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REVIEW ARTICLE

Saphenous vein graft disease, pathophysiology, prevention, and treatment. A review of the literature

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Abstract

Background: The saphenous vein remains the most frequently used conduit for coronary artery bypass grafting, despite reported unsatisfactory long-term patency rates. Understanding the pathophysiology of vein graft failure and attempting to improve its longevity has been a significant area of research for more than three decades. This article aims to review the current understanding of the pathophysiology and potential new intervention strategies.

Methods: A search of three databases: MEDLINE, Web of Science, and Cochrane Library, was undertaken for the terms "pathophysiology," "prevention," and "treatment" plus the term "vein graft failure."

Results: Saphenous graft failure is commonly the consequence of four different pathophysiological mechanisms, early acute thrombosis, vascular inflammation, intimal hyperplasia, and late accelerated atherosclerosis. Different methods have been proposed to inhibit or attenuate these pathological processes including modified surgical technique, topical pretreatment, external graft support, and postoperative pharmacological interventions. Once graft failure occurs, the available treatments are either surgical reintervention, angioplasty, or conservative medical management reserved for patients not eligible for either procedure.

Conclusion: Despite the extensive amount of research performed, the pathophysiology of saphenous vein graft is still not completely understood. Surgical and pharmacological interventions have improved early patency and different strategies for prevention seem to offer some hope in improving long-term patency.

KEYWORDS
cardiovascular pathology, clinical review, coronary artery disease

1 | INTRODUCTION

Coronary artery bypass grafting (CABG) remains the gold standard treatment for severe coronary artery disease, especially for patients with diabetes and low ejection fraction.[1] The most frequently used conduits for CABG are the left internal thoracic artery (LITA) and the long saphenous vein (LSV). While the LITA has been shown to have an excellent long-term patency rate, it is limited by its length and therefore it is not generally suitable for multiple grafts.[2,3] The LSV, on the other hand, is readily available in greater lengths to construct

more than one graft and can be harvested at the same time as the LITA. For these reasons, the LSV remains one of the most commonly used conduits for CABG.[3] Other conduits not extensively used are the radial artery and the right internal thoracic artery.[1]

Despite its extensive use, the LSV graft suffers short-term failure and has a low long-term patency rate resulting in lower long-term survival and event-free survival compared with arterial grafts.[2,4]

Over the years, there has been increased interest in understanding the pathophysiology involved in the development of vein grafts disease as although many therapeutics have been suggested, none has been successful enough to make them widely adopted. This is in part related to our limited understanding of the complex pathological processes involved in the development of the disease starting from vascular inflammation (VA) to superimposed atherosclerosis, the cross-talk between the different cells forming the LSV and the influence of the circulating cells and other molecules. The overall process is thought to be marked by complex interactions between several factors owned to either the patient or the technique which will ultimately impact the pathophysiology of the disease, making its study challenging.

2 | METHODS

Original research articles and reviews were selected as they related to the pathophysiology, prevention, and treatment of SV graft failure. A literature search was performed using MEDLINE, Web of Science, and Cochrane Library. The search was focused on human, translational, in vitro, and animal studies.

3 | RESULTS

3.1 | Pathophysiology of LSV graft failure

The pathophysiology of LSV graft failure has been described as driven by four interconnected and related processes: early acute thrombosis (AT), VA, intimal hyperplasia (IH), and late accelerated atherosclerosis.[5,6]

3.1.1 | Acute thrombosis

It is widely accepted that AT is responsible for the majority of early vein graft failures.[5,7] This process starts from the harvesting of the LSV, where surgical injury combined with hypoxia caused by damage to the vasa vasorum, oxidative stress, wall distention, and acute elevation of shear stress can lead to endothelial dysfunction and activation and make it switch to a prothrombotic state, or even de-endothelialize the vessel exposing the extracellular matrix (ECM) to the blood in the lumen.[6,8] This results in a loss of balance between antithrombotic and prothrombotic systems in favor of the latter with a marked reduction of nitric oxide (NO), prostacyclin (PGI$_2$),

thrombomodulin, and heparin-like substances in injured endothelium associated with increased expression of adhesion molecules and the sensitivity of the vascular smooth muscle cells (VSMC) to vasoconstrictors.[6,9] Furthermore, there is simultaneous activation of the coagulation cascade resulting in platelet activation and adherence to the de-endothelialized areas with the generation of different pro-coagulation factors such as thromboxane A2, fibrinogen, fibronectin, thrombospondin, von Willebrand factor, platelet factor IV, and b-thromboglobulin.[6,7,9-11] These processes combined can culminate in 3% to 12% early graft occlusions.[7]

It has been described that the endothelial lining of the grafts can recover after this initial process, although, as described below, the new endothelium can be dysfunctional.[10,12]

