The role of the innate and adaptive immune system on vascular remodeling

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Chapter 2

Vein graft failure: from pathophysiology to clinical outcomes

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Abstract

Bypass grafting is a standardized technique to circumvent occlusive atherosclerotic lesions. Both CABG surgery and peripheral bypass surgery are performed on a daily basis in hospitals worldwide. Veins are commonly used conduits for surgical revascularization, however, they are associated with a high failure rate. Therefore, preservation of vein graft patency is essential for long term success. With the exception of 'no touch' techniques, and lipid lowering and antiplatelet (aspirin) therapy, no intervention has hitherto unequivocally proven to be clinically effective in preventing vein graft failure. In this Review, we describe both preclinical and clinical studies evaluating the pathophysiology behind vein graft failure and the latest therapeutic options to improve patency for both coronary and peripheral grafts.

Introduction

Occlusive arterial disease is a leading cause of mortality globally owing in part to a continually aging population and shifting demographics. Bypass graft surgery is, besides balloon angioplasty, the most commonly performed revascularization strategy CABG surgery is the standard of care for patients with left main coronary artery disease (CAD) and three-vessel CAD, while peripheral artery bypass grafting (PABG) surgery is performed in patients with late-stage peripheral artery occlusive disease (PAOD)[1-4]. The internal mammary artery is the graft of choice for revascularization of the left anterior descending coronary artery. However, veins (almost exclusively the great saphenous vein) remain the most commonly used conduits owing to availability and length, especially for PABG surgery (Figure 1a)[5].

Adaptation of vein grafts to its new arterial environment is characterized by structural vessel wall remodeling and intimal thickening. The appearance of intimal hyperplasia after vein graft surgery was first described by the Nobel prize-winning surgeon Alexis Carrel more than a century ago[6]. Moderate intimal hyperplasia formation is necessary for proper arterialization and long-term graft patency. However, why some grafts stop remodeling after arterialization while others progress to a clinical stenosis remains unclear. Patency rates of vein grafts diminish from 98% immediately after surgery to <88% within the first month, owing to acute thrombosis. Intimal hyperplasia, atherosclerosis, and rupture of plaques formed in the vein grafts result in an overall patency of 60% after 10 years (Figure 1b and c)[3, 7, 8]. Risk factors associated with vein graft failure (VGF) include diabetes mellitus[9], hypercholesterolaemia[10, 11], chronic kidney disease[12], age, ethnicity, and sex[13-15]. Several factors associated with the graft surgery are also thought to predict VGF, including increased diameter and poor quality of the vein (such as those affected by pre-existing medial hypertrophy and intimal hyperplasia[16, 17]). Additional factors that can predict VGF include the outflow area of the vein, and location of the artery distal to the occlusion where the bypass will be attached (with grafts to the left anterior descending territory performing better), as well as surgical handling of the vein graft during harvesting and when making the anastomosis[18]. VGF can be observed in asymptomatic patients, but can also cause symptoms of ischemia, depending on the extent of the supplied territory, the presence of native artery disease, and the function of other grafts and collaterals.

The most obvious difference between coronary artery grafts and peripheral grafts is the anatomic location. In addition, the length of the grafts (up to 60 cm in peripheral grafts) and the flow and haemodynamic patterns differ between the locations. However, risk factors, patency rates, and the cellular and molecular processes

underlying the pathophysiology of vein grafts are comparable between both graft types. The similarities and differences between CABG surgery and PABG surgery are listed in Table 1. This Review focuses on VGF in general and identifies parallels and differences between CABG surgery and PABG surgery.

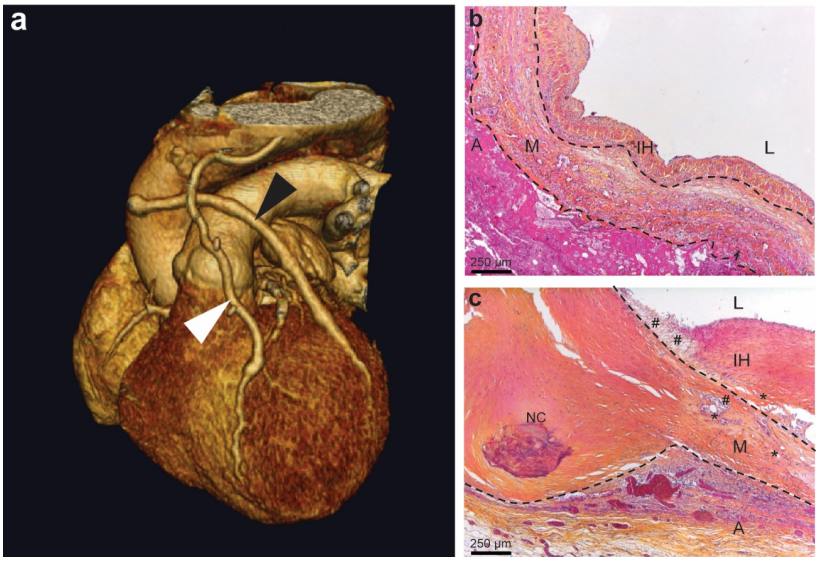

Figure 1. Macroscopic and microscopic views of a human vein graft. **a** Frontal view of a 3D reconstruction of a heart via CT scan. This scan is an example of a saphenous vein used as a graft from the aorta to the ramus circumflexus (black arrowhead). The left internal mammarian artery (white arrowhead) is grafted on the left anterior descending (LAD) coronary artery. b| These histologic sections of failed human saphenous vein grafts stained with haematoxylin, phloxin, and saphron show extensive smooth muscle cell accumulation and extracellular matrix deposition in the intimal hyperplasia. c| Atherosclerosis in a vein graft lesions is characterized by a de-cellularized region including a calcified necrotic core (NC), foam cells (hash), and neovessels (asterisk). Abbreviations: A, adventitia; M, media; intimal hyperplasia, intimal hyperplasia; L, lumen.

At present, statins and antiplatelet therapy (specifically, aspirin) are the only medications recommended by the ESC and the ACC Foundation/AHA Task Force for the prevention of VGF[4, 19-21]. Despite numerous preclinical studies on potential new targets and therapies for the prevention of VGF, an unequivocally effective treatment has not been found[3, 22]. Gene therapy is an attractive option, since graft conduits can be treated *ex vivo*[22]. In this Review, we discuss the pathophysiological mechanisms underlying the development of VGF, including the cellular and molecular processes involved in vein graft remodeling and intimal hyperplasia formation, and summarize potential therapeutic options that can improve patency from the results of both preclinical experimental studies and the latest clinical trials.

Table 1. Characteristics of CABG surgery and PABG surgery

	CABG surgery	PABG surgery
Typical patient symptoms	Angina pectoris	Critical limb ischemia
Preferred bypass	Arteria mammaria interna	Vena saphena magna
Other bypasses used	Vena saphena magna	Polytetrafluoroethylene
	Arteria radialis	Dacron
	Arteria gastroepiploica	Biological veins
Location proximal graft anastomosis	Aorta	Arteria femoralis
Bypass length	6 cm (single) – 30cm (jump graft)	40–60 cm
Diameter diseased artery	1.5–3.0 mm	4.0–10 mm
Blood pressure in conduit	High	Medium
10-year overall patency	≈60%	≈60%
Mechanism of primary stenosis		
Thrombosis	+	+
Intimal hyperplasia	++	+++
Atherosclerosis	+++	+/-

Pathophysiology of vein grafting

Preclinical imaging studies using *in vivo* models have enabled researchers to construct a timeline of the events that begins with harvesting of the vein grafts to eventual VGF (Figure 2). Immediately after harvesting, venous conduits undergo a period of ischemia and reperfusion after engraftment, resulting in endothelial cell and smooth muscle cell (SMC) damage[23]. *In situ* saphenous vein grafts used in PABG surgery do not experience ischemia, since the *vasa vasorum* are still fully intact. The temporary closure of the lumen and reperfusion in these grafts cause damage to the vessel wall. Engraftment in the arterial circulation increases flow and longitudinal and circumferential shear stress, resulting in additional damage to SMCs and the extracellular matrix (ECM)[23, 24]. Platelets and fibrin are deposited, and circulating leukocytes attach and infiltrate the vessel wall. Growth factors are subsequently released from platelets, macrophages, and SMCs, leading to increased proliferation and migration of SMCs to the intima. Uncontrolled SMC proliferation, extensive ECM deposition, and the influx of macrophages all contribute to intimal hyperplasia within the vessel wall. Under hypercholesterolaemic conditions, increased uptake of lipids promotes foam cell formation. Macrophage apoptosis, and subsequent necrotic core formation and intraplaque haemorrhage, further accelerate the process of VGF by forming unstable atherosclerotic lesions[25, 26].

