Review of risk factors, treatment, and prevention of saphenous vein graft disease after coronary artery bypass grafting

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Abstract
Saphenous vein graft disease (SVGD) is a type of vascular disease that may develop after coronary artery bypass grafting (CABG). SVGD seriously affects the short-term and long-term effects of CABG and increases the incidence of major adverse cardiovascular events. It is very important to identify patients at greatest risk and carry out prevention and treatment measures to determine the risk factors for SVGD. Many factors contribute to SVGD when the vein is grafted into an arterial environment, such as surgery-related factors, smoking, diabetes mellitus, hyperlipidemia, and others. In this review, we discuss the risk factors for SVGD, current surgical and pharmacologic therapies with which to manage SVGD, and the prevention of SVGD.

Keywords
Saphenous vein graft disease, coronary artery bypass grafting, risk factor, intimal hyperplasia, major adverse cardiovascular events, China

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Introduction
According to data from the China Cardiovascular Disease Report 2015,¹ coronary artery bypass grafting (CABG) is one of the most important cardiovascular surgical procedures in China, and the number of CABG procedures performed has exceeded 40,000 annually. Owing to population aging

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and the development of various risk factors in China, the performance of CABG is increasing at a rate of 10% annually. At present, the saphenous vein graft (SVG) is still the main graft material used in CABG; however, the long-term patency rate seriously affects the long-term efficacy of CABG. The 1-, 5-, and 10-year postoperative patency rates are 93%, 74%, and 41%, respectively.² In addition, some studies have shown that up to 12% of SVGs become occluded within the first 6 months after CABG, with 3.4% occluding as early as 2 to 3 weeks.³,⁴ Thrombosis formation is the main cause of SVG failure in the early period (<1 month) after CABG; however, abnormal hyperplasia of the neointima is the main cause of SVG failure in the subacute phase (1–12 months) after CABG, and atherosclerosis formation is the main cause of SVG occlusion in the later period (>1 year) after CABG.⁵ Scholars have recently clarified the definition of SVG disease (SVGD) for the first time. In SVGD, the SVG exhibits ≥50% stenosis, which is associated with the recurrence of ischemic symptoms (excluding distal anastomotic occlusion).⁶⁻⁸ The annual rate of revascularization due to relapse of ischemic symptoms after CABG ranges from 8.6% to 10.4%.⁹ How to treat and prevent SVGD is thus a major clinical challenge. The objective of this review is to discuss the risk factors for SVGD, current surgical and pharmacologic therapies with which to manage SVGD, and prevention techniques for SVGD and provide a theoretical basis for the prevention and treatment of SVGD in daily clinical practice.

Risk factors for SVGD

The long-term life of an SVG is far inferior to that of an arterial graft bridge. Arteries have the advantage of thick elastic fibers and a smooth muscle layer; however, the diameter of veins is only 4 to 5 mm. Blood stagnation, lipid accumulation, and thrombosis are prone to occur in SVGs. The risk factors for SVGD include the following.

1. Surgery-related factors: Deppe et al.¹⁰ conducted a meta-analysis of 51 studies and found that CABG under non-extracorporeal circulation conditions has a relatively high incidence of postoperative graft occlusion and revascularization. Kim et al.¹¹ analyzed the efficacy of CABG in which different saphenous vein acquisition methods were used and found that the early (<1-month) and 1-year patency rates of the traditional acquisition method were significantly lower than those of the No-Touch technique. Compared with the conventional acquisition method, the No-Touch technique can reduce surgical injury/trauma from vein harvesting, improve the integrity of the vascular endothelium, reduce atherosclerosis progression, preserve the intact vasa vasorum and the perivascular adipose tissue and collagen fibers, and avoid high-pressure vein distension.¹²,¹³ Several studies have demonstrated that the No-Touch technique is associated with improved morphological architecture, improved endothelial function indices, preservation of endothelial nitric oxide synthase, and a reduction in adhesion molecule expression and neutrophil adhesion.¹⁴,¹⁵ A study by Verma et al.¹⁶ also showed that the No-Touch technique exhibited an early molecular and morphological pattern consistent with decreased vascular smooth muscle cell activation compared with conventional harvesting. The types of target vessels, extent of the lesion, vascular diameter, and anastomosis all affect the SVG patency rate after CABG.¹⁷ SVG patency to the left anterior descending artery is better than that to the right coronary or circumflex artery. Studies have shown that when an SVG is grafted to the right coronary artery, the long-term patency rate is relatively favorable when the SVG–right
coronary artery diameter ratio is ≤2.8.\textsuperscript{18,19} In the 2016 ORACLE-NIRS study by Danek et al.,\textsuperscript{20} intravascular ultrasound and optical coherence tomography were used to evaluate SVG outcomes. The study showed that older SVGs were associated with a higher lipid core burden index and smaller lumen area and diameter, which significantly affected the long-term patency of the SVG. Hess et al.\textsuperscript{21} reported that a long surgical time, endoscopic vein harvesting, and low quality of target arteries were risk factors for SVG failure.