3.1.2 | Intimal hyperplasia

IH is a chronic disease where the VSMCs in the medial layer switch from a quiescent state to a synthetic proliferative, resulting in migration to the intimal layer where they proliferate causing further thickening of the intimal.[8,13] The function of both VSMCs and endothelial cells (ECs) is linked by their physical and paracrine interactions, which controls vascular tone, cell proliferation and response to inflammation.[14] In a healthy state the interaction between ECs and VSMCs keeps the VSMCs in a quiescent state; via EC-derived homeostatic molecules like NO which help regulate the tone of the medial layer and suppress VSMC phenotypic switching to synthetic cells.[14] Local inflammation and endothelial injury cause the ECs to switch to a prothrombotic state and, therefore, this interaction is disrupted.[10] This, can be further enhanced by the release of cytokines like interleukin-6 (IL-6), IL-8, and thromboxane A2 and growth factors like platelet-derived growth factor and fibroblast growth factor from activated platelets and leukocytes contributing to VSMC phenotypic switching to synthetic phenotype and proliferation.[10,15] Also, it is known that both ECs and VSMCs secrete ECM proteins, and this may be a way of indirect communication, which induces VSMC phenotypic switching and proliferation.[14] ECs may also induce VSMCs proliferation via microRNAs. For example, increased levels of endothelial-derived miR-126 resulted in higher VSMC turnover (proliferation and apoptosis).[16] On the other hand, ECs microRNAs miR-143/145 have been associated with decrease IH possibly through downregulation of VSMC phenotypic switching mechanism; while miR-126 seems to contribute to the formation of IH since its depletion in mice resulted in IH suppression.[17] However, these studies relate specifically to IH and not in the context of LSV graft.

After the initial denudation, new ECs can be seen as early as the first week after surgery in experimental models, however, after the endothelium is restored the process of IH does not reverse, this is thought to be in part due to the increase of shear stress on the wall which makes the new endothelium dysfunctional and partly due to the now chronic localized inflammatory response.[5,11,18]

Some studies on VSMCs have identified the importance in the development of IH, of Kruppel-like factor 4 (KLF4) and Kruppel-like

factor 5 (KLF5), both protein-coding genes. KLF4 acts as a down-regulator of VSMCs contractile markers such as smooth muscle α-actin, SM22α, and smooth muscle myosin heavy chain, thus switching the cell to a synthetic state. However, KLF4 may serve as an athero-protective factor, its overexpression in ECs induces the upregulation of anti-inflammatory and antithrombotic factors.[19] KLF5 has been seen to increase in response to vascular injury and atherosclerotic lesions.[19] KLF5 may activate VSMCs to switch, migrate and proliferate as is preferentially expressed in de-differentiated VSMCs. A study also found an association between KLF5 positive VSMCs and a higher risk of graft restenosis in rabbits.[19,20]

Other important factors in the development of IH that have been studied are p38 mitogen-activated protein kinase (p38), and nuclear factor kappa-light-chain-enhancer of activated B cells both have been evidenced to induce VSMC proliferation in vitro using models of cultured VSMCs and on coculture models of VSMCs and ECs.[21-23]

The development of IH is, a complex process in which the VSMCs and the ECs play a crucial role, but the entire process is not yet completely understood, and by expanding our comprehension of this process we may find new therapeutic targets to reduce the rate of LSV graft failure.

3.1.3 | Accelerated atherosclerosis

Atherosclerotic disease progresses much rapidly in LSV grafts as compared to native arteries, as its lipolysis is slower and suffers from accelerated lipid uptake.[24] Compared to native atherosclerotic plaques, the LSV plaque is more highly populated with foam cells and other inflammatory cells, including multinucleated giant cells. It has been detected that some of these cells may originate from venous VSMCs rather than from circulating cells, making IH an important contributor to the speed and severity of atherosclerosis in vein grafts.[24]

Like the native artery atherosclerosis, the vein graft atherosclerosis can suffer plaque rupture and AT, which has been described in necropsy samples.[25] However, the vein graft atherosclerosis tends to be diffuse, concentric, and friable with a poorly developed or absent fibrous cap and little evidence of calcification, making it more prone to rupture than native artery atherosclerotic plaques.[6,18,26,27]

3.1.4 | The role of inflammation

At any time during the development of the previous three mechanisms of LSV graft failure, there can coexist a certain degree of localized acute or chronic inflammation, which exacerbates the pathophysiological stage of the graft failure. During the initial phase of this process the exposure of the ECM to the lumen of the vessel in an area of de-endothelialisation recruits leukocytes and platelets. These cells infiltrate the intima, this process will alternate between acute and chronic with more or less leukocyte activation.[10] IH is enhanced by growth factors and cytokines IL-1, IL-6, and tumoral necrosis

factor-alpha released by inflammatory cells. In a later stage, monocytes infiltrate the IH layer and differentiate into macrophages as is developing into an atherosclerotic plaque and develop into foam cells as they would on the artery's atherosclerosis due to uptake of lipid, but the localized chronic inflammatory changes make this process happen faster than in native arteries. Intimal macrophages secrete matrix metalloproteinases which lead to ECM and cell-to-cell contact cleavage further inducing VSMCs migration into the intima and proliferation. The presence of VSMCs within the intimal layer, triggers further inflammation, attracting additional macrophages into the IH layer, thus accelerating atherosclerosis (see above).[18]

During this process of inflammation damage to perivascular fat will release cytokines and recruit lymphatic cells in the vessel's adventitia which will, in turn, secrete proinflammatory cytokines, disruption of perivascular fat also reduces the bioavailability of NO which acts as a regulator of vascular tone and signals the VSMCs to stay in a contractile state.[10,18]

3.2 | Prevention of LSV failure

The quest for modifiable factors that influence graft failure has occurred for more than three decades. Some of the following are methods that may reduce the incidence of graft failure.