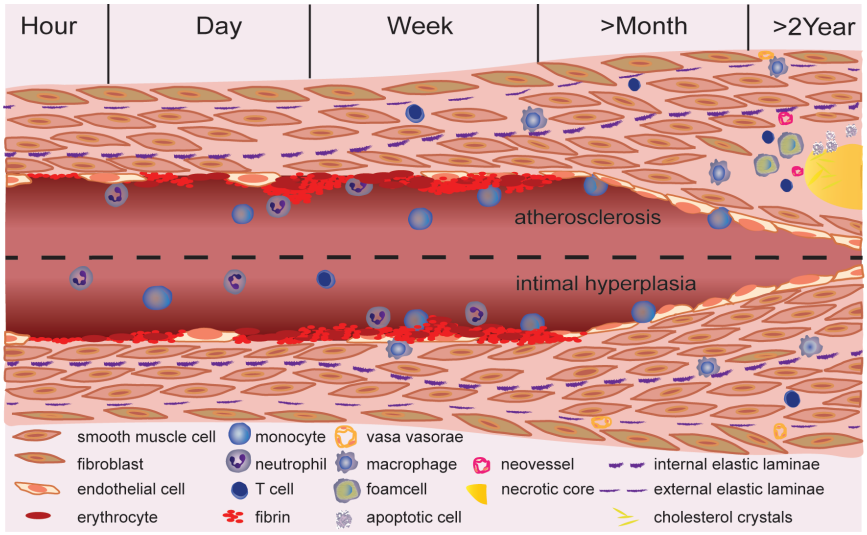

Figure 2. Vein graft development over time.
The vein graft procedure results in damage to the endothelial layer. Within hours, the luminal surface is covered by fibrin rich layers, and circulating white blood cells including neutrophils, monocytes, and lymphocytes, attach and infiltrate the fibrin layer and intima. Smooth muscle cells in the media and fibroblasts in the adventitia are activated and start migrating towards the intima, forming the intimal hyperplasia. Growth factors and cytokines released by cells in the vessel wall, such as inflammatory cells, enhance proliferation of smooth muscle cells and induce extracellular matrix deposition, resulting in further growth of the intimal hyperplasia. Under atherogenic conditions, and especially after CABG surgery, macrophages in the vessel wall can uptake lipids to become foam cells. A necrotic core is formed by dying foam cells, apoptosis, and cholesterol depositions. The atherosclerotic process in vein grafts is depicted in the upper part of the illustration.

De-endothelialisation and thrombosis

As mentioned above, during a bypass procedure, most venous conduits undergo a period of ischemia followed by reperfusion, resulting in the generation of damage-associated molecular patterns (DAMPs) and reactive oxygen species (ROS). Together with the damage caused by graft handling and distension during the high-pressure check for leakage, ischemia–reperfusion injury increases oxidative stress and cytotoxic activation, which culminates in loss of endothelial cells and SMCs[27-29]. Endothelial cells become activated, and express intercellular adhesion molecule 1, vascular cell adhesion protein, selectins, thrombomodulin, and growth factors. Some endothelial cells might show apoptosis and increased blebbing, vacuolisation, and of Golgi and rough endoplasmatic reticulum on electron microscopy[30-32]. Reduced endothelial nitric oxide synthase (eNOS) and nitric oxide (NO) production in the damaged endothelium results in impaired vasorelaxation[33]. In porcine venous grafts,

the increase in superoxide production compared with levels in arterial conduits was associated with reduced synthesis of NO and decreased superoxide dismutase activity[34]. The increase in oxidative stress and endothelial apoptosis, and the subsequent endothelial damage seen in veins (but not in arterial conduits) contributes to the unfavourable patency rates of vein grafts in experimental models[34-36].

As a result of endothelial denudation, the underlying ECM proteins (for example, collagen, elastin, and proteoglycans) become exposed to the circulation, thus promoting platelet and fibrin deposition on the thrombogenic luminal surface. Tissue factor proteins become available and initiate thrombin formation. Impaired NO and prostacyclin production in the venous conduits further enhance platelet aggregation[28]. Platelets generate a number of thrombogenic, chemotactic, and vasoconstricting substances, including platelet derived growth factor (PDGF), transforming growth factor-β (TGF-β), fibrinogen, fibronectin, and von Willebrand factor[28]. Activated platelets express adhesion molecules, such as P-selectin and E-selectin, and bind circulating leukocytes, which in turn attach to and infiltrate in the vessel wall[37]. The CD40 ligand, which has both prothrombotic and proinflammatory activity, is exposed and excreted by activated platelets, further accelerating the thrombogenic process[38]. The deposition and subsequent resolution of fibrin is tightly regulated through the thrombogenic and fibrinolytic pathways and play an important role in the onset of intimal hyperplasia formation[39]. Targets to improve endothelial function comprise Endothelin-1, eNOS and NAD(P)H oxidase. These mediators are all capable of influencing haemodynamics and intimal hyperplasia formation via increasing NO and/or inhibition of superoxide production[40-42].

Re-endothelialisation

Restoration of the endothelial monolayer begins rapidly after initial damage. Proliferating endothelial cells can be seen as early as three days after vein graft surgery in experimental models[31, 32]. In these models, the endothelial lining is largely intact 4 weeks after the surgery[23, 32, 35, 43]. The duration of the re-endothelialisation process in humans is likely to be longer, although the exact time frame is not known and will depend on the length of the vein graft segment used[44]. Murine and human progenitor cells from bone marrow and the adventitia have been shown to contribute to the re-endothelialisation process[45-48]. The homing of these progenitor cells is thought to be integrin β3-dependent[49, 50], and is directed by inflammatory-type macrophages[51]. In addition, inducible nitric oxide synthase can enhance endothelial progenitor cell attachment and differentiation[52]. Evidence of the origin of venous graft endothelial cells in humans is still lacking, however, human allografts endothelial cells were found to be derived from both host and donor cells[53]. Endothelial cells in mature human

Box 1 Coronary artery bypass grafting

- Coronary artery disease (CAD) is the most common type of heart disease, and occurs when atherosclerotic lesions narrow the coronary arteries leading directly, or more common indirectly via thrombi, to reduced oxygenation of the myocardium. Symptoms of CAD include chest pain (angina) or myocardial infarction.
- Treatment options include lifestyle changes, medication, percutaneous coronary intervention with or without stenting, or CABG surgery
- Conduit choice in CABG depends on many patient-specific factors, including location and severity of the target coronary artery stenosis, comorbidities, estimated life expectancy, number of bypasses needed, and availability of graft material.
- When revascularizing the left anterior descending coronary artery, the left internal mammary artery (IMA) is the preferred graft for CABG surgery[4, 19]. Alternatives include the right IMA, the radial artery (RA), right gastroepiploic artery, and the saphenous vein.
- The use of the saphenous vein graft is advantageous over arterial conduits for several reasons: they are easily harvested, easily handled when making anastomoses, are not influenced by vasospasm, do not increase the risk of sternal wound infection, and are readily available in most patients.
- In general, arterial conduits are considered to have higher patency rates[296, 297]. RA patency is lower than that of IMA grafts and more dependent on the severity of the target coronary artery stenosis[298]. Furthermore, vasospasm can also occur, owing to the muscular nature of the RA wall.
- Inconsistent results have been reported for patency rates in saphenous vein grafts and RA grafts[299-301]

vein grafts display endothelium-dependent relaxation, and thus are seemingly functional[44]. However, how non-host endothelial cells affect the functioning of the endothelium in the graft is still unknown. Results from preclinical studies have thus far shown that enhanced re-endothelialisation is beneficial in preventing VGF, but so far no therapies exist to facilitate this process. The promotion of endothelial progenitor cell homing could be a potential future therapeutic target.

Vein graft arterialisation

In 1964, Sziliagyi and colleagues first suggested that a vein needs to undergo a ≥50% increase in dimension to adapt to the increased pressure in the arterial circulation[54]. Although this initial adaptation is necessary for veins to acquire an artery-like structure, this process can also lead to substantial VGF. Arterialisation of venous bypass grafts involves processes such as intimal hyperplasia, geometric remodeling, wall stiffening, and inflammation[24].

Arterial and venous blood vessels have a similar structure made up of three distinct layers: the adventitia, the media, and the intima. Cellular and fibrous components within veins are considerably limited in number and size compared with arteries. Furthermore, veins contain valves to prevent blood reflux. The venous wall is highly adapted for continuous changes in blood volume, but the pressure and flow in the venous system is low compared with the arterial system. Interpositioning of a vein into a high pressure and flow arterial environment leads to morphologic and geometric changes in the venous conduit[55]. Intimal hyperplasia or vessel wall thickening is a direct result of SMCs and ECM expansion induced by increased pressure, shear stress, and inflammatory responses[3]. For example, shear stress in the saphenous vein rises from 0–4 dynes/cm^2 to up to 30 dynes/cm^2 after engraftment[44].

The geometric adaptation of the vein is thought to be primarily mediated through the endothelium, as it is sensitive to haemodynamic stresses[3, 56, 57]. The three geometric parameters that are generally used to determine the mode of remodeling are lumen calibre, wall thickness, and lesion area. The haemodynamic forces together with the geometric parameters maintain the vessel in a state of maximum efficiency for the transport of blood. According to the law of Poiseuille, circumferential, longitudinal, and radial stress results in dilatation of the vessel[58]. The venous conduit in the arterial system has been suggested to direct stress in nine different directions[59]. Constrictive remodeling or loss of lumen calibre is associated with low level of shear stress[24, 60]. Interestingly, Zilla *et al.* demonstrated that the saphenous vein displays different degrees of remodeling in coronary bypasses compared to infrainguinal bypasses, owing to different flow patterns, and stress and shear force. They also showed that coronary grafts in a nonhuman primate model express a high degree of lumen loss and intimal hyperplasia formation, while infrainguinal grafts display increased dilatation[61].

Tomographic intravascular ultrasound (IVUS) imaging enables the visualization of the full circumference of the vessels, thus allowing evaluation of early geometric vascular remodeling *in vivo*[62, 63]. Early wall thickening and expansive remodeling

of vein grafts occurs within the first few weeks post-implantation, as observed on IVUS, with these changes stabilising after 6 months[3, 64]. Expansive or positive outward remodeling is believed to delay the development of lumen loss, although this is frequently inadequate for the preservation of luminal size in the long term[65-67]. In the first year after surgery, a considerable portion of the vein grafts show constrictive or inward remodeling, a compensatory response to vessel wall thickening[68]. Unlimited expansive remodeling and inward remodeling are detrimental to vein graft arterialisation. Gasper *et al.* demonstrated that early remodeling was predictive for future VGF, and suggested that patients at risk should be closely monitored[69]. Use of an external support that could prevent shear stress and decrease wall tension and thereby prevent SMC proliferation, outward remodeling, and intimal hyperplasia formation, has proven to be an potential strategy in both human tissue cultures and experimental models,[70-74] and will be discussed detail below.

