels to help repair damaged heart tissue. For example, a group of researchers created an injectable gel made from pig heart cells that helped support the growth and survival of several types of heart cells in rats. Another study involved implanting hollow tubes filled with immature heart cells into adult rats' arteries. These studies are promising but need further testing on hearts affected by myocardial infarction [73].

Wang et al. developed a hydrogel made of PEG derivative and a-cyclodextrin to encapsulate bone marrow MSCs. At the same time, Walker et al. implanted PET mesh-reinforced PHEMA hydrogel into the canine epicardium without significant fibrosis or thickening for 12 months after implantation. However, trace calcification was observed, raising concerns about biocompatibility over time [74-76].

Elangwe et al. mentioned that hydrogels synthesized from natural polymers, such as pullulan, have high-water retention capacity and are promising candidates for wound dressings due to their ability to provide a moist environment and accelerate wound healing. Pullulan is a polysaccharide that has gained attention in the pharmaceutical and biomedical fields due to its unique physical and chemical properties. It is derived from Aureobasidium pullulans, a polymorphic fungus, and has potential applications in wound dressing and tissue engineering [77].

The use of hydrogel scaffolds for tissue engineering still faces significant challenges. Some of these include poor cell penetration and irregular cell seeding, difficulties in engineering complex tissues with multiple cell types, the limited mechanical properties of hydrogels which restrict their application to soft tissues only, and a lack of microvasculature leading to loss of function and viability due to insufficient nutrient transportation.

Scaffolds Techniques for Tissue-Engineered Vascular Grafts

Tissue-engineered vascular grafts (TEVGs) are being developed as a potential solution for vascular surgery. Different approaches have been used to construct TEVGs, including scaffold-based vascular grafts made of synthetic, natural, or hybrid materials or self-assembled vascular grafts. Ideal scaffolds for tissue engineering should be nonimmunogenic, nontoxic, and flexible with enough surface for cell adhesion and proliferation, adequate 3D structure/space for ECM regeneration, and proper degradation rate for tissue regeneration, and should also provide biological clues to guide cell differentiation. The scaffold-based method is a common approach used in tissue-engineered vascular grafts (TEVGs) for clinical use (Figure 4).

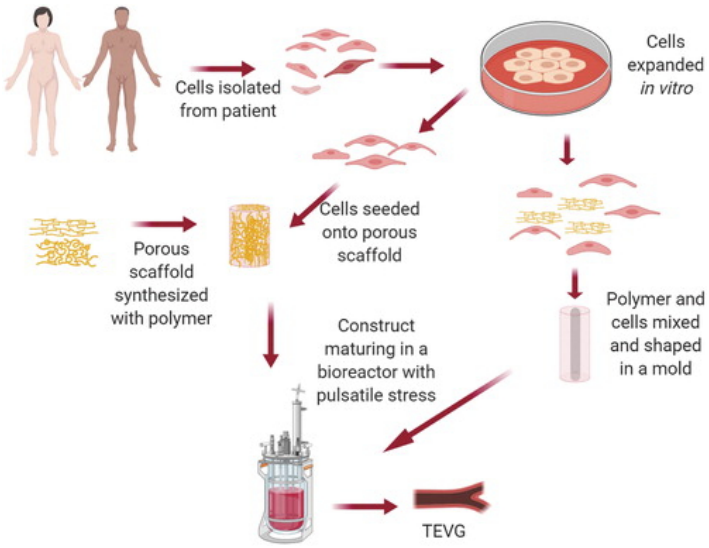

Figure 4: Developing scaffold-based TEVG. Split the patients' tissues and specific types of cells and culture in vitro. Then, seed cells onto synthetic or natural polymer to shape a tubular mold. Reprinted from ref. [78].