3.2.1 | Reducing atherosclerosis risk factors

Atherosclerosis associated risk factors are still present in the patient after CABG, some of which have been directly associated with poor prognosis of the LSV grafts.[6]

- Smoking: Multiple studies have identified the role of smoking habit in the development of both long and short-term LSV graft disease and inferior survival after CABG.[7,28,29]
- Dyslipidaemia: Evidence points towards hyperlipidaemia as one of the main risk factors in the development of vein graft disease; cholesterol levels higher than 240 mg/dL have shown a significant increase in the rate of LSV graft obstruction, similarly as found in native coronary disease with the relation between LDL cholesterol and HDL cholesterol is as important as the total serum cholesterol. The elevation of triglycerides in the serum has also been related to late vein graft failure. Furthermore, there is a strong association between dyslipidaemia and long-term morbidity and mortality after CABG. Aggressive treatment and prevention of hyperlipidaemia has been associated with better long-term outcomes.[30-32]
- Hypertension: Despite its role in systemic atherosclerosis, studies looking at hypertension as a risk factor for LSV failure have found no such association.[6]
- Diabetes mellitus (DM): There is conflicting evidence regarding the influence of DM on vein graft disease. Some studies have found that poorly controlled DM is associated with worse survival after CABG, while others found no significant difference in the rate of

LSV graft occlusion.[30,33] No prospective study has explicitly looked at DM as a risk factor for LSV graft failure, and several laboratory studies have shown that DM impairs some of the vasodilator mechanisms, suggesting a role in graft disease.[30,33]

3.2.2 | Surgical technique

There is compelling evidence that a technique or surgical strategy affects LSV graft failure.

- Endoscopic vs Open LSV harvesting: Minimizing surgical trauma and improvement in patient's quality of life was the driving for the development of endoscopic vein harvesting. However, there is now concern over this technique due to lower long-term patency rates of LSV grafts retrieved endoscopically.[34-36]
- Distention: There is a large body of evidence that harvesting and subsequent distention of the LSV at more than 150 mm Hg causes endothelial denudation exposing the ECM to the lumen, and increases rates of long-term graft failure.[18,37,38]
- Harvesting, skeletonized vs "no-touch" LSV harvesting: Preserving the vein adventitia and the perivascular fat let to the development of the "no-touch" technique, which consists of harvesting the LSV with its perivascular fat and ligating the tributaries at least one centimeter away from the vein. This technique associated with nonabove-arterial pressure distention has demonstrated in some studies to provide substantially better long-term outcomes in terms of vein graft patency. However, it has the disadvantage of being associated with a higher incidence of graft site complications in the early postoperative period.[38-42]
- Vein preservation media: The choice of preservation media during storage of the LSV prior to its use has been associated with increased concentration of free oxygen radicals and ischemia in all layers of the vein.[43] On this subject, ex-vivo studies have shown a benefit in using the patient's heparinized blood, but this benefit has not been able to be demonstrated in clinical practice.[43] However, recent studies have demonstrated that a pH buffer in either crystalloid or blood media has provided a significant clinical benefit.[43,44]
- Technical aspects: Anastomotic technique is thought to be crucial for graft longevity, with poor technique and excessive surgical trauma associated with early vein graft failure. Accurate graft length is critical, both too short and too long grafts suffer from worse outcomes. There is evidence that graft longevity is dependent on the target vessel and its capacity to provide a good runoff flow. Advocates of the good runoff theory suggest that sequential anastomoses achieve a better runoff and lesser peripheral resistance to flow and therefore, improved long-term patency.[41,45-48] While some evidence supports this statement a recent paper found worse rates of LSV graft failure with sequential anastomoses.[41,45-48]
- Flow measurement: Transit time flow measurement (TTFM) may provide the surgeon with a tool for assessing both anastomosis quality and distal runoff while still in the operating theater; the current guidelines are that it should be considered. However, there are discrepancies in what values are considered acceptable and studies looking at this technique as a predictor for graft failure tend to use different values which are sometimes arbitrary. Despite these limitations, TTFM has shown to be useful in determining technical graft problems as is highly specific when a graft has a negative flow or high resistance, which can be caused by problems in the anastomosis.[48-51]

3.2.3 | External graft support

External stenting has been proposed to reduce the rate of IH on vein grafts, by imposing LSV graft symmetry, more laminar flow and the subsequent reduction of shear stress, and also by providing a protective environment for the formation of new adventitia. However, despite promising results in animal models,[52] early clinical trials have shown conflicting results such as a higher failure rate on right-sided grafts.[53] Further trials will be needed before its application in clinical practice.[52-56]

3.2.4 | Topical pretreatment

Storage of the LSV before its use provides a window of opportunity for topical treatments.[18,57]