Intimal hyperplasia formation

Smooth muscle cells

The intima and media of veins consists of several cell layers. During harvesting and after engraftment, SMCs within these layers undergo ischemia and apoptosis[23, 31]. Matrix turnover and the proliferation, migration, and death of SMCs are key components in intimal hyperplasia formation. During migration from the media to the intima, or from the anastomosed artery towards the intima of the graft, SMCs change from a quiescent contractile phenotype to a dedifferentiated, proliferating, or synthetic phenotype[75-77]. Smooth muscle-like cells derived from adventitial fibroblasts also contribute to intimal hyperplasia formation[78, 79].These adventitial fibroblasts are highly proliferative and produce higher levels of superoxide compared with SMCs, owing to reduced activity of superoxide dismutase[34]. Veins do not contain substantial elastic laminae, and consequently, fibroblasts in the adventitia can easily migrate to the intima in veins. However, intact elastic laminae within arteries prevent transmural migration, which contributes to the difference in intimal hyperplasia formation between arterial and vein grafts. Adventitial and bone marrow-derived progenitor cells also contribute to vein graft intimal hyperplasia[47, 80-85]. Interestingly, bone marrow-derived cells are reported to express a SMC phenotype, but do not fully acquire the definitive SMC lineage[86]. The CXC-chemokine ligand CXCL12 (also known as stromal cell-derived factor 1)/CXCR4 (also known as platelet factor 4) axis is essential for homing of bone marrow-derived cells. Vein grafting in $CXCR4^{-/-}$ mice resulted in reduced vein graft thickening[87]. Most bone marrow cells express fibroblast-specific protein 1 (FSP-1), which lead the cells to home in a (platelet-derived) CXCL12 dependent manner. Knock down of FSP-1 in bone marrow cells prevented formation of intimal hyperplasia[88].

Box 2 Peripheral artery occlusive disease

- Peripheral arterial occlusive disease (PAOD) is a common circulatory problem characterized by narrowing of peripheral arteries owing to atherosclerosis, which subsequently reduces blood flow to the lower limbs.
- Many patients with PAOD are asymptomatic (Fontaine I)[302]. The most frequent presentation of PAOD is intermittent claudication, defined as reproducible lower extremity muscular pain induced by exercise and relieved by standing still (Fontaine II)[303].
- Several treatment options are available for symptomatic PAOD, including exercise therapy and pharmacotherapy. In case of ischaemic rest pain (Fontaine III), ulceration or gangrene (Fontaine IV), and when conservative treatments are unsuccessful, surgical treatment options are required.
- Invasive endovascular treatment, such as balloon angioplasty, is recommended for these patients. Balloon angioplasty combined with stent implantation improve patency rates compared to balloon angioplasty alone.
- Owing to the length or the location of the occlusion, balloon angioplasty is not always an option. In such situations, bypass surgery is the preferred treatment strategies.
- Autologous veins (such as the saphenous vein) are the first conduits of choice
- Alternative conduits include polytetrafluoroethylene, Dacron grafts, or modified decellularized umbilical cords
- Bypass surgery is only possible when there is sufficient patency of the blood vessel distal to the occlusion.
- When bypass surgery is technically impossible, or in case of critical limb ischemia with extensive necrosis or infectious gangrene, amputation is the last treatment option.

SMCs and other cells in the vein grafts express numerous growth factors such as vascular endothelial growth factor (VEGF), PDGF, basic fibroblastic growth factor (bFGF), TGF-β, and endothelin-1, which are major stimulators of SMC migration, proliferation, and apoptosis[89-93]. Targeting of growth factor receptors *in vivo* interferes with intimal growth[93-98]. The mitogen-activated protein kinase (MAPK), extracellular signal regulated kinase (ERK), and Akt (also known as RAC-alpha serine/threonin-protein kinase) signaling pathways are critical for the regulation of cell cycle progression,[99-101] and can also directly influence SMCs and intimal hyperplasia formation[101, 102]. The expression of growth factors and signal transduction pathway

factors vary between arterial and venous grafts[103-105]. For example, higher MAPK and Akt activity levels were observed in venous SMCs compared with arterial SMCs,[106] which might contribute to the low patency of venous grafts.

Extracellular matrix

Remodelled vein grafts contain a large repertoire of matrix metalloproteinases (MMPs), predominantly MMP2 and MMP9[107-110]. MMPs degrade collagen and other components of the ECM in the vessel wall. Doxycycline, a general MMP inhibitor, suppressed intimal hyperplasia formation in murine vein grafts[109]. Furthermore, specific gene silencing of MMP2 and MMP9 in cultured saphenous vein SMCs resulted in a decreased cell migration through a Matrigel barrier[111]. Interestingly, vein grafting in mice deficient in MMP9 did not alter intimal hyperplasia growth compared with control mice, however, MMP9-deficient mice did show an increase in collagen content[112]. Endogenous tissue inhibitors of MMPs (TIMPs) have also been the focus of much research related to vein grafts. Overexpression of TIMP1, 2, and 3 in various vein graft models resulted in inhibition of MMP activity and a reduction in SMC migration and proliferation, thereby preventing intimal hyperplasia formation[25, 113-117].

Whereas MMPs regulate ECM breakdown, TGF-β is known to enhance matrix depositions. During early stages of vein graft adaptation, upregulation of TGF-β is associated with increased mRNA expression of C-C motif chemokine (CCL) 2, collagen I, and collagen III[92, 118]. Abrogation of TGF-β signaling in rats resulted in decreased intimal hyperplasia and increased MMP expression[98]. In addition, SMCs also generate hyaluronic acid, a glycosaminoglycan and important constituent of the ECM. Human saphenous vein grafts are characterized by increased deposition of hyaluronic acid and elevated expression levels of all three isoforms of hyaluronic acid synthase[119].

Increased expression of members of the plasminogen activation system has been observed in failed human vein grafts[120, 121]. Aside from their role in fibrinolysis and proteolysis, plasminogen activators (PAs) can also exert their activity on SMCs and the ECM. Components of the ECM, such as laminin and fibronectin, can be cleaved by plasmin that is formed by conversion of plasminogen by plasminogen activators, resulting in activation of cell surface receptors and MMPs[122]. The plasminogen activation system consists of two main PAs, urokinase-type PA (uPA) and tissue-type PA (tPA). uPA is essential in extracellular proteolysis, cell migration, and matrix remodeling, while tPA is mainly involved in fibrinolysis[123]. Overexpression of tPA in porcine vein grafts resulted in reduction of early vein graft thrombosis[124]. Plasminogen activator inhibitor 1 (PAI1), through its regulation of PA activity, has been shown to regulate proliferation, migration, and apoptosis of SMCs and endothelial cells[125].

Intimal hyperplasia was enhanced in PAI1 deficient mice owing to increased thrombin activity[126].

Given that inhibition of either PAs or MMPs has been shown to reduce intimal hyperplasia *in vivo*, a hybrid protein consisting of TIMP1 and the receptor-binding amino terminal fragment (ATF) of urokinase was constructed to more efficiently inhibit protease activity locally[127]. This construct enhanced the inhibitory effect of murine vein graft intimal hyperplasia and preservation of luminal area compared with their individual counterparts[128]. A further construct was created by adding bovine pancreas trypsin inhibitor (BPTI), a potent protease inhibitor capable of inhibiting both MMP and plasmin activity at the cell surface, to the existing TIMP1. ATF construct, which resulted in retardation of intimal hyperplasia and outward remodeling[129]. Adenoviral overexpression of the hybrid protein ATF.BPTI also reduced intimal hyperplasia formation in human saphenous vein grafts *in vitro*[130].

Inflammatory mediators

Inflammatory mediators are critical in all phases of vein graft development[131, 132]. Early after-engraftment DAMPs such as proteoglycans, heat shock proteins, and biglycan are among the first mediators of inflammation[133, 134]. Endogenous DAMPs activate Toll-like receptors (TLRs) that are expressed by endothelial cells, SMCs, and macrophages in the vein grafts[134, 135]. Genetic deletion and RNA silencing of TLR4 in a murine model of VGF reduced outward remodeling and intimal hyperplasia formation, as a result of a suppressed inflammatory response[134]. Interestingly, carotid ligation in TLR4-deficient mice showed outward remodeling without intimal hyperplasia formation in the nonligated artery,[136] suggesting that TLR4 affects vascular remodeling independently of intimal hyperplasia formation; TLR4, therefore, might have a role in haemodynamic adaptations.

Other TLR4 ligands include oxidized LDL (oxLDL) and phosphorylcholine, both known for their role in the development of atherosclerosis. The role of oxLDL and subsequent lipid retention in VGF has been observed, especially under hypercholesterolaemic conditions[23]. Low levels of natural antibodies against phosphorylcholine in humans are associated with VGF, while passive immunization with anti-phosphorylcholine antibodies prevents vein graft atherosclerosis in a hypercholesterolaemic murine model.[137, 138]. With the exception of TLR3, all TLRs signal via the myeloid differentiation primary response protein 88 (MyD88) pathway, which activates nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB)and results in induction of proinflammatory cytokines[139]. NFκB is one of the most important transcription factors for promotion of inflammatory responses in vein graft remodeling. In experimental

models, strategies to inhibit NFκB resulted in attenuation of intimal hyperplasia formation by reducing inflammation[140-142]. NFκB can activate the cytokines CCL2 and tumor necrosis factor α (TNFα), both of which have been extensively studied in VGF[143, 144]. A dominant receptor antagonist of CCL2, 7ND-MCP-1, reduced vein graft atherosclerosis and monocyte invasion in mice on a hypercholesterolaemic diet[145]. Furthermore, RNA silencing of the CCL2 receptor, CCR2, resulted in reduced SMC proliferation and migration *in vitro* and abrogation of intimal hyperplasia *in vivo*[145]. As a result of the early induction of TLRs, TNFα is upregulated in early vein graft development. In TNF receptor-1-deficient mice, vein graft intimal hyperplasia was reduced as a result of reduced CCL2 expression and SMC proliferation[146]. In addition, TNF receptor-2-deficient mice showed abrogated vein graft intimal hyperplasia as a result of endothelial cell apoptosis[147]. These studies illustrate the various mechanisms that can contribute to reducing vein graft intimal hyperplasia.