Cell Sources for Tissue-Engineered Vascular Grafts (TEVGs)

Blood vessels are composed of different layers that perform specific functions, primarily elasticity and anti-inflammatory/anti-thrombogenic roles. Smooth muscle cells (SMCs) and endothelial cells (ECs) are the critical components of these layers, respectively, while fibroblasts make up the outer layer that anchors the vessel to surrounding tissue [79]. Therefore, in designing and creating TEVGs, considering the role of these various cell types and their origin will avoid graft rejection in implantation [79]. Although autologous cells are the ideal approach to creating vascular grafts, it is not always possible in patients with widespread arterial disease. Additionally, adult cells have limited ability to grow and regenerate. Therefore, researchers are exploring using mesenchymal stem cells (MSCs) and induced pluripotent stem cells (iPSCs) as sources of cells for TEVGs [80]. During the past decade, considerable interest has been directed toward using stem cells in TEVGs, because stem cells and endothelial progenitor cells (EPCs) [81-82] can differentiate into vascular lineages, and the outcome can restore vascular systems.

Endothelial cells (ECs)

Researchers have shown that endothelial cells play a crucial role in regulating vascular tone and blood coagulation by producing nitric oxide in response to blood flow-induced shear stress. In addition, physiological pulsatile shear stress is important in fabricating EC-seeded tissue-engineered vascular grafts (TEVGs) for improved graft patency. When TEVGs contain multiple layers of ECs, they are less likely to experience these complications, enhancing their success as a graft [83]. In addition, ECs can regulate various significant physiological processes. For example, ECs can sense blood flow-induced shear stress, which stimulates them to produce nitric oxide and regulate vascular tone and blood coagulation. ECs can also induce pro-inflammatory or anti-inflammatory responses depending on whether or not the blood flow is disturbed [84]. In most studies, the cells used are sources of ECs are embryonic stem cells, human umbilical vein, microvascular ECs, human Dermal, and endothelial colony-forming cells (Figure 5).

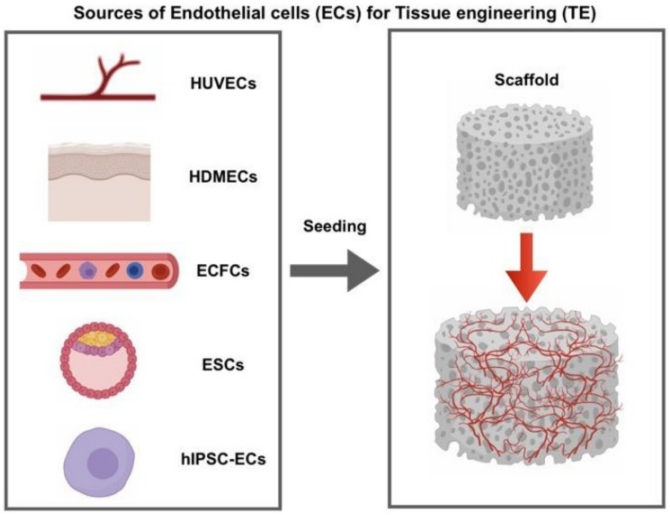

Figure 5: The Summary of endothelial cell bases utilized in the scaffold-based tissue engineering method. Reprinted from ref. [85].

Consequently, due to countless restrictions of ECs, the alteration has been concerned with other cell bases such as pluripotent stem cells, EPCs, and MSCs [79-80, 86-87]. These cells expand quickly in vitro environments with determined angiogenic assets and are excellent resources for medical purposes. Furthermore, cell-based therapy for vascular regeneration is promising since most cells significantly influence the process of vascular regeneration and induce vessel-like network formation in the ischemic tissues.