Gene therapy of the graft before implantation, have shown encouraging results in experimental animal models but contrasting results in the clinical context.[9,58-60] There has been a success in ex-vivo models with TIMP-3 gene therapy and a clinical trial has been proposed.[61]

3.2.5 | Pharmacological therapy

- Aspirin: Several prospective randomized trials have looked at the influence of aspirin vs placebo after CABG and demonstrated an increase in graft patency in patients receiving aspirin.[62,63] Current trials recommend that aspirin therapy should be started as soon as possible after the operation as it has shown that if it started after the third day after surgery, it provides no benefit.[62] Consequently, its implementation in the first-day postoperation showed a significant reduction of both early and late graft failure. Another important consideration is that it has been demonstrated that part of the population appears to be nonresponsive to aspirin and does not experience the same benefits as responding to patients.[2,62,63]

Current indications suggest starting aspirin as early as 6 hours after surgery and continuing high dose aspirin for at least a year, also if tolerated low dose aspirin is indicated after that for secondary prevention of atherosclerosis.[1]

- Dual antiplatelet: Recent guidelines recommend dual antiplatelet therapy with clopidogrel and aspirin for patients undergoing

CABG. Recent studies have shown a decrease in cardiovascular mortality in patients with dual antiplatelet therapy; however, it is still unclear whether different antiplatelets therapies combined with aspirin provide different outcomes.[35,41,64] There is a need for trials that evaluate the efficacy of different antiplatelet agents when compared to each other.

- Statins: Hyperlipidaemia is a major contributor to LSV graft disease, and statin therapy has a beneficial effect on event-free survival after CABG.[32] The American Heart Association recommends the use of statins after CABG in the absence of contraindications.[32,65-67]

3.3 | Treatment after LSV failure

When vein graft failure results in clinical events or symptoms, it will require treatment. Deciding the appropriate therapy after LSV graft failure is often problematic and should be a decision taken by a multidisciplinary heart team.[7] The treatment options are usually percutaneous coronary intervention (PCI) and repeat CABG; both have significantly increased risks as compared to first-time intervention. Therefore, some patients will be deferred to medical management instead. [7]

3.3.1 | Vein graft angioplasty

PCI after vein graft failure accounts for 5% to 10% of all PCIs performed in the United States in a year,[68] the procedure is technically challenging, especially if treating early graft failure, the risk of distal embolization is high, and some authors suggest the use of distal embolic protection devices. Regarding the choice of the stent, recent studies suggest that drug-eluting stents may offer an advantage over bare-metal stents. Long-term results are better with PCI than with medical treatment alone but are far from ideal and are indeed worse than outcomes of patients without vein graft failure.[7,69]

3.3.2 | Reoperation

Repeat CABG may be an option for patients with LSV graft disease. However, is with a significantly higher risk of mortality and morbidity, which is increased in cases when one or more of the grafts are patent, or for of lack available conduits. Comparison between long-term outcomes between reoperation and PCI is difficult as there is a substantial selection bias, but similarly to PCI long-term outcomes after reoperation are worse than those of patients with no graft failure. [70]

3.3.3 | Medical management

Although both PCI and reintervention offer better long-term outcomes than medical therapy sometimes the initial elevated risk may preclude patients from receiving either intervention, in those cases patients will be managed with a combination of medical therapy and control of risk factors to achieve at least symptomatic control.[7,71]

4 | CONCLUSIONS

Vein graft failure is a multifactorial process embedded in an already complex disease, atherosclerosis. Recent studies have helped further our understanding of the pathophysiology of this condition and have already yielded advancements in its secondary prevention; there is still to be seen the impact of these advancements in the reduction of long-term vein graft failure.

The clinical significance of LSV graft failure remains debated.[34] The main limitation to research on this subject is the lack of a standardized classification of graft failure as some authors consider flow limitation and occlusion as comparable and others think this should be analyzed separately.[36] This is also important when researching factors that affect LSV graft patency as there is much discrepancy in the literature in the definition of patency and of what constitutes early-, mid-, and long-term failure; this makes a comparison between studies particularly difficult in this subject.

Another problem in ascertaining the real clinical consequences of LSV failure is the wide variety of techniques used on bypass grafting, which have demonstrated to influence the rate of failure and long-term survival and symptoms, an example will be a study that demonstrated that LSV failure impaired long-term survival when it was grafted in the left anterior descending artery.[72] This may no longer be valid as currently, most surgeons prefer to use the LITA for this coronary graft.

In the variety of studies that have investigated the clinical impact of LSV failure, most have found an increased need for reintervention as compared with patients who underwent CABG but did not have LSV failure, on the long-term survival. however, studies have shown opposing results with some showing a decrease on survival with graft failure and others no difference.[34,36]

Research in this area is still required as the saphenous vein remains an essential conduit for CABG and by further our understanding of the mechanism of its failure, we may discover even more therapeutic approaches to both the treatment and the prevention of this condition.