In general, cytokines are proinflammatory mediators that induce cell remodeling by activating inflammatory cells, SMCs, and endothelial cells[132, 148-150]. In their role as pattern recognition receptors, TLRs are central in the induction of inflammatory responses, and can activate inflammatory cells of both the innate and adaptive immune system, in addition to activating complement factors. Like TLRs, complement factors are present in the vein graft wall, enhancing cross-talk between these components of the innate immune system. Complement factors are expressed in both genes and proteins in murine grafts, indicating that they are produced by the vessel wall as an extra-hepatic source[116, 151]. Interference with the key complement factor C3, and alternative pathway component C1 and C5 resulted in reduced intimal hyperplasia by preventing endothelial cell damage, inhibiting SMC proliferation, and reducing inflammatory signaling in murine vein grafts[151-153]. Complement factors are thus very promising targets for treating VGF in humans. An exploratory analysis of the PRIMO-CABG I and II trials[154] reported that intravenous administration of pexelizumab, an antibody against complement factor C5, improved mortality in high-risk surgical patients undergoing CABG surgery.

Inflammatory cells that invade the vein graft reside in specific locations in the vessel wall. Neutrophils are found mainly in the fibrin layer that is formed on the de-endothelialised lumen during early onset of intimal hyperplasia formation[155, 156]. Neutrophils produce a wide array of angiogenic growth factors and proteases such as MMP-9, but their main role is to regulate neighbouring inflammatory cells such as macrophages[157]. Macrophages represent the vast majority of inflammatory cells in the intima and media[158]. Monocytes roll, attach, and invade the graft via the lumen, but can also enter via neovessels in the adventitia. Under the influence of macrophage

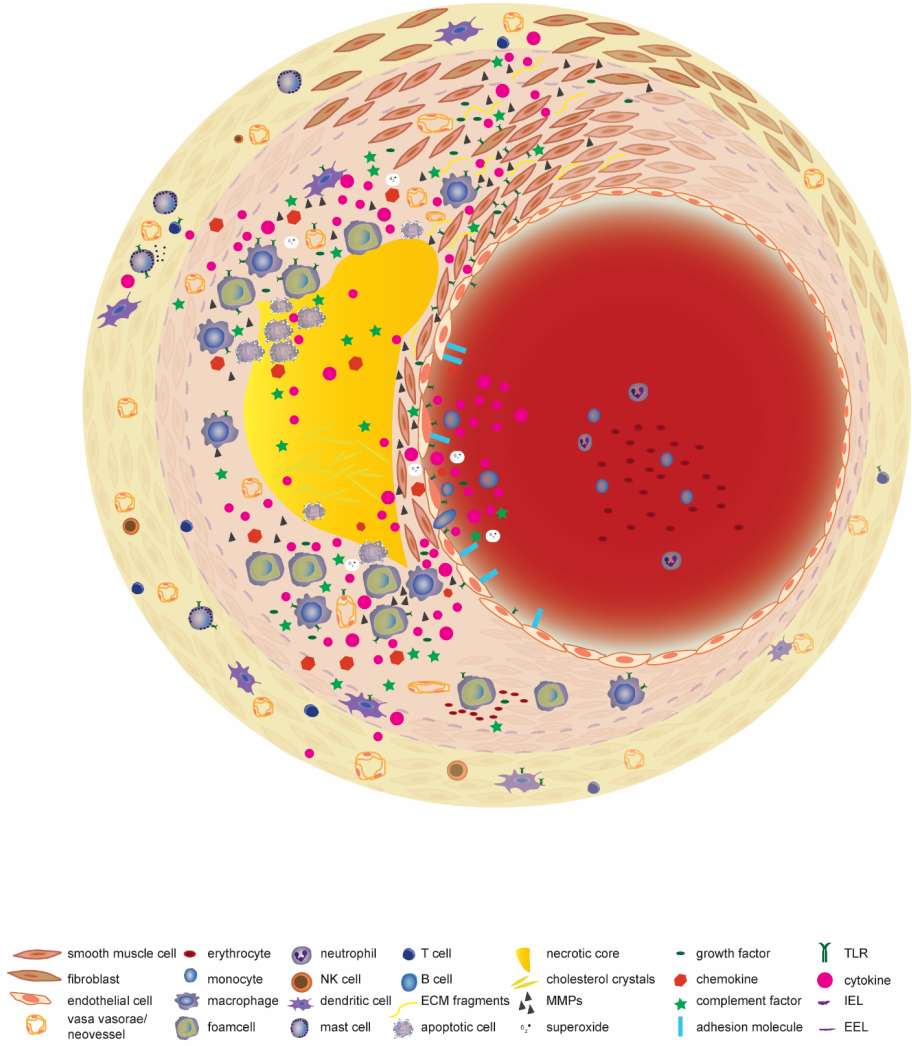

Figure 3. Inflammation in vein graft failure. Toll like receptors (TLRs), superoxide, and adhesion molecules are produced by activated endothelial cells. Monocytes and other inflammatory cells respond to locally produced cytokines and chemokines by migrating into the vein graft wall. In response to local growth factors, monocytes differentiate into macrophages, which then takes up oxidised LDL particles to form foam cells. One or multiple necrotic cores are formed by dying foam cells and cholesterol depositions. Danger associated molecular patterns promote the production of many proinflammatory molecules by activating TLRs on various cells in the vessel wall, stimulating proliferation and migration of smooth muscle cells as well as extracellular matrix (ECM) production. T cells, primarily located in the adventitia, undergo activation after interacting with antigen-presenting cells, such as macrophages or dendritic cells. Other cells in the adventitia such as mast cells and natural killer (NK) cells are activated and enhance the inflammatory process. Fibroblasts in the adventitia migrate through the external elastic lamina (EEL) and internal elastic lamina (IEL) to the media and intima under the influence of growth factors, contributing to the concentric vessel wall thickening. MMP, matrix metalloproteases.

colony stimulating factor, monocytes become macrophages, which produce and release a broad array of cytokines and growth factors. In the case of vein grafts, SMCs are the predominant target of these macrophages[159]. In rabbit and murine vein grafts, indirect inhibition of macrophages, for instance by targeting macrophage activating factors, has been shown to be a successful strategy in preventing the inflammatory response and VGF[141, 160, 161].

The adventitia, made up of loose connective tissue, small neovessels, and perivascular fat, is an important source of inflammatory cells; dendritic cells, T and B cells, mast cells and natural killer (NK) cells seem to have a preference for the adventitia[162]. Dendritic cells originate from Ly-6C^{lo} monocytes and specialize in presenting antigens to T cells[163]. Dendritic cells are also capable of triggering T cells by expressing co-stimulatory factors, and can thereby regulate vein graft remodeling[162, 164]. Mast cells are large granular cells that can actively release granules containing tryptase, chymase, and histamine. Aside from the classical activation route of binding to immunoglobin E[165], mast cells can also be activated via cytokines (TNFα, IL1) and complement factors (C3a and C5a)[166]. Vein grafts are rapidly repopulated with mast cells; both resting and activated mast cells can be found within the perivascular region in murine vein grafts[153, 167]. Mast cells have been linked to the development of atherosclerosis, but are mostly thought to be effector cells of plaque rupture and erosion[168, 169]. Local activation of mast cells resulted in increased unstable lesions and vein graft rupture.[153] Furthermore, vein grafts in mast cell-deficient mice have reduced intimal hyperplasia[153]. Also present in the adventitia are NK cells, a small subset of lymphocytes initially described for their 'natural' capacity to kill cells depending on the expression of activating and inhibiting NK cell receptors specific for major histocompatibility complex class I molecules. NK cells can be activated by secretion of lytic granules containing perforin and granzymes, but also by secretion of various cytokines[170]. Limited numbers of NK cells are found in the perivascular region of vein grafts[171]. BALB/C mice lack crucial NK cell genes of the Ly49 receptor family, resulting in a reduced NK cell function. Vein graft surgery performed in BALB/c mice congenic for the C57BL/6 NK gene region showed similar degree of intimal hyperplasia compared to C57BL/6 mice, while BALB/c mice showed significantly less intimal hyperplasia[171]. This difference was accompanied with a decrease in inflammatory cells and interferon-γ expression in the vein graft[171].

In general, components of the innate immune system are known to accelerate intimal hyperplasia formation and graft failure (Figure 3). The role of adaptive immunity is less clear, although both T and B cells have been identified in vein grafts[172], as well as the crucial T cell co-stimulatory molecule CD40[164]. The role of the adaptive

immunity in related vascular diseases, atherosclerosis, and restenosis has been well established[173, 174]. Further studies are needed to investigate the role of T and B cells in VGF.

Atherosclerosis and rupture

Atherosclerotic lesion formation is characteristic of late phase VGF[175-177]. Human autopsy studies have shown that coronary vein grafts undergo more rapid atherosclerotic lesion development than native arteries[8]. Coronary vein graft atherosclerotic lesions are more concentric and diffuse compared with native atherosclerotic lesions, and are more vulnerable to thrombosis and rupture[26]. In contrast to coronary vein grafts, the morphological organisation and development of late-phase peripheral vein graft lesions has received less attention and is not as well studied. Westerband *et al.* showed that peripheral lesions have a predominance of highly proliferative SMCs[178]. Furthermore, occluded peripheral grafts are associated with high rates of inflammatory cells[179]. However, to what extent atherosclerosis contributes to late phase stenosis in peripheral grafts is unclear.

