Chapter 13

Treatment of Coronary Artery Bypass Graft Failure

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Additional information is available at the end of the chapter

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1. Introduction

1.1. History of surgical revascularization

The concept of surgical revascularization for coronary artery disease (CAD) originated in the early 20th century. A pioneer in this field is Beck, a surgeon who in 1935 developed an indirect technique of myocardial revascularization by grafting a flap of the pectoralis muscle over the exposed epicardium to create new blood supply. [1] Later, Beck also developed another revascularization technique by anastomosis between the aorta and the coronary sinus. [2] In 1946, the Vineberg procedure was introduced in which the internal mammary artery (IMA) was used to implant directly into the left ventricular and is hence considered the forerunner of coronary artery bypass grafting (CABG). This technique was the first intervention documented to increase myocardial perfusion and was successfully performed in over 5,000 patients between 1950 till 1970. [3-5] The major breakthrough in surgery, however, was the invention of the heart-lung machine in 1953, which allowed surgeons to perform open-heart procedures on a non-beating heart and controlled operating field while protecting other vital organs. [6] Still it was not until 1960 when the first successful human coronary artery bypass surgery was performed by Goetz and Rohman, who used the IMA as the donor vessel for anastomosis to the right coronary artery. [7] The bypass graft technique as we know today was developed by Favaloro in 1967. [8] In his physiologic approach in the surgical management of coronary artery disease, Favaloro and his team initially used a saphenous vein autograft to bypass a stenosis of the right coronary artery. Shortly hereafter, Favaloro began to use the saphenous vein as a bypassing conduit. After the saphenous vein bypass procedure was extended to include the left arterial system by Johnson [9], the use of the IMA for bypass grafting was performed by Bailey and Hirose in 1968. [10] Arguably, the first successful IMA – coronary artery anastomosis was already performed 4 years earlier by the Russian surgeon Vasilii Kolesov. [11] Use of the radial artery (RA) as a bypass conduit was introduced by

Carpentier in 1971 and fell into disrepute shortly after its introduction because of high failure rates but was revisited as many of these original grafts appeared widely patent at 6 years. [12, 13] Initially used as a free graft in a fashion similar to that of the saphenous vein graft, more recently the RA has been used as a T or Y graft from the left IMA (LIMA) or an extension graft from the distal right IMA (RIMA). On the basis of superior long-term outcomes of arterial conduits compared with vein grafts, other arteries have been used in CABG such as the gastroepiploic artery (GEA), the inferior epigastric artery (IEA), the splenic artery, the subscapular artery, the inferior mesenteric artery, the descending branch of the lateral femoral circumflex artery, and the ulnar artery. However none of these arteries have shown similar patency rates as the internal mammary artery.

Surgical revascularization in the current era - A number of studies and trials have consistently shown the benefit of CABG in select patient populations. Indisputable, surgical revascularization which in most cases is performed utilizing the saphenous vein for bypassing non LAD-lesions and arterial bypass grafts for LAD lesions, has dramatically changed the management of patients with ischemic heart disease. Currently, over 300,000 patients undergo CABG in the United States each year. [14] Although the short-term outcomes of CABG are generally excellent, patients remain at risk for future cardiac events due to progression of native coronary disease and/or coronary bypass graft failure. [15-18] To illustrate, over half of saphenous vein grafts (SVG) are occluded at 10 years post CABG and an additional 25% show significant stenosis at angiographic follow-up. [19] Additionally, diseased grafts represent an increasing proportion of culprit lesions and acute graft occlusion may cause acute coronary syndromes (ACS). [20] In the next paragraphs we will describe in further detail the pathophysiologic mechanisms that lead to coronary artery bypass graft failure, and elude to management strategies.