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REFERENCES

1. Neumann F-J, Sousa-Uva M, Ahlsson A, et al. ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. 2018;40(2):87-165. https://doi.org/10.1093/eurheartj/ehy394

2. Goldman S, Zadina K, Moritz T, et al. Long-term patency of saphenous vein and left internal mammary artery grafts after coronary artery bypass surgery. *J Am Coll Cardiol*. 2004;44(11):2149-2156. https://doi.org/10.1016/j.jacc.2004.08.064

3. Bello SO, Peng EW, Sarkar PK. Conduits for coronary artery bypass surgery: the quest for second best. *J Cardiovasc Med*. 2011;12(6):411-421. https://doi.org/10.2459/JCM.0b013e328345a20d

4. Tatoulis J, Buxton BF, Fuller JA. Patencies of 2127 arterial to coronary conduits over 15 years. *Ann Thorac Surg*. 2004;77(1):93-101. https://doi.org/10.1016/S0003-4975(03)01331-6

5. Ward AO, Caputo M, Angelini GD, George SJ, Zakkar M. Activation and inflammation of the venous endothelium in vein graft disease. *Atherosclerosis*. 2017;265:266-274. https://doi.org/10.1016/j.atherosclerosis.2017.08.023

6. Motwani JG, Eric MD, Topol J, M. Aortocoronary saphenous vein graft disease pathogenesis, predisposition, and prevention. *Circulation*. 1998;97:916-931. https://doi.org/10.1111/j.1365-2929.2005.02205.x

7. Harskamp RE, Lopes RD, Baisden CE, De Winter RJ, Alexander JH. Saphenous vein graft failure after coronary artery bypass surgery: Pathophysiology, management, and future directions. *Ann Surg*. 2013;257(5):824-833. https://doi.org/10.1097/SLA.0b013e318288c38d

8. Sur S, Sugimoto JT, Agrawal DK. Coronary artery bypass graft: why is the saphenous vein prone to intimal hyperplasia? *Can J Physiol Pharmacol*. 2014;92(7):531-545. https://doi.org/10.1139/cjpp-2013-0445

9. Wan S, George SJ, Berry C, Baker AH. Vein graft failure: current clinical practice and potential for gene therapeutics. *Gene Ther*. 2012;19(6):630-636. https://doi.org/10.1038/gt.2012.29

10. Muto A, Model L, Ziegler K, Eghbalieh SDD, Dardik A. Mechanisms of vein graft adaptation to the arterial circulation. *Circ J*. 2010;74(8):1501-1512. https://doi.org/10.1253/circj.CJ-10-0495

11. Newby AC, Zaltsman AB. Molecular mechanisms in intimal hyperplasia. *J Pathol*. 2000;190(3):300-309. https://doi.org/10.1002/(SICI)1096-9896(200002)190:3<300::AID-PATH596>3.0.CO;2-I

12. Owens CD, Gasper WJ, Rahman AS, Conte MS. Vein graft failure. *J Vasc Surg*. 2015;61(1):203-216. https://doi.org/10.1016/j.jvs.2013.08.019

13. Owens CD. Adaptive changes in autogenous vein grafts for arterial reconstruction: Clinical implications. *J Vasc Surg*. 2010;51(3):736-746. https://doi.org/10.1016/j.jvs.2009.07.102

14. Li M, Qian M, Kyler K, Xu J. Endothelial–vascular smooth muscle cells interactions in atherosclerosis. *Front Cardiovasc Med*. 2018;5:151. https://doi.org/10.3389/fcvm.2018.00151

15. Wainwright C, Miller A, Wadsworth R. Inflammation as a key event in the development of neointima following vascular balloon injury. *Clin Exp Pharmacol Physiol*. 2001;28(11):891-895. https://doi.org/10.1046/j.1440-1681.2001.03543.x

16. Zhou J, Li Y-S, Nguyen P, et al. Regulation of vascular smooth muscle cell turnover by endothelial cell–secreted microRNA-126. *Circ Res*. 2013;113(1):40-51. https://doi.org/10.1161/CIRCRESAHA.113.280883

17. Hergenreider E, Heydt S, Tréguer K, et al. Atheroprotective communication between endothelial cells and smooth muscle cells through miRNAs. *Nat Cell Biol*. 2012;14(3):249-256. https://doi.org/10.1038/ncb2441

18. de Vries MR, Quax PHA. Inflammation in vein graft disease. *Front Cardiovasc Med*. 2018;5:3. https://doi.org/10.3389/fcvm.2018.00003

19. Alaiti MA, Orasanu G, Tugal D, Lu Y, Jain MK. Kruppel-like factors and vascular inflammation: implications for atherosclerosis. *Curr Atheroscler Rep*. 2012;14(5):438-449. https://doi.org/10.1007/s11883-012-0268-6

20. Hoshino Y, Kurabayashi M, Kanda T, et al. Regulated expression of the BTEB2 transcription factor in vascular smooth muscle cells: analysis of developmental and pathological expression profiles shows implications as a predictive factor for restenosis. *Circulation*. 2000;102(20):2528-2534. http://www.ncbi.nlm.nih.gov/pubmed/11076828. Accessed February 25, 2019.

21. Zhao M, Liu Y, Bao M, Kato Y, Han J, Eaton JW. Vascular smooth muscle cell proliferation requires both p38 and BMK1 MAP kinases. *Arch Biochem Biophys*. 2002;400:199-207. www.academicpress.com. Accessed February 15, 2019.