Foam cell formation in vein grafts has been observed as early as one year post-graft surgery[180]. A necrotic core tends to develop between 2 to 5 years after surgery, and is often accompanied by intraplaque haemorrhage from leaky angiogenic neovessels[7, 180]. Yazdani *et al.* demonstrated that lesions that form post-CABG surgery that have a thin fibrous cap and contain large haemorrhagic necrotic cores have a high frequency of plaque rupture[180]. Furthermore, features of late phase failure, such as necrotic cores, angiogenic neovessels, intraplaque haemorrhage and rupture, could be observed in an experimental vein graft model in hypercholesterolemic mice (Figure 4)[25]. The appearance of plaque neovessels and intraplaque haemorrhage are frequently observed in this model (Figure 5), which is rarely seen in atherosclerotic experimental models. Upregulation of TIMP1 resulted in improved lesion stability and decreased plaque rupture[25]. Targeting inflammatory factors such as annexin A5, mast cells, and complement factor C5a in this murine vein graft model is an effective strategy to not only diminish intimal hyperplasia, but also to reduce atherosclerosis and plaque rupture by enhancing lesion stability[153, 160, 181].

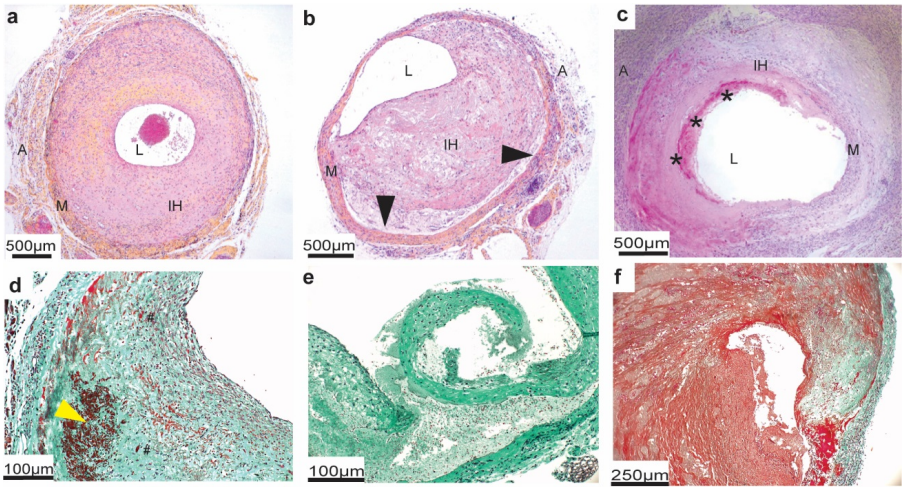

Figure 4. Murine vein graft lesions in hypercholesterolaemic mice. **a.** Extensive smooth muscle cells accumulate and extracellular matrix deposits in the intimal hyperplasia (IH). **b.** Atherosclerosis in a vein graft lesion is accompanied by a fibrin and blood-filled dissection (arrowhead). **c.** Atherosclerosis in a vein graft lesion is characterized by an eroded endothelium and an intramural thrombus (asterisk). Upper panel sections are stained with haematoxylin, phloxin, and saffron. Lower panel sections are detailed photographs of murine atherosclerotic vein graft lesions showing plaque rupture features such as intraplaque haemorrhage, dissections and erosions (stained with Masson's trichrome). **d.** Lesions with neovessel (asterisk) and intraplaque haemorrhage (yellow arrowhead) are present within the graft. **e.** Rupture-like dissection connects the lumen (L) and media (M). The connecting gap is filled with blood and thrombi. **f.** Erythrocyte rich intramural thrombus can be observed in this 28-day-old vein graft lesion. A, adventitia.

Vein graft handling during surgery

When a vein graft is used for coronary revascularization, the surgeon takes into account several technical factors to minimize the risk of early and late VGF. These factors include choosing the optimal site for the distal anastomosis (aiming at a high outflow target area and minimizing the size discrepancy between the vein and the target vessel), and careful measurement of bypass length to prevent kinking or flattening that will lead to turbulent or decreased flow. Although sequential venous grafting has a potential downside of increased risk of proximal stenosis, this technique reduces resistance to graft flow, which might explain the higher patency rates of sequential venous grafts compared with single venous grafts[182]. In general, graft patency of sequential vein grafts is highest when the last distal anastomosis is made to the coronary artery with the largest runoff. However, proper vein harvesting is likely to be at least equally as important in determining vein graft patency.

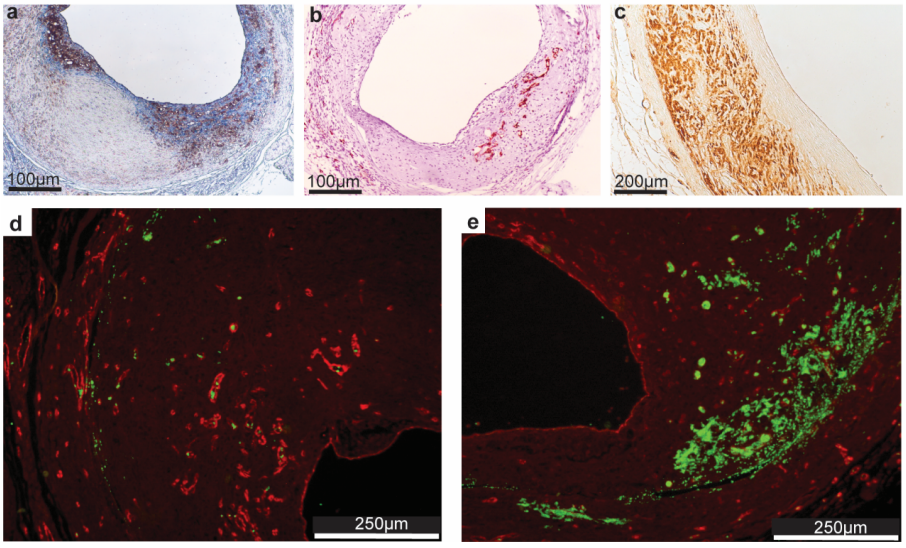

Figure 5. Immunohistochemical characterization of hypercholesterolaemic murine vein grafts. **a.** Macrophage (brown) and smooth muscle cell (blue) double staining showing heterogeneous areas highly positive for both cell types. **b.** CD31-stained endothelial cells (red) highlight neovessels in an advanced atherosclerotic vein graft lesion. **c.** Fibrin deposition (brown) in an early (14-day-old) vein graft section. **d.** and **e.** Immunofluorescent double staining of CD31 positive neovessels (red) and erythrocytes (green) showing a lesion with intact matured neovessels. All erythrocytes are within the neovessels (d) and a lesion with leaky neovessels displaying intraplaque haemorrhage. Erythrocytes are found throughout the lesion and are not restricted by the neovessels (e).

No touch technique

During harvesting of the saphenous vein, forceful dilatation of the vein to alleviate spasm and check for leakage should be avoided, since it damages the endothelium (Figure 6). In 1996, the 'no touch' technique was introduced, whereby the vein is harvested with a pedicle of surrounding tissues, maintaining the vasa vasora and the nerves in the adventitia[183]. This technique improved short-term and long-term vein graft patency rates, alongside with reduced intimal hyperplasia formation in a randomized, controlled trial performed in 2002[184, 185]. Several subsequent trials also showed the beneficial effect of the no touch technique on vein graft patency. In the PATENT SVG trial[186], the no touch technique led to decreased SMC activation. Samano *et al.* reported higher patency rates for grafts harvested using the no touch technique compared with veins harvested using the conventional method in a study with a mean follow-up of 16 years[187]. The veins harvested using the newer technique had a patency rate of 83%, similar to that of left internal thoracic artery patency rates in this study (88%). However, only a limited number of patients (17 and 54 patients

respectively) were evaluated in these trials. A larger trial comparing the no touch technique to conventional harvesting is currently ongoing in 1550 patients undergoing CABG surgery, with primary end points of graft patency and mortality at 1 year[188].

Endoscopic versus open vein harvesting

Minimally invasive or endoscopic techniques for vein harvesting have the potential benefit of reducing wound-related complications and reducing postoperative pain and morbidity compared with conventional techniques[189, 190]. The ROOBY trial[191] reported improved 1-year graft patency with endoscopic saphenous vein harvesting compared with open harvesting. However, a higher rate of VGF and long-term mortality has also been linked with the minimally invasive endoscopic technique[192, 193]. Given the discordant results, no consensus has been reached on a gold standard method for vein harvesting[194, 195]. The ongoing REGROUP trial[196] aims to determine the best technique for vein graft harvesting with regard to reducing major adverse cardiac events.

Vein preservation

Extensive handling and desiccation during collection of the saphenous vein can result in spasm and endothelial damage. Numerous studies have sought to determine the best solution to preserve optimal endothelial function of the harvested vein and, therefore, maintain high graft patency rates. Many studies consistently demonstrate the detrimental effects of saline on vascular endothelium, including a study published in 2015 reporting that saline preservation of human saphenous veins led to acute cellular injury[197]. However, this is no clear consensus on whether heparinized autologous whole blood is superior to saline as a storage medium[198]. Randomized, controlled trials are needed to compare autologous whole blood with saline for vein graft preservation, and to determine the best time and temperature for saphenous vein graft storage. Aside from graft preservation fluid, surgical skin markers to orient conduits can also impair physiological function of the vein grafts as they contain methylene blue dye[199]. However, in a study published in 2015, a nontoxic dye alternative to current surgical skin markers called brilliant blue FCF was able to ameliorate vein graph injury in the porcine saphenous vein[200].

Graft configuration

Three techniques for saphenous vein graft placement have been described: reversed, in situ, and nonreversed translocated vein graft placement. The reversed graft configuration technique is considered the gold standard[201]. By reversing the saphenous vein graft, by connecting the distal end of the graft to the proximal part of the artery and vice versa, the venous valves do not obstruct the arterial blood flow. However, there are also disadvantages associated with this technique, including the size mismatch between the narrow distal end of the saphenous vein graft and the larger diseased artery, a shortcoming that is not present in nonreversed translocated vein graft placement.