Pluripotent Stem Cells

Pluripotent stem cells (PSCs) can replicate and grow indefinitely, differentiating into the kinds of cells found in all three layers of an embryo. This transformation makes these cells attractive for medically treating various diseases and injuries. Two types of PSCs are found in humans: embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs). While both

can differentiate into vascular cells, iPSC-derived endothelial cells (iPSC-ECs) have shown a different capacity to form capillaries than human umbilical vein endothelial cells (HUVECs) [88]. Induced pluripotent stem cells (iPSCs) are a promising source for generating neo tissues, including vascular grafts, due to their ability to differentiate into specific cell types. Unlike embryonic stem cells, iPSCs are not subject to ethical constraints and can be generated from a patient's own cells, reducing the risk of immune rejection. However, to use iPSCs in vivo, they must be induced to differentiate into specific lineages, such as smooth muscle cells (SMCs) and endothelial cells (ECs), to avoid the formation of teratomas [86, 89].

Luo and colleagues (2020) created artificial blood vessels using vascular SMCs derived from human iPSCs [86]. The cells were first differentiated into vascular SMCs, seeded onto a scaffold, and incubated to form the TEVGs. Next, human-induced pluripotent stem cells were turned into vascular SMCs using an embryoid body-based approach that takes 26 days to obtain mature vascular SMCs [86]. Pluripotent stem cells allow researchers to create models of human heart development and diseases in vitro, providing a foundation for heart disease treatment utilizing a patient's cardiac cells. However, directing cell differentiation into desired cell types requires understanding the stages of cardiovascular development, which research in model organisms can inform. Even when researchers use specific methods to turn stem cells into a particular cell type, it is still challenging to get a pure population. More research must improve these methods to get the desired cell populations [90].

Endothelial Progenitor Cells

EPCs are a promising stem cell resource for vascular regeneration. They are naturally obtained from adult stem cells involving peripheral blood [91], cord blood [92], and bone marrow [93]. However, the debate over these cells' source, isolation, and cellular role remains a prospective issue. Asahara et al. (1997) was the first to use adult stem cells to regenerate blood vessels [94]. They assumed pre-existing blood vessels originating from postnatal neovascularization were exclusively based on fully differentiated ECs. However, Asahara revealed that supposed hematopoietic precursors cells (CD34+, Flk-1+/KDR+) from human adult circulating blood cells might segregate into ECs in vitro and be known as EPCs [91]. Yet, several markers distinguish these cells. However, a powerful argument about the proper sort of EPCs and the specificity of these markers exists [93]. EPCs may also evaluate the possibility of vascular disease [94].

Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) are a promising source for creating tissue-engineered blood vessels because they can regenerate, regulate immune responses, and prevent clotting [95]. MSCs can be obtained from various sources, such as bone marrow or fat tissues [96]. They have a high rate of cell division compared to other adult cells. They can interact with different types of immune cells by reducing inflammation while increasing suppressive cytokines that help control rejection after transplantation [97]. MSCs can prevent blood clotting because of the heparan sulfate proteoglycans on their cell surfaces. They can also recruit endothelial cells through angiogenic factors they secrete. A study by Zhao et al. showed successful implantation of TEVG from MSC sheets in rats, resulting in complete endothelialisation after four weeks [87]. Mesenchymal stem cells (MSCs) can be turned into smooth muscle cells (SMCs) and endothelial cells (ECs). Researchers Gong and Niklason used this process to create tissue-engineered vascular grafts by seeding undifferentiated MSCs onto biodegradable scaffolds, adding TGFβ1 to induce differentiation into SMCs exposing them to pulsatile flow [98]. MSCs can be differentiated into various types of cells, including SMCs and ECs, making them a promising source for creating tissue-engineered vascular grafts (TEVGs) [99]. MSCs are a minor subpopulation of bone marrow [100]. MSCs discovered by Frieden stein et al. adhered to plastic and had a fibroblast-like morphology [101]. Cell-based therapy and bone marrow-derived MSCs have embraced the potential for regenerating neo vessels that sustain blood flows in the ischemic blood vessels [102]. In addition, MSCs are a prospective therapy in regenerative medicine due to their ability to expand and secrete paracrine factors with antigenic effects and are robust in low oxygen circumstances [103]. Using MSCs at the position of limb ischemia improved pain at the ankle-brachial index as a measurement of vascular function [104-105]. Clinical trials using mononuclear cells from bone marrow or peripheral blood have also shown promising effects. Accordingly, alternate beneficial cell types are preferred for treating peripheral artery disease.