22. Wang G, Qiu J, Zheng Y, et al. Biomechanical regulation of vascular smooth muscle cell functions: from in vitro to in vivo understanding. https://doi.org/10.1098/rsif.2013.0852

23. Mehrhof FB, Schmidt-Ullrich R, Dietz R, Scheidereit C. Regulation of vascular smooth muscle cell proliferation role of NF-B revisited. *Circ Res*. 2005;96(9):958-964. https://doi.org/10.1161/01.RES.0000166924.31219.49

24. Sarjeant JM, Rabinovitch M. Understanding and treating vein graft atherosclerosis. *Cardiovasc Pathol*. 2002;11(5):263-271. https://doi.org/10.1016/S1054-8807(02)00125-4

25. Kalan JM, Roberts WC. Morphologic findings in saphenous veins used as coronary arterial bypass conduits for longer than 1 year: Necropsy analysis of 53 patients, 123 saphenous veins, and 1865 five-millimeter segments of veins. *Am Heart J*. 1990;119(5):1164-1184. https://doi.org/10.1016/S0002-8703(05)80249-2

26. Bennett MR, Sinha S, Owens GK. Vascular smooth muscle cells in atherosclerosis. *Circ Res*. 2016;118(4):692-702. https://doi.org/10.1161/CIRCRESAHA.115.306361

27. Gomez D, Owens GK. Smooth muscle cell phenotypic switching in atherosclerosis. *Cardiovasc Res*. 2012;95(2):156-164. https://doi.org/10.1093/cvr/cvs115

28. Voors AA, van Brussel BL, Thijs Plokker HW, et al. Smoking and cardiac events after venous coronary bypass surgery. A 15-year follow-up study. *Circulation*. 1996;93(1):42-47. http://www.ncbi.nlm.nih.gov/pubmed/8616939. Accessed November 15, 2018.

29. van Domburg RT, Meeter K, van Berkel DF, Veldkamp RF, van Herwerden LA, Bogers AJ. Smoking cessation reduces mortality after coronary artery bypass surgery: a 20-year follow-up study. *J Am Coll Cardiol*. 2000;36(3):878-883. http://www.ncbi.nlm.nih.gov/pubmed/10987614. Accessed November 15, 2018.

30. Campeau L, Enjalbert M, Lespérance J, et al. The relation of risk factors to the development of atherosclerosis in saphenous-vein bypass grafts and the progression of disease in the native circulation. *N Engl J Med*. 1984;311(21):1329-1332. https://doi.org/10.1056/NEJM198411223112101

31. Daida H, Yokoi H, Miyano H, et al. Relation of saphenous vein graft obstruction to serum cholesterol levels. *J Am Coll Cardiol*. 1995;25(1):193-197. http://www.ncbi.nlm.nih.gov/pubmed/7798501. Accessed November 15, 2018.

32. Kulik A, Voisine P, Mathieu P, et al. Statin therapy and saphenous vein graft disease after coronary bypass surgery: analysis from the CASCADE randomized trial. *Ann Thorac Surg*. 2011;92(4):1284-1291. https://doi.org/10.1016/j.athoracsur.2011.04.107

33. Sun Y, Kang L, Li J, et al. Advanced glycation end products impair the functions of saphenous vein but not thoracic artery smooth muscle cells through RAGE/MAPK signalling pathway in diabetes. *J Cell Mol Med*. 2016;20(10):1945-1955. https://doi.org/10.1111/jcmm.12886

34. Lopes RD, Mehta RH, Hafley GE, et al. Kou M on behalf of the P of EVVGE via TI (PREVENT II). Relationship between vein graft failure and subsequent clinical outcomes after coronary artery bypass surgery. *Circulation*. 2012;125(6):749-756. https://doi.org/10.1016/j.diagmicrobio.2007.07.018.Prevalence

35. Une D, Kulik A, Voisine P, Le May M, Ruel M. Correlates of saphenous vein graft hyperplasia and occlusion 1 year after coronary artery bypass grafting: analysis from the CASCADE randomized trial.

Circulation. 2013;128(SUPPL.1):213-218. https://doi.org/10.1161/CIRCULATIONAHA.112.000328

36. Harskamp RE, Williams JB, Hill RC, De Winter RJ, Alexander JH, Lopes RD. Saphenous vein graft failure and clinical outcomes: toward a surrogate end point in patients following coronary artery bypass surgery? *Am Heart J.* 2013;165(5):639-643. https://doi.org/10.1016/j.ahj.2013.01.019

37. Khaleel MS, Dorheim TA, Duryee MJ, et al. High-pressure distention of the saphenous vein during preparation results in increased markers of inflammation: a potential mechanism for graft failure. *Ann Thorac Surg.* 2012;93:552-558. https://doi.org/10.1016/j.athoracsur.2011.10.035

38. Souza DSR, Dashwood MR, Tsui JCS, et al. Improved patency in vein grafts harvested with surrounding tissue: results of a randomized study using three harvesting techniques. *Ann Thorac Surg.* 2002;73(4):1189-1195. https://doi.org/10.1016/S0003-4975(02)03425-2