However, in nonreversed saphenous vein grafts, blood flow is disrupted owing to the presence of venous valves. In both reversed and nonreversed graft configurations, the saphenous vein graft is completely removed and thus might be traumatised or twisted and subjected to a period of ischemia. *In situ* saphenous vein grafts, used in PABG surgery, do not suffer from ischemia owing to preservation of the vasa vasorum. Previous studies have shown that graft configuration appears to have little influence on patency outcomes[201-203].

Preventive strategies

Established pharmacology

As previously described, venous segments undergo extensive endothelial damage during the bypass procedure. The loss of the endothelial cell layer can promote platelet adhesion and thrombosis[204]. Given that platelet activation and thrombin production have been shown to be the main cause of early VGF, Antiplatelet therapy is thought to be beneficial after surgery to prevent early vein graft thrombosis in both CABG surgery and PABG surgery (Table 2).

The first randomized trials on antiplatelet drugs and anticoagulants were conducted in the late 1970s to evaluate their efficacy in improving vein graft patency after bypass surgery[205-207]. In early trials, no beneficial effects of antiplatelet and anticoagulant drugs were seen on graft patency, likely owing to late drug administration (typically ≥3 days after surgery). Subsequent randomized, controlled trials showed that aspirin alone[208] and dual antiplatelet therapy[209] compared to placebo were effective in preventing graft occlusion. These positive results might be associated with administration of the drugs directly before and after surgery, since the thrombotic process begins during the operation when the endothelium becomes damaged.

Antiplatelet therapy

The ESC recommends low-dose aspirin (75–100 mg/day) for all patients with CAD (class of recommendation I, level of evidence A) and PAOD after revascularization (class of recommendation I, level of evidence C)[20, 210]. In the USA, the ACC foundation/ AHA task force advises that 100–325 mg/day of aspirin should be administered to patients undergoing CABG surgery, preferably preoperatively, or within 6 hours postoperatively to prevent VGF (class of recommendation I, level of evidence A)[19]. Similarly, after PABG surgery, patients should receive antiplatelet therapy indefinitely (class of recommendation I, level of evidence A)[21]. The optimal dosage of aspirin to prevent VGF still needs to be determined.

Several antiplatelet agents have been evaluated for their capacity to prevent VGF, including clopidogrel and ticlopidine, which are both P2Y12 adenosine diphosphate receptor inhibitors. Ticlopidine has been reported to be beneficial for graft patency[211, 212]. However, clopidogrel should be used in preference postoperatively if it is available, as it has fewer side effects[213-215]. Currently, clopidogrel is an accepted alternative in case of aspirin intolerance after CABG surgery as recommended by the ESC (class of recommendation I, level of evidence B).[210], and the ACC foundation/AHA task force (Class of recommendation IIa, level of evidence: C)[19]. After PABG surgery, dual antiplatelet therapy with aspirin and clopidogrel is recommended for below-knee polytetrafluoroethylene grafting, (class of recommendation IIb, level of evidence B)[20] based on results of the CASPAR trial[216]. However, antiplatelet therapy was only beneficial after prosthetic bypass grafting, whereas no benefit was observed after autogenous saphenous vein grafting. Antiplatelet therapy is, therefore, not routinely recommended for autogenous vein grafts.

Several studies have reported beneficial effects of adding clopidogrel to aspirin therapy on reducing VGF[217-220]. Currently, dual antiplatelet therapy is recommended after CABG surgery in patients with acute unstable angina undergoing urgent surgical revascularization, but to date, not all surgeons prescribe dual therapy for this patient cohort[19]. The use of dual therapy is not unequivocally proven to be beneficial for patients undergoing PABG surgery.

Given inconsistent results in the literature, whether the addition of dipyridamole, an anti-clotting agent, to aspirin has a beneficial effect on graft patency is still under debate[221-223]. In a meta-analysis by Bedenis *et al*, 16 studies comparing the effect of different antiplatelet agents and oral anticoagulants on graft patency and limb salvage were reviewed[235]. The investigators concluded that antiplatelet therapy with aspirin or aspirin plus dipyridamole had a beneficial effect on primary graft patency of PABG surgery compared with placebo or no treatment. However, dual antiplatelet therapy in patients receiving a prosthetic graft, compared with a venous graft, appeared to be more beneficial than monotherapy,[224] suggesting that dipyridamole should only be added to aspirin in the context of prosthetic grafts. However, current European guidelines recommend dual antiplatelet therapy of aspirin and dipyridamole only after infrainguinal bypass graft surgery, and no distinction is made in graft material[20].

Table 2a. Effect of antiplatelet drugs on vein graft patency after CABG surgery

Antiplatelet drugs	Study	Randomisation	Vein graft patency
Aspirin or dual antiplatelet	*Pantely 1979*[205]	ASA/DIP vs. OAC	No differences
	McEnany 1982[206]	ASA vs. OAC vs. placebo	No differences
	Sharma 1983[207]	ASA/DIP vs. ASA	No differences
	Chesebroe 1984[209]	ASA/DIP vs. placebo	Higher patency rates with ASA/DIP
	Goldman1989[208]	ASA vs. ASA/DIP vs. sulfinpyrazone vs. placebo	Higher patency rates with ASA
	Fremes 1993[222]*	ASA vs. ASA/DIP vs. OAC vs. placebo vs. no therapy	Higher patency rates with ASA or OAC
	van der Meer 1993[221]	ASA vs. ASA/DIP vs. OAC	No differences
	Lim 2003[223]	ASA 300-325 mg vs. ASA 75-100mg	Higher patency rates with 300-325 mg ASA
Indobufen	*Rajah 1994*[227]	Indobufen vs. ASA/DIP	No differences
	Cataldo G 1998[228]	Indobufen vs. ASA/DIP	No differences
Clopidogrel	*Ibrahim 2006*[304]	ASA vs. ASA/clopidogrel	No differences
	Kulik 2010[305]	ASA vs. ASA/clopidogrel	No differences
	Ebrahimi 2014[306]	ASA vs. ASA/clopidogrel	No differences
	Mujavonic 2009[218]	ASA vs. ASA/clopidogrel	Higher patency rates with ASA/clopidogrel
	Gao 2009[307]	Clopidogrel vs. ASA/clopidogrel	No differences
	Gao 2010[219]	ASA vs. ASA/clopidogrel	Higher patency rates with ASA/clopidogrel
	Sun 2010[220]	ASA vs. ASA/clopidogrel	Higher patency rates with ASA/clopidogrel in radial artery grafts
	Mannacio 2012[308]	ASA vs. ASA/clopidogrel	Higher patency rates with ASA/clopidogrel
	Deo 2013[217]*	ASA vs. ASA/clopidogrel	Higher patency rates with ASA/clopidogrel
Ticlopidine	*Chevigné 1984*[211]	Ticlopidine vs. placebo	Higher patency rates with ticlopidine
	Limet R 1987[212]	Ticlopidine vs. placebo	Higher patency rates with ticlopidine

Table 2b. Effect of antiplatelet drugs on vein graft patency after PABG

Antiplatelet drugs	Study	Randomisation	Vein graft patency
Aspirin or dual antiplatelet	*Kohler 1984*[309]	ASA/DIP vs. placebo	No differences
	Satiani 1985[310]	ASA vs. no therapy	No differences
	Clyne 1987[311]	ASA/DIP vs. placebo	No differences
	McCollum 1991[312]	ASA or ASA/DIP vs. placebo or no therapy	No differences
	Edmondson 1994[313]	ASA/DIP vs. LMWH (Fragmin)	LMWH higher patency rates
	Algra 2000[230]	ASA vs. OAC	OAC more effective in SVG, ASA more effective in PTFE grafts
	Johnson 2002[231]	ASA vs. ASA/OAC	No differences
	Bedenis 2015[224]*	ASA or ASA/DIP vs. placebo or no therapy	Higher 1 year patency rates ASA and ASA/DIP
Indobufen	*D'Addato 1992*	Indobufen vs. ASA/DIP	No differences
Clopidogrel	*Belch 2010*[216]	Clopidogrel/ASA vs. ASA	No differences
	Monaco 2012[314]	Clopidogrel/OAC vs. clopidogrel/ASA	Higher patency rates with clopidogrel/OAC
Ticlopidine	*Becquemin 1997*[213]	Ticlopidine vs. placebo	Higher patency rates with ticlopidine

Abbreviations: ASA = aspirin, DIP = dipyridamole, LMWH = Low molecular weight heparin, OAC = oral anticoagulant, SVG = saphenous vein graft, PTFE = polytetrafluoroethylene * = meta-analysis

Indobufen, an antiplatelet agent that prevents platelet aggregation by reversibly inhibiting cyclooxygenase, has been investigated as a potential alternative for aspirin[225]. In a crossover study, researchers showed that indobufen was as effective as aspirin in inhibiting platelet aggregation. Several clinical trials have also showed similar benefits of indobufen and aspirin plus dipyridamole in preventing VGF[226-228]. Whether indobufen could be considered as an alternative treatment for dual antiplatelet therapy is still under investigation. No recommendations have been made in current guidelines regarding the use of indobufen.

Oral anticoagulants

Oral anticoagulants are recommended after CABG surgery if the patient is considered to be at risk for a thromboembolic event. According to the ESC, anticoagulation should be considered for at least three months, with reassessment of stroke risk thereafter (class of recommendation I, level of evidence C)[4]. Oral anticoagulants such as vitamin K antagonists, factor Xa inhibitors, or direct thrombin inhibitors can inhibit and even prevent thrombus formation on the luminal surface. At present, a consensus has not yet been reached regarding the use of oral anticoagulants alone or in addition to antiplatelet therapy in the prevention of VGF. Patients undergoing infrainguinal venous graft surgery are more likely to benefit from vitamin K antagonists than antiplatelet therapy[229]. In the Dutch BOA study[241], oral anticoagulation appeared to be more effective in preventing VGF, while aspirin prevented cases of **polytetrafluoroethylene** graft occlusions[230]. Furthermore, Johnson et al. demonstrated that addition of warfarin therapy to aspirin therapy did not improve vein graft patency rates[231].