2. **Smoking:** Smoking increases the risk of SVG calcification\textsuperscript{22} and induces the expression of matrix metalloproteinases 2 and 9 to reduce the patency of the SVG.\textsuperscript{23,24} An in vitro study conducted by Sharif et al.\textsuperscript{25} showed that smoking impairs endothelium-dependent vasodilation. Muir et al.\textsuperscript{26} investigated the correlation between saphenous vein and internal mammary artery endothelial relaxation in patients undergoing CABG. The authors found that the endothelium-dependent relaxation response of the internal mammary artery in patients who smoked was significantly weakened, while the saphenous vein relaxation response increased significantly. Higman et al.\textsuperscript{27} showed that smoking impairs the endothelium-dependent vasodilatation of veins and increases vascular tension, platelet aggregation, and the proliferation of smooth muscle cells; all of these effects increase the risk of graft occlusion. On the basis of their multivariate regression analysis, Sen et al.\textsuperscript{28} also suggested that smoking is an independent risk factor for SVGD.

3. **Diabetes mellitus:** SVG restenosis in patients with diabetes mellitus undergoing CABG is a pathophysiologic process involving both immune and non-immune factors. The metabolic disorders that occur in patients with type 2 diabetes mellitus lead to long-term dysfunction of vascular endothelial cells.\textsuperscript{29} Large numbers of inflammatory and growth factors are released after endothelial injury, which further induces the abnormal proliferation and migration of vascular smooth muscle cells and causes restenosis.\textsuperscript{30} Aberrancies of endothelial cell function may help to explain the increased risk of SVG failure in patients with type 2 diabetes mellitus.\textsuperscript{31} Koshizaka et al.\textsuperscript{32} evaluated the association of diabetes and its treatment with 1-year angiographic graft failure and 5-year clinical outcomes in patients undergoing CABG. The authors found that the 1-year rates of vein graft failure were similar in patients with and without diabetes, and at 5 years, the rates of death, myocardial infarction, or revascularization were higher among patients with than without diabetes (adjusted hazard ratio, 1.57; 95% confidence interval, 1.26–1.96; $P < 0.001$). Further studies are needed to better understand the mechanisms behind these findings.

4. **Hyperlipidemia:** Studies have shown that a low level of high-density lipoprotein (HDL) is associated with graft vascular occlusion and intimal hyperplasia; specifically, the lower the HDL level, the higher the risk of SVGD.\textsuperscript{33} Another study showed that if low-density lipoprotein cholesterol (LDL-C) was controlled to <80 mg/dL and the LDL/HDL ratio is <1.5 after CABG, eccentric plaques, yellow plaques, and thrombosis could largely be prevented.\textsuperscript{34} In contrast, eccentric plaque formation occurred in 78.6%, yellow plaque occurred in 100%, and thrombosis occurred in 78.6% of patients whose blood lipid levels were not well-controlled (LDL-C, 130.2 mg/dL; LDL/HDL ratio, 2.64).\textsuperscript{34} Therefore, active lipid control after CABG is believed to reduce the risk of SVGD.