39. Dashwood MR, Savage K, Tsui JCS, et al. Retaining perivascular tissue of human saphenous vein grafts protects against surgical and distension-induced damage and preserves endothelial nitric oxide synthase and nitric oxide synthase activity. *J Thorac Cardiovasc Surg.* 2009;138(2):334-340. https://doi.org/10.1016/j.jtcvs.2008.11.060

40. Kim YH, Oh HC, Choi JW, Hwang HY, Kim KB. No-touch saphenous vein harvesting may improve further the patency of saphenous vein composite grafts: early outcomes and 1-year angiographic results. *Ann Thorac Surg.* 2017;103(5):1489-1497. https://doi.org/10.1016/j.athoracsur.2016.09.024

41. Moshkovitz Y, Raanani E. The art of saphenous vein grafting and patency maintenance. *J Thorac Cardiovasc Surg.* 2016;151(2):300-302. https://doi.org/10.1016/j.jtcvs.2015.09.004

42. Papakonstantinou N, Baikoussis N, Goudevenos J, Papadopoulos G, Apostolakis E. Novel no touch technique of saphenous vein harvesting: is great graft patency rate provided? *Ann Card Anaesth.* 2016;19(3):481. https://doi.org/10.4103/0971-9784.185537

43. Woodward LC, Antoniades C, Taggart DP. Intraoperative vein graft preservation: what is the solution? *Ann Thorac Surg.* 2016;102(5):1736-1746. https://doi.org/10.1016/j.athoracsur.2016.05.097

44. Osgood MJ, Hocking KM, Voskresensky IV, et al. Surgical vein graft preparation promotes cellular dysfunction, oxidative stress, and intimal hyperplasia in human saphenous vein. *J Vasc Surg.* 2014;60(1):202-211. https://doi.org/10.1016/j.jvs.2013.06.004

45. Barner HB, Farkas EA. Conduits for coronary bypass: vein grafts. *Korean J Thorac Cardiovasc Surg.* 2012;45:275-286.

46. Ghista DN, Kabinejadian F. Coronary artery bypass grafting hemodynamics and anastomosis design: a biomedical engineering review. *Biomed Eng Online.* 2013;12(1):1-28. https://doi.org/10.1186/1475-925X-12-129

47. Prim DA, Zhou B, Hartstone-Rose A, Uline MJ, Shazly T, Eberth JF. A mechanical argument for the differential performance of coronary artery grafts. *J Mech Behav Biomed Mater.* 2016;54:93-105. https://doi.org/10.1016/j.jmbbm.2015.09.017

48. Gaudino M, Antoniades C, Benedetto U, et al. Mechanisms, consequences, and prevention of coronary graft failure. *Circulation.* 2017;136(18):1749-1764. https://doi.org/10.1161/CIRCULATIONAHA.117.027597

49. Lehnert P, Møller CH, Damgaard S, Gerds TA, Steinbrüchel DA. Transit-time flow measurement as a predictor of coronary bypass graft failure at one year angiographic follow-up. *J Card Surg.* 2015;30(1):47-52. https://doi.org/10.1111/jocs.12471

50. Mujanović E, Kabil E, Bergsland J. Transit time flowmetry in coronary surgery-an important tool in graft verification. *Bosn J Basic Med Sci.* 2007;7(3):275-278. https://doi.org/10.17305/bjbms.2007.3059

51. Kieser TM, Rose S, Kowalewski R, Belenkie I. Transit-time flow predicts outcomes in coronary artery bypass graft patients: a series of 1000 consecutive arterial grafts. *Eur J Cardio-Thoracic Surg.* 2010;38(2):155-162. https://doi.org/10.1016/j.ejcts.2010.01.026

52. Angelini GD, Lloyd C, Bush R, Johnson J, Newby AC. An external, oversized, porous polyester stent reduces vein graft neointima formation, cholesterol concentration, and vascular cell adhesion molecule 1 expression in cholesterol-fed pigs. *J Thorac Cardiovasc Surg.* 2002;124(5):950-956. https://doi.org/10.1067/mtc.2002.127004

53. Toeg HD, Boodhwani M. External stenting of vein grafts: primum non nocere. *J Thorac Cardiovasc Surg.* 2015;150(4):774-775. https://doi.org/10.1016/j.jtcvs.2015.06.056

54. Desai M, Mirzay-Razzaz J, Von Delft D, Sarkar S, Hamilton G, Seifalian AM. Inhibition of neointimal formation and hyperplasia in vein grafts by external stent/sheath. *Vasc Med.* 2010;15(4):287-297. https://doi.org/10.1177/1358863X10366479

55. Taggart DP, Ben Gal Y, Lees B, et al. A randomized trial of external stenting for saphenous vein grafts in coronary artery bypass grafting. *Ann Thorac Surg.* 2015;99(6):2039-2045. https://doi.org/10.1016/j.athoracsur.2015.01.060

56. Taggart DP, Webb CM, Desouza A, et al. Long-term performance of an external stent for saphenous vein grafts: the VEST IV trial. *J Cardiothorac Surg.* 2018;13(1):117. https://doi.org/10.1186/s13019-018-0803-9