Lipid Lowering

The ESC recommends statin therapy in patients undergoing CABG surgery (class of recommendation I, level of evidence A) with an initial LDL-cholesterol goal of <70 mg/dl (<1.8 mmol/l)[210]. In addition, the ACC/AHA guidelines recommend an LDL-cholesterol goal of <100 mg/dL and at least a 30% lowering of LDL-cholesterol (class of recommendation I, level of evidence C)[19]. Statins are also indicated for all patients undergoing PABG surgery to strive for a target LDL-cholesterol level of <100 mg/dL, and <70 mg/dl for patients with lower extremity PAD at very high risk of ischaemic events (class of recommendation IIa, level of evidence B)[21].

The beneficial effect of statin therapy is thought to be based on its inhibitory effects on SMC proliferation and its anti-inflammatory effects, which result in decreased intimal hyperplasia formation[232-236]. Statin therapy was also reported to be protective against perioperative mortality after CABG surgery[237]. While most studies focus on

lowering LDL-cholesterol level in these patients, the CASCADE trial showed that HDL level <40 mg/dl were associated with a trend towards increased VGF, suggesting that higher levels of HDL-cholesterol might slow the process of VGF[238].

Emerging treatment strategies

Ticagrelor

Ticagrelor, a P2Y12 antagonist, was reported to be safe and efficient for platelet inhibition in a phase II trial in patients with critical limb ischemia[239]. Hansson *et al.* observed a lower overall incidence of major bleeding complications in patients undergoing CABG surgery treated with ticagrelor compared with clopidogrel[240]. Compared with clopidogrel, discontinuing ticagrelor for <24 hours before surgery increased the risk of complications, while discontinuing ticagrelor 3 or 5 days before peripheral endovascular procedures showed no differences in complications[241]. Furthermore, the PLATO trial showed that combined ticragrelor and aspirin treatment was superior to combined clopidogrel and aspirin treatment in patients with acute coronary syndrome[242]. The ongoing TiCAB trial aims to prospectively investigate the efficacy and safety of ticagrelor compared with aspirin in patients undergoing CABG surgery[243], with the primary end point of cardiovascular death, myocardial infarction, target vessel revascularization, and stroke. Although the use of ticagrelor after CABG surgery has been studied extensively, whether it is beneficial for patients undergoing PABG surgery is not yet known.

Direct platelet receptor inhibitors

Platelets play a major role in the development of CAD, PAOD, and VGF. VGF still occurs despite dual antiplatelet therapy, likely owing to the complexity of the thrombus formed. Thrombin, a potent platelet agonist that acts via protease-activated receptors (PAR), might be a potential target to further prevent thrombus formation. Antiplatelet drugs do not affect platelet activation mediated by thrombin,[244] and thus blocking PAR might inhibit VGF.

Several phase II and III trials have been performed to study the efficacy and safety of the PAR-1 antagonists vorapaxar and atopaxar[245]. In a phase II study published in 2009, vorapaxar treatment was compared with placebo in patients with CAD undergoing balloon angioplasty. Vorapaxar was well tolerated among treated patients, and did not increase the risk of bleeding[246]. The phase III TRA 2°P-TIMI 50 study[247, 248], a randomized, double-blind, placebo-controlled trial, evaluated the efficacy and long-term safety of vorapaxar in 26,449 patients with previous atherothrombosis. Vorapaxar reduced cardiovascular death, myocardial infarction, or stroke in stable patients with a history of previous myocardial infarction[247, 248]. The

subsequent TRACER trial[249] reported similar results in patients with non-ST-segment elevation acute coronary syndrome who are undergoing CABG surgery. Together, these results suggest that vorapaxar might be safe for the prevention CABG-related bleeding, but whether vorapaxar has a clinical benefit on vein graft patency in patients undergoing bypass grafting remains to be elucidated.

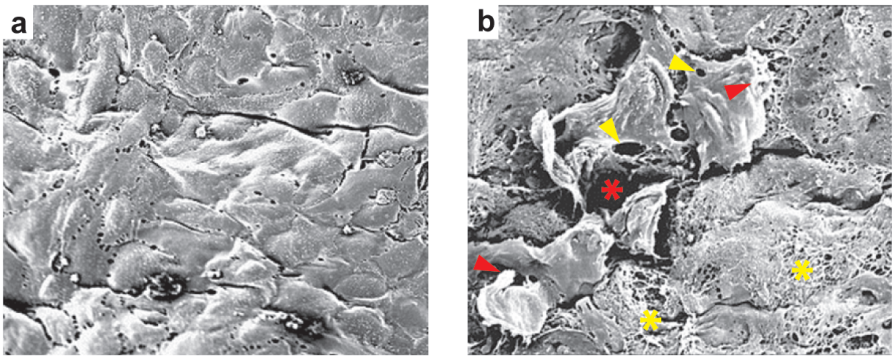

Figure 6. Scanning electron microscopy photographs of saphenous veins. **a.** An almost uninterrupted, continuous layer of endothelial cells in a saphenous vein is shown (magnification x430). **b.** Part of the venous conduit show signs of de-endothelialization (red asterisk) after handling and before engraftment, resulting in exposure of collagen fibres (yellow asterisk). The remaining endothelial cells show early signs of apoptosis in the form of blebbing (red arrowhead) and vacuolisation (yellow arrowhead; magnification x1400).

The safety and efficacy of atopaxar for patients with acute coronary syndromes and chronic CAD has also been evaluated in a phase II trial[250]. The J-LANCELOT investigators reported that atopaxar did not increase clinically significant bleeding compared with placebo[250]. Kogushi *et al.* demonstrated inhibition of SMC proliferation *in vitro* and reduced intimal hyperplasia *in vivo* with atopaxar[251]. Atopaxar reduced early ischemia on Holter monitoring without significantly increasing major or minor bleeding events in patients after acute coronary syndrome in a phase II trial published in 2011[261]. A subsequent phase II trial reported more minor bleeding with atopaxar compared with placebo, and numerically, but not statistically fewer ischaemic events in patients with CAD[252, 253]. Phase III trials are needed to confirm the beneficial effect of direct thrombin inhibitors in preventing VGF.

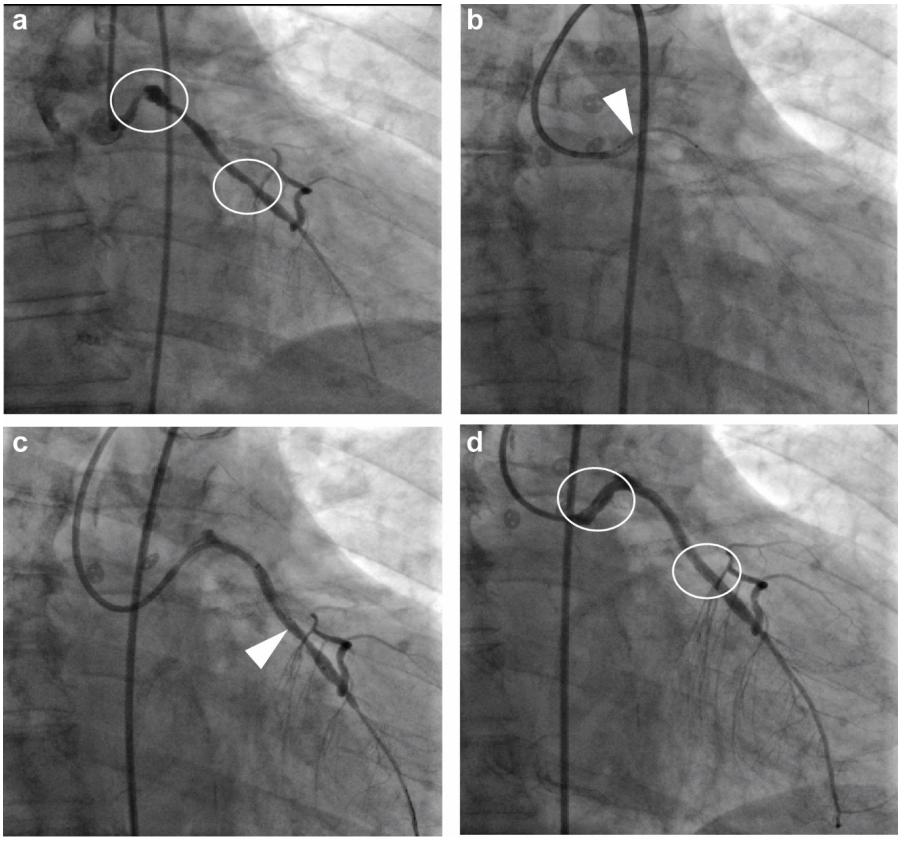

Figure 7. Angiograms of a patient aged 84 years who underwent CABG surgery 11 years prior who is now experiencing unstable angina. A revascularization of the saphenous vein graft from the r. descendens anterior to the left anterior descending artery is shown, with drug eluting stent placement. **a.** The angiogram shows a very proximal lesion and a more distal lesion in the saphenous vein graft. **b.** Drug-eluting stent placement in the proximal part of the graft **c.** Drug eluting stent placement in more distal part of the graft is indicated by the arrow. **d.** Angiographic result after stent placement shows the restoration of blood flow.