MSCs have been extensively researched because they are present in many tissues in the body and can turn into many kinds of cells [106]. In addition, scientists have discovered that when introduced into the body, these cells move to areas of inflammation, produce substances that can reduce inflammation, and the body's immune system does not reject MSCs. Research conducted in vitro has also indicated that these cells can potentially treat problems related to clotting (thrombosis) in implants [107].

Mesenchymal stem cells (MSCs) have the ability to differentiate into smooth muscle cells (SMCs) and endothelial cells (ECs), making them a promising cell source for tissue-engineered vascular grafts (TEVGs). MSCs can be induced to become SMCs or ECs, essential cell types in forming functional blood vessels. The ability of MSCs to differentiate into multiple cell types makes them a valuable tool in developing TEVGs [108].

Cell Sheet Approach

Despite improved techniques, using materials outside the body in scaffold-guided tissue engineering techniques can still interfere with compatibility. Living cells ideally remodel TEVGs based on their surrounding environments. In scaffold-based TEVGs, the breakdown of products of biodegradable materials and the denatured proteins of the decellularized cellular matrix (ECM) may disrupt the remodelling process. Using self-assembled approaches to create TEVGs is advantageous because it allows cells to form connections with each other and build natural networks without using scaffolds [109].

L'Heureux et al. (1998) generated the first cell sheet-based TEVGs without synthetic or external biomaterials [110]. They used human umbilical vein smooth muscle cells (SMCs) and human skin fibroblasts cultured with ascorbic acid for four weeks to enhance collagen synthesis. The subsequent TEVGs produced abundant ECMs. The SMC layers were manually peeled and wrapped around a mandrel to mimic the tunica media, and the constructs were cultured in a bioreactor with pulsatile flow. Fibroblast sheets were manufactured and wrapped around the SMC constructs to mimic the tunica adventitia. These constructs were cultured for an additional seven weeks before human umbilical vein ECs were seeded to the inner side of each construct. Each layer was fused one week after the ECs were seeded, and the entire process took four months from start to implantation [110]. The burst pressure of 2594 ± 501 mmHg was comparable to that of the human saphenous vein. Implantation in the canine femoral artery revealed that the grafts were well-sutured and could withstand blood pressure in vivo. However, the graft patency was 50% seven days after implantation due to clotting.

Endothelial cell (EC) seeding was omitted in the animal study to avoid acute rejection [111]. The inspiration for this strategy came from a medical treatment used on severe burns called epithelial cell sheets [112]. This procedure involves using heat to separate fibroblasts and other cells into thin layers, creating a "sheet" or "cell sheets." These cell sheets are then placed into a tube-shaped scaffold and cultured in a bioreactor. Following the procedure, these artificial blood vessels have high burst pressures, similar proteins to natural tissue, and strong suture strength with functional endothelialisation. In addition, engineered blood vessels have high primary patency and functional flow in a canine model [113]. In another study, researchers took cells from elderly patients with advanced CVD and created TEVGs using a unique technique called self-assembled cell sheets. These TEVGs were evaluated in rats for up to 180 days [110, 114].

Researchers have developed cell sheet engineering to avoid the limitations of tissue reconstruction using biodegradable scaffolds or single-cell suspension injection. Cell sheets prepared at 37°C allow various cells to adhere and proliferate. In addition, scientists found that when the temperature is below 32°C, the cells can detach without using proteolytic enzymes. This approach to constructing cell sheets has been used for various tissue reconstructions, including cardiac patches and periodontal ligaments [115].