2. Pathophysiology of coronary artery bypass graft failure

The use of the SVG, arterial grafts or both during CABG is largely depending on the site of anatomic obstruction, the availability of good quality conduits, patient preferences, and the clinical condition of the patient. Adequate arterial conduits are not always available, in contrast SVG are usually of good quality and calibre and are easily harvested, and are thus commonly used as conduits. However, there is an increasing interest for the use of arterial conduits as coronary artery bypass grafts, especially for bypassing the left coronary artery. Although, the choice to use arterial conduits partly depends on the coronary run-off, the long-term patency of arterial grafts is superior for CABG compared to SVG. As more than half of SVG are occluded at 10 years post CABG and an additional 25% show significant stenosis at angiographic follow-up. [19] SVG failure is the main cause of repeat intervention either by redo CABG or PCI and is even more common than the progression of native coronary artery disease in patients whom underwent CABG. In spite the fact that SVG failure remains a significant clinical and economic burden, the majority of CABG procedures continue to use SVG. [21]

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The concept of the 'failing graft' is one of a patent graft whose patency is threatened by a hemodynamically significant lesion in the inflow or outflow tracts or within the body of the graft. Salvage of the failing and failed bypass graft remains an important clinical and technical challenge. The high incidence of graft failure has led to the evolution of graft surveillance programs to detect 'failing' grafts and research has focussed on means to control the development of intimal hyperplasia. [22]

3. Histology of saphenous vein

The saphenous vein consists of three layers: the intima, media, and adventitia. The intima is composed of a continuous layer of endothelial cells on the luminal surface of the vessel. Beneath lies the fenestrated basement membrane embedded with a fragmented internal elastic lamina. The media comprises of smooth muscle cells (SMC) arranged in an inner longitudinal and an outer circumferential pattern with loose connective tissue and elastic fibers interlaced. The middle muscle layer is most extensive at the insertion points of the valves and leaflets. The adventitia forms the outer layer and consists of longitudinally arranged SMC, collagen fibers and a network of elastin fibers, in addition to vascular and nerve supplies to the vessel.The great saphenous vein is the most frequently used conduit for myocardial revascularization but other venous conduits such the short saphenous vein or upper extremity veins (cephalic and basilica) can be used as well.

4. Saphenous vein graft failure

Studies of saphenous veins harvested for bypass procedures have shown that many have abnormal histological and physical attributes. [23,24] Moreover, the quality of the saphenous vein can have significant clinical consequences. Therefore, vein grafts in the arterial circulation must be considered as a viable, constantly adapting and evolving conduit.

Several intrinsic and extrinsic factors may play a role in the mechanism of SVG failure. At the time of harvest, the quality of the saphenous veins may be poor, demonstrating a spectrum of pre-existing pathological conditions ranging from significantly thickened walls to post phlebitic changes and varicosities. Between 2% and 5% of saphenous veins are unusable and up to 12% can be considered diseased which reduce the patency rate by one half compared to non-diseased veins. [25] In addition, the inevitable vascular trauma that occurs during SVG harvesting itself can also lead to damage to the endothelium and SMC and thereby contribute to graft failure. Surgical manipulation and high-pressure distension to reverse spasm during harvesting leads to loss of endothelial integrity and the antithrombogenic attributes of the endothelium, rendering the SVG prone to subsequent occlusive intimal hyperplasia and/or thrombus formation. [26] During harvesting the vasa vasorum and nervous network of the SVG are devided, making the graft dependent on diffusion for weeks until adequate circulation is esthablished.

[27-32] Ischemic insult and decreased production of nitric oxide and adenosine may cause SMC proliferation. [33] As it has been demonstrated that intimal hyperplasia does not occur in vein-to-vein isografts, it can be stated that pathologic changes seen in SVG in the arterial circulation are predominantly caused by hemodynamic and physiochemical changes. [34]

SVG failure can be divided into three temporal categories: early (0 to 30 days), midterm (30 days to 1 year) or late (after 1 year). Early SVG failure due to thrombotic complications is mainly attributable to technical errors during harvesting, anastomosis or comprised anatomic runoff. [19,35-37] It occurs in 15% to 18% of VG during the 1st month. [38-40] Early thrombotic complications in SVG in the arterial circulation are caused by a reduction of tissue plasminogen activator, attenuation of thrombomudulin and reduced expression of heparin sulphate. [41]