Inhibition of SMC proliferation and migration

SMC proliferation and migration to the intima is tightly regulated by growth factors such as VEGF, PDGF, TGF-β, and bFGF. SMC proliferation and migration is necessary for arterialization that occurs in response to injury after bypass surgery. However, excessive SMC stimulation ultimately leads to formation of intimal hyperplasia[254]. Inhibition of SMC proliferation and migration is one of the primary targets for the treatment of VGF. The cyclin-dependent kinase inhibitor 1B (also known as p27Kip1), plays an important role in maintaining SMC quiescence. p27Kip1 reduction led to

diminished intimal hyperplasia formation in experimental vein graft models[255, 256]. Interestingly, a single nucleotide polymorphism in the promoter region of the p27Kip1 gene is associated with peripheral graft patency[257].

Immunosuppressant drugs such as paclitaxel and sirolimus have also been shown to reduce SMC-driven intimal hyperplasia in various experimental models[258-260]. To date, clinical trials assessing the benefit of these anti-proliferative drugs for VGF have not yet been performed. However, the use of drug-eluting stents (DES) containing paclitaxel or rapamycin to revascularize failing grafts have been proven beneficial, and is discussed below.

E2F transcription factor oligonucleotide decoys

Edifoligide is an oligonucleotide decoy that binds to and inhibits E2F transcription factors and, therefore, might prevent intimal hyperplasia formation and VGF. While experimental studies have shown favourable results,[261] no clinical trials to date have demonstrated the benefit of edifoligide for prevention of VGF. Edifoligide has been studied in four PREVENT trials. The PREVENT I trial was a pilot study in patients (n = 41) undergoing PABG surgery and reported that edifoligide is safe, feasible, and could achieve sequence-specific inhibition of cell-cycle gene expression and DNA replication[262]. The PREVENT III trial and PREVENT IV trial were initiated to evaluate the efficacy and safety of edifoligide for the prevention on VGF at 1 year in patients undergoing PABG surgery (n = 1400) or CABG surgery (n = 3000), respectively. Despite promising results of the first two trials, edifoligide was no more effective than placebo in preventing VGF in these two patient cohorts after 12–18 months[263]. Although the results of the PREVENT trials were disappointing, they are the first clinical trials to evaluate the use of intraoperative gene therapy in preventing VGF. Whether or not edifoligide should be used to prevent VGF is still under debate and should be further investigated[263, 264].

Future potential treatment strategies

Gene therapy

Gene therapy has emerged as a potential therapy for the treatment and prevention of VGF. Saphenous vein grafts are ideally suited for gene therapy because they can be genetically modified *ex vivo* during the surgical procedure and prior to grafting[265]. Direct local delivery of recombinant viral vectors is possible and the risk of systemic exposure can be reduced[266]. Preclinical studies on a number of gene transfer strategies using specific genes delivered intraoperatively have been effective in either preventing intimal hyperplasia by limiting SMC proliferation or inflammation, or in improving endothelial function[128, 130, 134, 267]. Although these experimental approaches

have not been consistently successful, the practical benefits of gene therapy in vein grafts make it a promising technique and hopefully promising preclinical trials results will be translated into clinical applications in due time[22, 261].

External stenting

External stenting is another promising technique for the prevention of VGF. The use of external stents significantly reduced intimal hyperplasia in animal models, as discussed previously. In theory, external stenting should reduce wall tension, reduce stretching of endothelial cells, and function as a protective outer layer[268]. Despite the promising results obtained in experimental studies, the results from clinical studies were less positive. Graft patency rates were low after external stenting[269-271], likely owing to the stent size and material used, and the use of fibrin glue. Fibrin glue was used to attach the external stent to the outer layer of the vein graft; its use is no longer recommended as it has been associated with chronic inflammation and VGF[272]. More promising results of external stenting has been published in the past year. Ferrari *et al.* reported positive preliminary clinical results using a newly designed external mesh device that could improve long-term graft durability.[272] Similarly, Taggart *et al.* showed reduced intimal hyperplasia with use of external stenting 1 year after CABG surgery[268]. The material, stent size, and placement of the external stent is of critical importance[70]. Further studies are needed to investigate the effect of external stenting on graft patency rates after bypass surgery. The first-in-human study with the aim of testing the preliminary safety and efficacy of the Angioshield wrap, an external vein graft support device, is currently ongoing[273].

Graft complications and aneurysms

Coronary vein graft aneurysms have been described incidentally since 1975, however, peripheral vein graft aneurysms have not yet been reported[274]. Vein graft aneurysms might be asymptomatic, though symptoms can arise from associated complications such as distal embolization into the grafted artery, vessel rupture, fistula formation on adjacent vascular compartments, or compression of neighbouring structures. The mechanisms responsible for aneurysmal dilatation of the vein grafts are poorly understood, but atherosclerosis and inflammatory factors are known to contribute to weakening of collagen in the vessel wall[275]. A review of 209 cases of aortocoronary saphenous vein graft aneurysms showed that in 90% of patients, CABG surgery was performed >5 years prior to detection of the aneurysm[276].

Treatment strategies

Treatment strategies for VGF consists of medical therapy, thrombectomy, redo bypass graft surgery, or balloon angioplasty with or without stenting (Figure 7)[4, 277]. The most appropriate treatment modality for each individual patient will depend on severity of symptoms, presence and extent of ischemia, and the relative benefits and risks involved (such as the patient's general condition and presence of patent arterial grafts). Repeat bypass graft revascularization is associated with a fourfold higher mortality rate than primary CABG surgery[278, 279]. No consensus has been reached on how to treat the diseased vein grafts during repeated surgical revascularization. Some surgeons prefer to leave them untouched to prevent distal embolization, and make a new distal anastomosis on the target artery. When the original distal anastomosis is still patent, the vein can be transected at that level and the new graft can be anastomosed at this site[279]. Other surgeons prefer to ligate the diseased vein graft, or to completely remove it. However, in redo bypass graft surgery, particular for peripheral grafts, the saphenous vein is no longer available and other graft materials will need to be used.

Balloon angioplasty alone has proven to be efficacious for the treatment of VGF, although high rates of restenosis and major adverse events have been reported for both CABG surgery and PABG surgery[280, 281]. Mechanical embolic protection devices are useful during balloon angioplasty of vein grafts for the prevention of distal embolization[282,283]. Stents are known to dramatically reduce restenosis[284]. The SAVED trial[285] was the first study that compared balloon angioplasty with bare metal stents (BMS) on clinical outcomes in patients with obstructive disease of saphenous vein grafts. BMS reduced the need for revascularization of the target lesion and reduced major cardiac events compared with balloon angioplasty[285]. Various studies have compared balloon angioplasty alone, balloon angioplasty with BMS and or balloon angioplasty with DES in VGF. Inconsistent results have been reported for the use of balloon angioplasty alone or balloon angioplasty with either BMS or DES in the treatment of VGF after PABG surgery or CABG surgery[280,286-288]. No specific recommendations have been made by either the European and the American guidelines for revascularization after CABG surgery and PABG surgery[4, 19-21]. However, in the clinical setting of CABG surgery, balloon angioplasty with DES is the most frequently used technique, and has been shown to be a safe and effective treatment for patients with failing saphenous vein grafts[289].

Vein graft interventions are risk-prone procedures that are associated with poor long-term prognosis; however, the use of these techniques is unavoidable. The preferred percutaneous revascularization strategy of uncomplicated stenotic grafts are

balloon angioplasty with DES in combination with optimal medical therapy (such as antiplatelet therapy) and distal protection devices, when applicable[283]. Redo bypass graft surgery might be the preferred option for old or diffusely diseased venous grafts instead of percutaneous revascularisation. The optimal revascularisation strategy should ultimately take into account patient-specific and procedure-related factors.

Future perspectives

The barriers in finding a real breakthrough in treatment of VGF are attributable to the multifactorial nature of the processes involved in VGF and the frequently observed comorbidities in the patients with VGF. Mimicking this complex process using *in vitro* cultured human saphenous vein segments is challenging[114, 130, 152, 290]. In this respect, animal models of VGF that suffer from comorbidities such as hypercholesterolaemia or diabetes are crucial for research[25, 291]. Interestingly, despite the major advances in genetic analysis of cardiovascular disease and predictive values of single-nucleotide polymorphism analysis for assessment of cardiovascular risk, yet no other genetic factors are found that are linked to increased risk of VGF besides p27Kip1[257,292]. New methods for predicting adaptions, remodeling, and even failure of vein grafts via a dynamic system that takes into account shear stress have been described[293, 294]. Furthermore, advances in imaging technologies such as optical coherence tomography definitely will lead to less invasive analysis of vein graft remodeling and will provide more insight in the progression of VGF in patients after CABG surgery and PABG surgery[295].

Conclusions

Vein graft surgery is one of the preferred surgical treatment options for occlusive arterial disease. Although the use of vein grafts has diminished over the past few years and has been replaced by arterial grafts and balloon angioplasty, a substantial number of patients still require one or more vein grafts. Therefore, the issue of low patency rates owing to VGF needs urgent attention. Given their anti-inflammatory properties and ability to reduce plasma cholesterol levels, statins are recommended for the prevention of VGF[4, 19-21]. New therapies for the treatment of VGF, such as gene therapy and external stenting are promising, but require more research. Although the PREVENT studies did not show increased patency rates with the use of E2F oligonucleotide decoys as initially hypothesized, the results provided much insight in the development of VGF. The vein graft harvesting technique, duration of the surgery, graft handling, and the size and condition of the conduit and target vessel are all predictors of VGF. Preclinical and histopathological studies of human vein grafts further demonstrate that constrictive remodeling, intimal hyperplasia formation, and unstable atherosclerotic lesions contribute to long-term VGF. These studies have

shown that inflammatory components, especially those from the innate immune system, are crucial in all stages of vein graft development and failure, and have thus suggested targeting inflammatory mediators for treatment of VGF. Furthermore, VGF can also be treated by preventing endothelial cell damage, stimulating endothelial regrowth, and inhibiting SMC migration and proliferation. Additional studies are required to unravel the full potential of these treatment targets in preventing VGF and optimizing arterialization, and finding the best revascularization strategies for failing grafts.

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