The cell sheet must be carefully removed from the surface of its growing container. Removal can be difficult without damaging the sheet by excessive mechanical stress [113]. Fortunately, the sheet can be detached from the surface without external forces. Using a temperature-sensitive chemical material, the surface of the container becomes hydrophobic at a regular temperature, allowing the cells to multiply and form the sheet. When the temperature [116-119] is lowered, the surface of the container becomes hydrophilic and allows the cells to detach from the surface without the risk of tearing or damage [120]. This process enables the removal of the sheet without damaging the intercellular connections. The limitations of this process are an extended culture period and specialized equipment to create a 3-dimensional structure [120].

A faster technique that does not require specialized equipment is a non-adhesive agarose template to form the tissue [121]. This technique outcomes in a cohesive tissue ring formed by the cells settling and aggregating. The mechanical properties could be better than the cell-sheet-based approach. Though the results are promising, this process still takes a long time due to the maturation process in the bioreactor [122]. However, growing the vascular tissue directly in the patient's body can speed up this process.

Self-assembled cell-sheet-based techniques are a promising approach for TEVG. This technique uses a cell sheet composed of a single layer of cells to form a vascular graft. This technique can create a vascular graft that closely mimics the native tissue's structure and function. Additionally, this technique can reduce the risk of transmitting pathogens from the donor to the recipient.

3D Bioprinting

3D printing was invented to create three-dimensional Molds and supports from various materials [17]. 3D bioprinting is a newer technique that utilizes cells as a bio-ink to create 3D structures. Common bio-inks include hydrogels that provide a scaffold for supporting cells and spheroids, which allow cells to form cell-cell junctions and assemble their own ECM. While bio printed TEVGs are not yet available for clinical use, the technology is rapidly improving. This technology holds great promise in recreating the native vascular anatomy of living tissues [18].

3D models are based on cell culture, meaning scientists replicate many natural properties with cell-made structures [123-124]. This approach allows them to study natural cellular

behaviours, morphology, and functions, which cannot be done with traditional 2D cell cultures [125]. For example, spheroids - multicellular structures - will enable scientists to emulate how different cell types interact [124]. However, the bio-inks used to create these structures are currently limited in their ability to replicate the designs of native tissues due to their printability, mechanical properties, and ability to deposit a high density of cells into complex architectures [126-127]. In addition, bioprinting must place materials and cells in specific locations for complex systems, which helps scientists study structures and functions in greater detail. For example, researchers have been working on using 3D bioprinting to create cardiac patches, which are tissue-engineered materials to replace a damaged muscle. They use a layer-by-layer approach involving special "bio-inks" made from biomaterials [126-127] such as alginate, collagen, gelatin, hyaluronic acid, and decellularized ECM scaffolds [128].

Nakayama's research group created implantable bio printed TEVGs without scaffolds using spheroids made up of human umbilical vein ECs (40%), human aortic SMCs (10%), and human dermal fibroblasts (50%) [92]. In addition, they used a needle array to construct the tubular shaped TEVGs. After incubating for four days, the needle array was removed, and the tubular construct was perfused in a bioreactor for an additional four days. The consequent TEVGs were successfully implanted in the abdominal aortas of nude rats, where they maintained patency for five days. In addition, the TEVGs were histologically analyzed and exhibited endothelialisation after implantation [129].

Extrusion-based bioprinting creates anatomically relevant vessels like our circulatory system's veins and arteries. Despite some success, these scaffold-based patches can degenerate quickly. However, more advanced printing technologies such as selective laser sintering, stereolithography [123], digital light processing, and 2-photon polymerization are more suitable for printing smaller vessels, like capillaries [130].

In a clinical trial, researchers used a needle array to generate multicellular spheroids composed of human umbilical vein ECs, human aortic SMCs, and human dermal fibroblasts. After four days of incubation, the needle array was removed, and the tubular construct was perfused with a bioreactor for an additional four days. The resulting tissue-engineered vascular grafts (TEVGs) were successfully implanted in the abdominal aortas of nude rats, where they maintained patency until the end point of the study on postoperative day 5, demonstrating the potential feasibility of 3D bio printed TEVGs [131].