Midterm SVG failure is mainly caused by fibrointimal hyperplasia as it serves as the foundation for subsequent graft atheroma leading to occlusive stenosis. The release of a variety of mediators, growth factors, and cytokines by the injured endothelium, platelets and activated macrophages will cause migration and proliferation of SMC. Diminished production of endothelial nitric oxide (NO), prostaglandin 12 and adenosine will further contribute to and enhanced SMC proliferation, leading to development of neointimal hyperplasia. [19,33,37,42-44] Changes in the flow pattern within the vessel (shear stress) an ischemic insults may contribute to changes in the SVG at this stage. SVG are exposed to much higher mechanical pressure that they were adapted to (arterial versus venous blood pressure) which can potentially stimulate SMC proliferation. Moreover, after encountering arterial flow patterns increased levels of intracellular adhesion molecule-1, vascular cell adhesion molecule-1, and monocyte chemotactic protein-1 will facilitate leukocyte-endothelial interactions so that leukocyte infiltration of the lesions will ensue. [34] Finally, the adaptive response to hemodynamic factors, i.e. wall shear stress, may affect the distal site of the anastomosis leading to SVG failure. [45,46] Midterm SVG failure accounts for an additional 15% to 30%. [47,48] In the course of vessel remodelling, late SVG failure is characterized by progression of intimal fibrosis at the cost of a reduction in cellularity which may contribute to progression of SMC apoptosis. [19,34,41,44] In addition, perivascular fibroblasts may also be involved in neointimal formation and matrix deposition as these cells may exhibit contractile elements while migrating from the adventitia towards the media. [49] After 1 year most SVG stenosis is due to atherosclerosis but although vein graft atherosclerosis is accelerated compared to arteries, evidence show that a fully evolved plaque appear after 3 to 5 years of implantation. [35,47,50] In SVG there is no focal compensatory enlargement in the stenotic segments which is in contrast to native atherosclerotic arteries in which the development of an atherosclerotic plaque is associated with enlargement of the vessel and preservation of the lumen area until plaque progression exceeds the compensatory mechanism of the vessel. [51] Several studies show that SVG patency at 10 years is no more than 50% to 60%. [19,41,52,53] Finally, several studies have suggested a role of immune cells in neointimal formation as macrophages are found in the intima, while T-lymphocytes are present in the adventitia of neointimal lesions wit a predominance of CD4+ cells. [54-56]

In a later stage atherosclerotic lesions may be complicated by aneurysmal dilatation which is found to correlate with thrombosed SVG. (66) The occurrence of atheroembolism form the diseased graft or plaque rupture may cause late thrombosis necessitating revascularization therapy. [57,58] In general, SVG thrombosis is the major cause of morbidity and mortality. [19,41]

Predictors of graft patency 3 years after CABG were evaluated by Veterans Affairs Cooperative Study Group. [59] Multivariable analysis showed that the only factors that were predictive were vein preservation solution temperature ≤5ºC, serum cholesterol, the number of proximal anastomoses ≤2, and recipient artery diameter >5 mm. Thus, predictors of 3-year graft patency are most closely related to operative techniques and the underlying disease. In another study, factors that predict the late progression of SVG atherosclerosis were evaluated in 1248 patients in the Post-CABG trial. [47] Factors independently associated with the progression of disease were maximum stenosis of the graft at baseline angiography, years after CABG, moderate therapy to lower LDL cholesterol, prior MI, high triglyceride levels, small minimum graft diameter, low HDL concentration, high LDL concentration, high mean arterial pressure, low left ventricular ejection fraction, male gender, and current cigarette smoking. Finally, concerns have been raised about the possibility of worse outcomes when a SVG is used for multiple distal anastomosis compared to single anastomosis. In a substudy of the PREVENT IV trial, the use of SVG conduits with multiple distal anastomoses was associated with a significantly higher rate of ≥75 percent stenosis of the SVG on angiography at one year. [60] Moreover, clinical follow-up showed a trend towards a higher rate of the adjusted composite of death, MI, or revascularization at five years.