5. **Other risk factors:** A retrospective study conducted by Akboga et al.\textsuperscript{35} in 2016 included 112 patients with SVGD and 145 patients without SVGD. The study showed that a low level of albumin
and high ratio of monocytes to HDL cholesterol were risk factors for the development of SVG atherosclerosis. Cagirci et al.\(^3\) determined the level of asymmetric dimethylarginine in 42 patients with SVGD and 61 patients without SVGD using an enzyme-linked immunosorbent assay. The authors found that a high level of asymmetric dimethylarginine and the average platelet volume were independent risk factors for SVGD. Another study showed that a 1% increase in the red blood cell distribution width increased the risk of SVGD by 2.388-fold (95% confidence interval, 1.287–4.432).\(^3\) Furthermore, the platelet count, average platelet volume, plateletcrit, platelet distribution width, and platelet-to-lymphocyte ratio or neutrophil-to-lymphocyte ratio all predicted the occurrence of SVGD.\(^3\)–\(^4\) Sun et al.\(^4\) reported that a red blood cell distribution width of >0.1275 and a neutrophil-to-lymphocyte ratio of >3.34 were independent risk factors for late SVGD with odds ratios of 4.905 and 4.013, respectively. A low level of adiponectin, HDL, and 25-hydroxyvitamin D; a high level of erythropoietin; and elevated expression of matrix metalloproteinases were also shown to be associated with SVGD.\(^2\),\(^4\)–\(^7\) Perek et al.\(^8\),\(^9\) reported that thickening of the saphenous vein tunica media, chunky smooth muscle cell nuclei, and increased expression of cytokeratin 8 accompanied by calponin underexpression in the saphenous vein tunica media were independent risk factors for venous graft failure.

**Treatment of SVGD**

Determination of the optimal treatment of SVGD is challenging. The annual revascularization rate after CABG ranges from 8.6% to 10.4% because of recurrent ischemic symptoms. Because patients with SVGD are generally older and the underlying coronary artery disease is often severe, many SVGs exhibit the effects of aging after 3 years, and these patients are susceptible to severe ischemic events and refractory heart failure.\(^5\),\(^6\) Therefore, post-CABG revascularization is complex and should be managed on an individual basis.

1. **Drug treatment**: Anticoagulants, such as urokinase, unfractionated heparin, low-molecular-weight heparin, and abciximab, are often used with unsatisfactory effects. For example, Harskamp et al.\(^5\) found that the use of abciximab in SVG intervention did not improve clinical outcomes; rather, abciximab was associated with more bleeding. Contraindications for these treatments in patients with comorbidities undergoing CABG are also important to consider. For example, abciximab is contraindicated in patients with renal insufficiency and should be used as an adjuvant, not as a single drug.

2. **Redo-CABG**: The surgical difficulty, perioperative complications, and mortality of redo-CABG are all much higher than those of primary CABG. The symptom relief rate is low, and the 1-year postoperative graft occlusion rate is as high as 41%.\(^5\) Event-free survival is also low. Redo-CABG treatment has decreased in the last two decades. Therefore, redo-CABG is not recommended as a first choice for SVGD treatment.

3. **Percutaneous coronary intervention (PCI)**: PCI is still the first choice for myocardial ischemia after CABG. In China, most revascularization procedures are performed by PCI. With respect to revascularization strategies, both the feasibility of PCI and the blood flow competition between reconstructed vessels and the SVG should be taken into account. Intervention sites include the SVG and native vessel (NV). The efficacy of bare metal stents in SVGs is inferior to the efficacy in NVs. The long-term efficacy of stent implantation is poor, and the restenosis rate ranges from 30% to 60%. A recent meta-analysis\(^5\) suggested...
that drug-eluting stents (DESs) are better than bare metal stents when used in SVGs. DESs in SVGs yield the same effect as in NVs; however, the long-term safety, particularly late thrombosis associated with DESs, needs further evaluation. In a meta-analysis conducted by Lupi et al., DESs were shown to significantly reduce target vessel revascularization; however, there is no clear evidence to confirm that DESs can reduce mortality and myocardial infarction. Thus far, DESs have proven to be an acceptable method for SVGD. Covered stents, including self-expanding stents, are not recommended.

3.1 NV PCI: NV PCI-associated procedures are relatively simple, surgeons are more experienced, and instruments are complete. The treatment has a relatively high success rate, and its efficacy for complex coronary artery disease has improved. The advantage of NV PCI is that the coronary arteries are open to replace aging SVGs and supply blood; the long-term efficacy is more reliable. Notably, the complexity of NV lesions will inevitably affect the success rate of PCI.