Cell-free Vascular Graft

Cell-based technologies help make tissue-engineered vascular grafts (TEVGs). However, making TEVGs is lengthy and expensive and can be more complicated when working with primary adult cells or stem cells from older individuals with limited expansion potential. To help solve these issues, some researchers have created completely acellular vascular grafts that can be accessed more quickly and replace blood vessels to treat cardiovascular diseases. Of the many approaches, one method uses conjugate heparin [132-134], an anti-thrombogenic agent, onto the luminal surface of the vascular scaffold to prevent blood clotting. Scientists have recently reported developing cell-free grafts implanted successfully in a large, preclinical animal model (sheep carotid artery) [135] and following the animals for six months. Researchers revealed that the conjugate-heparin approach helped the implanted vessels maintain their patency and normal blood flow. Consequently, by the conjugating method, heparin [134] could support its function, and the body can mobilize those necessary cells over time and try to repair themselves.

SMCs are not required for the medial layer of the graft if the appropriate biomaterial is used [136]. Additionally, the properties of the biomaterial (like porosity) [137] become more critical for graft patency and remodelling [138]. Other studies have used a biodegradable elastomer (a type of flexible polymer) to create a new artery in rat models. Instead of using endothelial cells (ECs), other studies used growth factors and antibodies to attract host circulating EPCs [139]. Finally, Zhou et al. used heparin and a vascular endothelial growth factor protein to replace the endothelial lining and successfully implanted it in a canine arterial model [139]. Since free-cell vascular grafts form a functional confluent endothelium, are populated by host smooth muscle cells, and remodel within the host, they overcome many of the issues associated with cells.

Clinical Translation of TEVGs

Clinical trials have employed different methods of producing TEVGs, including using a biodegradable polymer for venous shunts in children with congenital heart disease and small-diameter TEVGs for arteriovenous shunts in adults undergoing haemodialysis. Despite positive outcomes, complications like intimal hyperplasia and thrombosis are still common [140].

Shin'oka and his team (2001) developed the Biodegradable Polymer-Based Approach for Venous Shunt [141]. It involves removing vascular cells from an autologous peripheral vein and planting them on a 50:50 copolymer of PLA and PCL scaffold. The TEVG with autologous vascular cells is then implanted into a low-pressure, high blood flow large-diameter venous system. Although the initial operation was successful, cell expansion required eight weeks. However, in their subsequent clinical trial, no significant complications were observed after 11 years of follow-up except for graft stenosis, where 28% of the patients required balloon angioplasty [142].

Decellularized grafts from animal and human veins may substitute for haemodialysis access. Clinical trials have tested commercially available grafts from different sources, demonstrating similar patency rates as conventional grafts made of ePTFE but with lower rates of complications like infection and thrombosis [41, 143].

A clinical trial involved a Cell Sheet-Based Approach for Arteriovenous Shunt. Researchers took autologous fibroblasts and ECs from the skin and superficial veins of ten patients with end-stage renal disease and generated TEVGs containing three layers [144]. Then, a bioreactor applied a pulsatile strain to the TEVGs. The total generation time they were ranged from six to nine months. Three of the ten patients experienced early graft failure, another was withdrawn due to gastrointestinal bleeding, and one died of unrelated causes. The grafts in the other five patients functioned for 6-20 months, with a primary patency of 78% at one month and 60% at six months after implantation [145].

A new method for creating TEVGs with an organized elastic fiber structure is vital because long-term use of vascular grafts is susceptible to graft stenosis, related to compliance mismatch between implanted grafts and native vessels. The innovative approach involves coating SMCs with fibronectin and gelatin and repeating the process to create a layered elastic fiber structure. In addition, mechanical stimulation, including hydrostatic pressure, is also discussed as an essential factor in TEVG development [145-146].