Noteworthy, the clinical impact of SVG failure is still debated. Not all grafts that have angiographic stenosis or occlusion will cause symptoms, and probably a substantial of SVG that fail do not impact outcomes.

5. Histology of arterial grafts

Several arterial conduits are suitable for myocardial revascularization and the arterial conduits can be divided into 3 types according to functional class (Table 1). Type I arterial grafts are the somatic arteries including the IMA, IEA, and subscapular artery. Type II arterial grafts are the splanchnic arteries including the GEA, splenic artery, and inferior mesenteric artery. Type III arterial grafts are the limb arteries including the RA, ulnar artery, and lateral femoral circumflex artery. Compared to functional class type II and III, type I is less spastic. [61] Although the full length of arterial grafts is reactive, the major muscular components are located at the two ends of the artery (muscular regulator). [62] Therefore, in terms of preventing vasospasm of arterial grafts, trimming off the small and highly reactive distal end of the grafts (IMA, GEA, IEA, or other grafts) may be important and clinically feasible.

Studies have demonstrated that there are differences between arterial and venous grafts: 1) arterial grafts are less susceptible to vasoactive substances then veins [63]; 2) the arterial wall

Type I - Somatic arteries	Less spastic	Internal mammary artery
		Inferior epigastric artery
		Subscapular artery
Type II - Splanchnic arteries	Spastic	Gastroepiploic artery
		Splenic artery
		Inferior mesenteric artery
Type III - Limb arteries	Spastic	Radial artery
		Ulnar artery
		Lateral femoral circumflex artery

Table 1. Functional classification of arterial grafts according to physiological and pharmacological contractility, anatomical, and embryological characteristic

is supplied by the vaso vasorum and in addition through the lumen, whereas the veins are only supplied by the vaso vasorum [64]; 3) the endothelium of the arteries may secrete more endothelium-derived relaxing factor [65]; 4) the structure of the artery is subject to high pressure, whereas the vein is subjected to low pressure. While the SVG have to adapt to the high pressure, the arterial grafts do not which may partly explain the difference in the long-term outcome.

Similar like SVG, the arterial grafts can also be divided into three layers: the intima, media, and adventitia. As a result of location at different parts of the body and supply to different organs, differences in gross anatomy among arterial grafts have been observed. Divergent anatomic structures of the arteries have been observed. One of the most obvious differences is that arteries such as the GEA, IEA, and RA contain more smooth muscle cells in their walls and are therefore less elastic compared to other arteries such as the IMA which may be more elastic because they contain more elastic laminae. [64] Such structure divergence may also explain the difference in phsysiologic and pharmacologic reactivity.

6. Arterial graft failure

The need for repeat revascularization is substantially reduced with the use of arterial conduits, since long-term patency is much higher compared to SVG. [66-68] In contrast to SVG, arterial grafts appear to be more resistant to the influence of atherogenic factors and incur only minor traumatic and ischemic lesions, since they are not removed from the blood circulation but are prepared locally, with few ligations and preservation of blood flow. [69] Since 1986, the LIMA has been used in more than 90% of CABG procedures. Less frequently, the RIMA is used. The early patency of a LIMA anastomosed to the left anterior descending (LAD) is reported to be almost 99%. [70] The mean patency of LIMA to coronary conduit at 5 years is reported 98%, at 10 years it is 95%, and at 15 years it is 88%. [71] Differences are observed between territory