57. Wallitt EJW, Jevon M, Hornick PI. Therapeutics of vein graft intimal hyperplasia: 100 years on. *Ann Thorac Surg.* 2007;84(1):317-323. https://doi.org/10.1016/j.athoracsur.2007.02.035

58. Petrofski JA, Hata JA, Gehrig TR, et al. Gene delivery to aortocoronary saphenous vein grafts in a large animal model of intimal hyperplasia. *J Thorac Cardiovasc Surg.* 2004;127(1):27-33. https://doi.org/10.1016/j.jtcvs.2003.07.032

59. Meng XB, Bi XL, Zhao HL, et al. Small interfering RNA targeting nuclear factor kappa B to prevent vein graft stenosis in rat models. *Transplant Proc.* 2013;45(6):2553-2558. https://doi.org/10.1016/j.transproceed.2013.03.045

60. Petrofski JA, Hata JA, Williams ML, et al. A G$\beta\gamma$ inhibitor reduces intimal hyperplasia in aortocoronary saphenous vein grafts. *J Thorac Cardiovasc Surg.* 2005;130(6):1683-1690. https://doi.org/10.1016/j.jtcvs.2005.01.024

61. George SJ, Wan S, Hu J, Macdonald R, Johnson JL, Baker AH Sustained Reduction of Vein Graft Neointima Formation by Ex Vivo TIMP-3 Gene Therapy. 2011. https://doi.org/10.1161/CIRCULATIONAHA.110.012732

62. Zimmermann N, Gams E, Hohlfeld T. Aspirin in coronary artery bypass surgery: new aspects of and alternatives for an old antithrombotic agent. *Eur J Cardio-thoracic Surg.* 2008;34(1):93-108. https://doi.org/10.1016/j.ejcts.2008.03.023

63. Goldman S, Copeland J, Moritz T, et al. Starting aspirin therapy after operation. Effects on early graft patency. Department of veterans affairs cooperative study group. *Circulation.* 1991;84(2):520-526. http://www.ncbi.nlm.nih.gov/pubmed/1860197. Accessed November 15, 2018.

64. Gao G, Zheng Z, Pi Y, Lu B, Lu J, Hu S. Aspirin plus clopidogrel therapy increases early venous graft patency after coronary artery bypass surgery: a single-center, randomized, controlled trial. *J Am Coll Cardiol.* 2010;56(20):1639-1643. https://doi.org/10.1016/j.jacc.2010.03.104

65. Kulik A, Abreu AM, Boronat V, Ruel M. Intensive versus moderate atorvastatin therapy and one-year graft patency after CABG: rationale and design of the ACTIVE (Aggressive Cholesterol Therapy to Inhibit Vein Graft Events) randomized controlled trial (NCT01528709). *Contemp Clin Trials.* 2017;59(March):98-104. https://doi.org/10.1016/j.cct.2017.06.006

66. Turner NA. Simvastatin inhibits MMP-9 secretion from human saphenous vein smooth muscle cells by inhibiting the RhoA/ROCK pathway and reducing MMP-9 mRNA levels. *FASEB J.* 2005;21:1-21. https://doi.org/10.1096/fj.04-2852fje

67. Sugimoto M, Yamanouchi D, Komori K. Therapeutic approach against intimal hyperplasia of vein grafts through endothelial nitric oxide synthase/nitric oxide (eNOS/NO) and the Rho/Rho-kinase pathway.

Surg Today. 2009;39(6):459-465. https://doi.org/10.1007/s00595-008-3912-6

68. Brilakis ES, Wang TY, Rao SV, et al. Frequency and predictors of drug-eluting stent use in saphenous vein bypass graft percutaneous coronary interventions. *JACC Cardiovasc Interv*. 2010;3(10):1068-1073. https://doi.org/10.1016/j.jcin.2010.07.009

69. Kheiri B, Osman M, Abdalla A, Ahmed S, Bachuwa G, Hassan M. The short- and long-term outcomes of percutaneous intervention with drug-eluting stent vs bare-metal stent in saphenous vein graft disease: an updated meta-analysis of all randomized clinical trials. *Clin Cardiol*. 2018;41(5):685-692. https://doi.org/10.1002/clc.22908

70. Christenson JT, Schmuziger M, Simonet F. Reoperative coronary artery bypass procedures: risk factors for early mortality and late survival. *Eur J Cardiothorac Surg*. 1997;11(1):129-133. http://www.ncbi.nlm.nih.gov/pubmed/9030801. Accessed November 15, 2018.

71. Saigan M, Isawa T, Ootomo T. Apixaban for the treatment of saphenous vein graft thrombosis presenting as unstable angina: a case report. *Thromb J*. 2017;15(1):1-3. https://doi.org/10.1186/s12959-017-0133-5

72. Lytle BW, Loop FD, Taylor PC, et al. Vein graft disease: the clinical impact of stenoses in saphenous vein bypass grafts to coronary arteries. *J Thorac Cardiovasc Surg*. 1992;103(5):831-840. http://www.ncbi.nlm.nih.gov/pubmed/1569763. Accessed November 14, 2018.