Clinical Translation of TEVGs in Blood Vessels

Several studies have reported positive mid-term performance of Tissue-Engineered Venous Grafts for up to 10 years [147]. Unlike traditional grafts, Tissue-Engineered Venous Grafts are not exposed to high arterial blood pressure and can have larger pore sizes to facilitate the infiltration of host cells. Researchers have experimented with different materials and structures, such as using an electrospun PGA outer layer on a PLCL sponge, to optimize TEVG design and minimize complications like aneurysm formation or graft stenosis.

In a study by Sugiura et al., early results from human clinical trials of a tissue-engineered venous graft showed favourable outcomes with no aneurysm formation, graft rupture, infection, or calcification. However, seven out of twenty-five patients developed intermediate stenosis, with only one requiring balloon angioplasty. Despite initial success, there was a high possibility of graft stenosis recurring after six months [142]. To investigate the mechanism behind this premature stenosis, Szafron et al. utilized a computational simulation model and speculated that the narrowing observed in clinical studies might be caused by an inflammatory mechanism that eventually resolves on its own [148].

Further investigation was conducted by implanting the tissue-engineered venous graft into a specific animal model, confirming the prediction that TEVG stenosis spontaneously resolves in the mid-term period [149]. These findings suggest that additional angioplasty may not be necessary for patients with primary stenosis, but careful medical monitoring is still crucial. Additionally, computer simulations indicate that modifying the scaffold design, such as the material composition, can reduce mid-term stenosis by minimizing initial inflammation and optimizing the TEVG structure.

The most favourable outcomes in clinical trials were observed for tissue-engineered vascular grafts, particularly in paediatric patients. However, further clinical trials are required to gather more evidence. The ongoing trials, summarized in Table 3 from the ClinicalTrials.gov database in Table 2, are mostly in Phase 1 or 2 and involve a limited number of cases. Additional results from these trials are eagerly anticipated [150].

Study Phase	Target Disease or Situations	Scaffold	Original Estimated Enrollment	Outcome Measurement	Follow Up	Status
1	Single ventricle cardiac anatomy	synthetic polymer	4	Primary: Graft failure requiring intervention Second: Graft growth	Three years	completed
2	Vascular conduits for extracardiac total cavopulmonary connections	synthetic polymer	24	Primary: Safety and tolerability Secondary: Efficacy of TEVG determined by MRI	Two years	recruiting
1	Chronic venous insufficiency	ECM	15	Primary: Thrombosis, infection, surgical complications Secondary: symptoms of target disease, QOL, Graft durability, Flow abnormality, wall degeneration	One year	recruiting
N/A	peripheral arterial disease	Collagen	20	Primary: Graft safety and adverse events Secondary: immunoreaction, graft patency, effect to symptoms a d ankle-brachial index	Two years	Active, not recruiting
1	Hemodialysis access	Collagen	20	Primary: graft patency, intervention, and adverse events Secondary: immunoreaction, patency, and interventions	Six months	completed
N/A	Hemodialysis access	Collagen	40	Primary: Safety, tolerability, and patency rate Secondary:	57 weeks	Active, not recruiting
N/A	Hemodialysis access	synthetic polymer	110	Primary: patency rate, freedom from device-related adverse events Secondary: implantation success rate, patency, interventions, infection	Six months	Recruiting
N/A	Hemodialysis access	synthetic polymer	20	Primary: device-related adverse events, patency Secondary: patency, adverse events	Five years	Active, not recruiting
N/A	Coronary artery bypass graft	synthetic polymer	15	Primary: Procedural success, device-related serious adverse events Secondary: intimal hyperplasia, patency, Major adverse events, mortality	Five years	Enrolling by invitation

Table 2: The current clinical trials of TEVG listed in the "ClinicalTrials.gov"

Promising Clinical Outlook

In this review, we reported the current state of tissue engineering using scaffolds and cell-based approaches in the cardiovascular field. Even though all the disciplines are developing and improving rapidly, they face many challenges.