grafted, the 10 year LIMA patency to the LAD is reported to be 96% and to the circumflex (Cx) 89%. [72] The early patency of the RIMA anastomosed to major branches of the left circumflex artery is approximately 94%. [70] The mean RIMA patency at 5 years is reported to be 96%, at 10 years it is 81% and at 15 years it is 65%. [71] Again differences are observed, the RIMA graft patency to the LAD artery is 95% at 10 years and 90% at 15 years. Ten-year RIMA patency to the Cx marginal is 91%, right coronary artery is 84%, and posterior descending artery is 86%. [72] In situ RITA and free RITA had similar ten-year patency, 89% vs 91% respectively. RA patency is reported to range between 83% to 98% at 1 to 20 years but lower rates have been reported. [73] The patency rate estimated by the Kaplan-Meier method for the GEA conduit was 96.6% at 1 month, 91.4% at 1 year, 80.5% at 5 years, and 62.5% at 10 years. [74] Arterial grafts are not uniform in their biological characteristics and difference in the perioperative behaviour and in the long-term patency may be related to different characteristics. It should be taken into account in the use of arterial grafts that some grafts need more active pharmacological intervention during and after operation to obtain satisfactory results.

Although, the IMA is the most used conduit to restore the blood flow to the LAD, it is less easy to use because of its complicated preparation and postoperative complications. Specific reasons for not to use the RIMA may include additional time to harvest, concerns over deep sternal wound infection, myocardial hypoperfusion, and unfamiliarity. Besides the potentially deleterious effect on the vascular supply of the forearm and hand, potential spasm and size matching to target coronary artery are the main drawback for the use of RA in CABG. [75,76]

Although all arterial grafts may develop vasospasm, it develops more frequently in the GEA and RA, than the IMA and IEA. [13,77] Two types of vasoconstrictors are found to be important spasmogens in arterial grafts. [78] Type I vasoconstrictors are the most potent and they strongly contracts arterial grafts even when the endothelium is intact. The constrictors are endothelin, prostanoids such as thromboxane A_2 and prostaglandin $F_{2\alpha}$, and alpha1-adrenoceptor agonists. Type II vasoconstrictors induce only weak vasoconstriction when the endothelium is intact, but play an important role in the spasm of arterial grafts when the endothelium is destroyed by surgical manipulation. Type II vasoconstrictor is 5-hydroxytryptamine.

Early IMA graft failure is attributed to technical errors and distal anastomosis. [79,80] Non-technical factors that may affect the patency of the arterial graft are high levels of LDL cholesterol and triglycerides, and high levels of lipoprotein(a), a thrombogenic molecule that is related to the hypercoagulable state. Other classical risk factors for coronary artery disease, such as diabetes mellitus, smoking and hypertension may also affect the patency of the arterial graft. Age may be of influence the quality of the arterial graft.

Furthermore, competitive flow and low-flow profoundly affect graft patency. Low-grade graft stenoses in the target artery proximally are a major cause of competitive flow which may lead to a decrease in antegrade flow in the arterial graft causing early failure ('disuse athrophy'). The SVG and IMA are more tolerant than the RA and GEA conduits. This is likely to be related to biological differences as the RA and GEA have a thick layer of smooth muscle or poor endothelial function in these muscular conduits. Therefore, it is recommended to avoid grafting target arteries with a stenosis less than 90% with RA grafts. [81]

Atherosclerosis in arterial grafts can develop before coronary grafting when the graft is in the in situ native position, or after. The incidence of atherosclerosis in native arteries in the in situ position in the four major arterial grafts is low, especially in the IMA. [64] The incidence of atherosclerosis in bypass grafts is also low, in IMA grafts even as late 15 to 21 years after CABG. [67,82] However, the degree of stenosis in the native vessel is a major predictor of IMA graft patency. The observed association between non-significant stenosis of the native artery and high occlusion rate of the arterial bypass conduit raises concerns about the use of IMA in the treatment of native vessels with only mild or moderate stenosis. [83] In addition, the target vessel for the IEA must be one that is completely occluded or severely stenotic, with low coronary resistance, and in territories not totally infarcted to avoid "string sign" (conduit <1 mm diameter). Although the incidence of atherosclerosis is low in arterial grafts, 2 other morphologic changes may be present in arterial graft, fibrointimal proliferation and fibrosis representing organized thrombus. [84] The presence of fibrointimal proliferation is associated with long-term IMA graft narrowing and may be an important factor for late graft failure. Despite hypertension was associated with increased fibrointimal proliferation in SVG, this correlation could not be found in IMA grafts. [84]