3.2 SVG PCI: SVG PCI is more effective than redo-CABG but is associated with the risk of intraoperative distal embolization and postoperative restenosis; the long-term effect of SVG PCI is inconclusive. Current guidelines do not recommend PCI for use in fully occluded SVGs. The intracoronary administration of nitroglycerin, diltiazem, or tirofiban has no significant effect on no reflow; the efficacy of distal protection devices is also controversial. Virtual histology intravascular ultrasound (VH-IVUS) is a recently developed imaging technique for detecting atherosclerotic plaques. A recent study used VH-IVUS to examine 125 patients with SVGD undergoing PCI before and after stent implantation. The study showed that in 19 patients with no reflow, the incidences of intraluminal masses, multiple plaque ruptures, plaque irregularities, and tissue prolapse were significantly higher than in patients with normal angiography findings. VH-IVUS can further identify plaque components, which is valuable in predicting slow flow and no reflow after PCI. The information obtained by VH-IVUS is also of significance in guiding PCI surgery, optimizing the treatment strategy, reducing operative risk, and improving patient prognosis.

Prevention of SVGD

1. No-Touch technique: Souza was the first to design the No-Touch technique to harvest the great saphenous vein in the 1990s. Johansson et al. conducted short-term (18 months) and long-term (8.5 years) randomized controlled trials to compare the efficacy of the No-Touch versus traditional techniques. The SVG stenosis rate, intimal thickness, and intimal hyperplasia were better in the No-Touch group than in the traditional group, while the vascular lumen diameter was greater in the No-Touch group than in the traditional group. A long-term study showed that the No-Touch group had fewer intravenous plaques. Rueda et al. also showed that the short-term patency rate and endothelial integrity were higher in the No-Touch group than in the traditional group. Kim et al. reported that the short-term and 1-year SVG patency rates of the No-Touch technique were significantly higher than those of traditional techniques. Harvesting the saphenous vein with surrounding tissues may increase SVG patency rates in a likely mechanism similar to the No-Touch technique. These findings favor the advantages of the No-Touch technique in preventing SVGD.

2. External stenting: The anti-expansion and anti-tension effects of external stents can influence SVG remodeling. Zurbrugg et al. encased SVGs implanted into the carotid arteries of pigs with biosynthetic
external stents. After 4 weeks, Taggart et al. found that the wall thicknesses of the medial and intimal layers were significantly lower than those in the control group, suggesting that external stents can prevent excessive expansion of grafts and mitigate intimal hyperplasia. Zheng et al. found that external stents after CABG improved lumen uniformity and reduced intimal hyperplasia. Different stents may have different preventive effects. Animal studies have shown that external restrictive polyester and nonrestrictive P(3HB-co-3HV) stents can prevent SVG intimal hyperplasia and restenosis. Porous silicone tube stents are superior to autologous neck fascia and cyanoacrylate adhesive stents in terms of vascular patency and intimal hyperplasia. Therefore, it may be more important to select appropriate stents in the prevention of restenosis.

Drug prevention

3.1 Anti-platelet aggregation drugs: Aspirin has been shown to improve the 1-year SVG patency rate and reduce the incidence of adverse cardiovascular events. Administration of aspirin within 6 to 24 hours after surgery can effectively prevent SVG occlusion. Aspirin is not beneficial if administered 48 hours after surgery. A meta-analysis showed that the best time for administration of aspirin was 6 hours after surgery; this timing did not increase the risk of bleeding. Wu et al. reported that aspirin at 100 mg/day significantly improved the perioperative vein patency after non-extracorporeal circulation CABG. Early application of aspirin after CABG has a positive effect on the prevention of SVG stenosis and long-term cardiovascular events. The current guideline recommends a routine daily aspirin dose of 75 to 150 mg.

3.2 Dual anti-platelet therapy (DAPT): Aspirin resistance is an important mechanism underlying early occlusion of CABG grafts. For patients who are suspected to be aspirin-resistant or -intolerant or in whom aspirin is contraindicated, early administration of low-dose clopidogrel (75 mg/d) is an alternative. With respect to clopidogrel or aspirin alone or in combination, Gao et al. found that there was no significant difference in the 1- and 12-month SVG patency rates after off-pump CABG between clopidogrel alone and clopidogrel combined with aspirin. Kulik et al. also showed that the combination of clopidogrel and aspirin did not significantly reduce SVG intimal hyperplasia; there was no significant difference in SVG patency between clopidogrel alone and the combination of the two drugs. Whether the combination of aspirin and clopidogrel can reduce perioperative myocardial infarction and improve long-term SVG patency remains controversial; however, the 2017 European Society of Cardiology guidelines updated the application of DAPT. Specifically, regardless of the revascularization method (PCI or CABG), the recommended regular DAPT course is 12 months. Six months of DAPT can be considered for patients at high risk of bleeding, while DAPT can be extended to >12 months for treatment-tolerant patients with no bleeding complications.