The field of generating TEVGs is constantly evolving with the introduction of innovative technologies such as iPSCs and 3D bioprinting. In addition, clinical trials are being conducted to advance this field further.

Future endeavours require innovative and improved methods for coupling biodegradation scaffolds with translational innovations to challenge the problematic remodelling of vascular grafts (Figure 6). Promising results await with new material combinations that will degrade but can create native blood vessels properly.

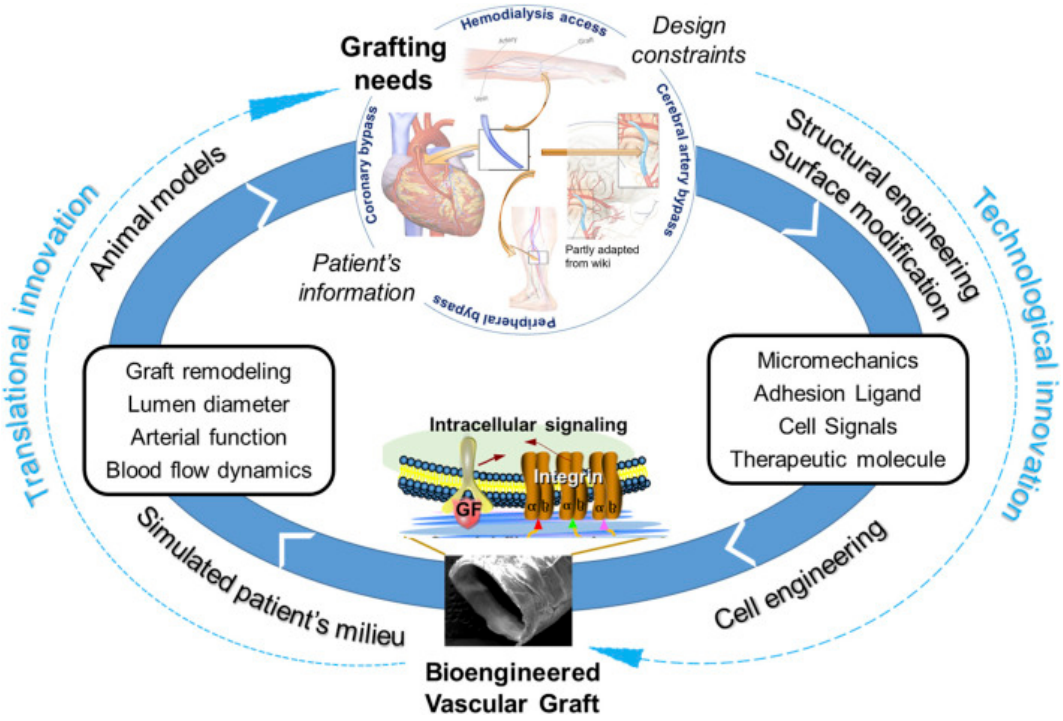

Figure 6: Vascular grafts for clinical applications with translational innovations. Reprinted from ref. [151].

On the other hand, electrospinning is currently the most used manufacturing method, offering standardization and industrialization of the TEVGs. Nonetheless, more studies are still required for manufacturing to reach an ideal fiber thickness and porosity for the grafts since cell migration can be affected while maintaining long-term graft mechanical properties.

Strategies such as decellularized blood vessels offer a suitable alternative for TEVGs since their mechanical properties are remarkably similar to native tissues and are successful in the regeneration process. However, standardization and industrialization are extraordinarily complex and require multiple commercial steps. Nevertheless, further advances in TEVG technology can result in favourable for patients with cardiovascular diseases.

Author Contributions

S.S. wrote - the original manuscript; T.W. - reviewed and edited; S.T.; supervised. All authors have read and agreed to the published version of the manuscript.

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