3.3 Statins: According to CABG surgery guidelines, all patients receiving CABG should be target subjects for lipid-lowering therapy. All patients should be administered statins unless contraindications exist. In a large-scale study, post-CABG coronary angiography showed that lovastatin significantly delayed atherosclerosis of the SVG. Patients in the aggressive-treatment group had a lower revascularization rate. Ouattara et al. showed that perioperative administration of statins reduced the incidence of adverse cardiac events after CABG and that the effect was dose-dependent. Kulik et al. found that early
treatment with statins (within 1 month after discharge) independently reduced all-cause mortality and major adverse cardiac events. The targets of lipid-lowering therapy are a total cholesterol level of <4.68 mmol/L, an LDL-C level of <2.60 mmol/L, a triglyceride level of <1.70 mmol/L, and an HDL-C level of >1 mmol/L. Simvastatin was also shown to inhibit the endothelial prothrombotic shift in the SVG in patients with well-controlled diabetes. A post-CABG follow-up study of 1 to 11 years in length showed that active reduction in the LDL-C level reduced the development of atherosclerosis in the SVG. Kang et al. agreed that long-term and active control of the LDL-C level with statins significantly delayed the progression of atherosclerosis in SVG and reduced the risk of atherosclerosis and post-CABG revascularization. For patients undergoing CABG, treatment with statins should be initiated during hospitalization. The perioperative application of statins significantly decreases the incidence of atrial fibrillation after surgery. Aggressive lipid-lowering therapy also decreases major end-point events and achieves greater clinical benefits. PROVE-IT suggested that in patients undergoing CABG with high-risk factors, the LDL-C level should be reduced to 1.82 mmol/L.

3.4 Other drugs: Animal model studies have shown that tacrolimus, tranilast, and ursolic acid can also inhibit SVG restenosis.

4. Gene technology: Gene technology can be used to prevent SVGD in two ways: by introducing a specific protein through gene-transfected cells or by suppressing the production of a specific protein with an antisense oligonucleotide. Safe and effective vectors are the basis of gene therapy. Current commonly used vectors include adenovirus, lentivirus, and non-viral vectors. In 1994, Chen et al. first reported soluble vascular cell adhesion molecule transgenic treatment of a porcine SVGD model mediated by adenovirus vector. Although the SVG was successfully transfected by soluble vascular cell adhesion molecule, no positive effect was observed. Mann et al. first reported the use of antisense oligonucleotides to inhibit intimal hyperplasia and atherosclerosis by regulating the cell cycle. Multiple studies have shown transfection with the tissue inhibitor of metalloproteinase 1, 2, and 3 genes inhibited vascular smooth muscle cell proliferation and intimal thickening. Additionally, the prolongation of vascular smooth muscle cells and intimal hyperplasia in SVGs is inhibited by transfection with microRNA-145, microRNA-221, Jag1, the early growth response factor 1 decoy oligonucleotide, and the Girdin gene. Transgenic treatment with endothelial nitric oxide synthase and inducible nitric oxide synthase has been shown to effectively inhibit inflammatory cell proliferation and intimal hyperplasia in the SVG and has a certain preventive effect against SVGD.

In summary, SVGD has a complex pathogenic mechanism. SVGD is closely associated with thrombosis, SVG intimal hyperplasia, and the formation of atherosclerosis. The pathogenesis and development of SVGD are associated with many factors, including common cardiovascular risk factors, surgery-related factors, and biochemical indicators. Some preventive measures targeting the SVGD mechanism and risk factors have been developed and clinically applied. For example, cardiac surgeons using No-Touch technology for CABG as well as physicians using antiplatelet aggregation, anticoagulation, and lipid-lowering therapy after CABG have achieved significant efficacy. The application of gene technology provides new strategies for SVGD prevention. The current treatment of SVGD includes anticoagulation, redo-CABG, and PCI. The strategy
of post-CABG revascularization should be implemented based on individual needs.

Declaration of conflicting interest
The authors declare that there is no conflict of interest.

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