7. Treatment of coronary artery bypass graft failure

Following graft revascularization, patients remain at very high risk for subsequent clinical events. In a large study from the Duke Cardiovascular Databank, patients who underwent catheterization 1 to 18 months after their first CABG were evaluated. [85] Patients were classified on the basis of their worst SVG stenosis as having no (<25%), noncritical (25% to 74%), critical (75% to 99%), or occlusive (100%) SVG disease and the primary outcome measure was the composite of death, MI or repeat revascularization. At 10-years, the corresponding adjusted composite event rates were 41.2%, 56.2%, 81.2%, and 67.1%, respectively ($p<0.0001$) and most events occurred immediately after catheterization in patients with critical and occlusive SVG disease. Multivariate analysis revealed critical, non-occlusive SVG disease as the strongest predictor of composite outcome (hazard ratio 2.36, 95% CI [2.00-2.79], $p<0.0001$).

Many patients with recurrent stable angina following CABG can be treated medically for their symptoms and risk factor reduction. Evaluation for ischemia is as in other patients with stable angina without prior CABG. However, early diagnostic angiography is suggested as the different anatomic possibilities, i.e. graft stenosis or progression of native vessel disease in nonbypassed vessels can lead to recurrent ischemia. In patients with recurrent angina, ACS, change in exercise tolerance, positive exercise test after CABG, an increased risk for coronary events is observed. [86-88]

8. Medical therapy

In all patients with coronary heart disease aggressive risk factor reduction is recommended which includes aspirin, treatment for hypertension and serum lipids, avoidance of smoking,

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and controlling serum glucose in diabetic patients. The bypass angioplasty revascularization investigation (BARI) trial illustrated that intensive risk-factor modification and hypolipid medication use slows atherosclerosis progression within native coronary arteries of CABG-treated patients and may to a lesser extent improve long-term patency of surgical conduits. [89]

Antiplatelet therapy - Antiplatelet therapy is recommended following CABG since it improves SVG patency and clinical outcomes. The 2008 EACTS guideline on antiplatelet and anticoagulation management in cardiac surgery [90] recommends that aspirin should be given postoperatively to all patients without contra-indications after CABG in order to improve the long-term patency of SVG. The recommended dose given is 150—325 mg. Several studies have shown a trend towards maximal benefit with 325 mg/day in the first year. [91-95] In contrast, there is no evidence that the use of aspirin after coronary artery bypass grafting improved the patency of arterial grafts. However, aspirin may be recommended on the basis of improved survival of patients in general who have atherosclerotic disease.

The optimal timing of the first dose of aspirin for patients after CABG was investigated in a meta-analysis of 12 studies and found that the benefit of aspirin was optimal if started at 6 h after surgery. [96] Although, the largest risk reduction was observed when aspirin was given at 1 h after operation, there was a non-significant increase in the rate of re-operation in this group. [91] In contrast, there was no benefit found in giving aspirin if starting more than 48 h postoperatively. [97] Practically, Aspirin should be commenced within 24 h of CABG.

Whether clopidogrel given in addition of aspirin to high-risk patients after CABG would reduce thrombotic complications was evaluated in several studies. Registry data showed that adding clopidogrel to aspirin was independently associated with a decrease in recurrence of anginal complaints and adverse cardiac events following off-pump CABG. Nonetheless, clopidogrel use beyond 30 days did not show a significant effect on adverse cardiac events. [98] In the randomized CASCADE (Clopidogrel After Surgery for Coronary Artery Disease) study, aspirin monotherapy was compared with aspirin plus clopidogrel in 113 patients undergoing CABG and SVG intimal hyperplasia was determined by intravascular ultrasound at 1 year. [99] Compared with aspirin monotherapy, the combination of aspirin plus clopidogrel did not significantly reduce SVG intimal hyperplasia 1 year after CABG. Although the study was not powered for clinical outcomes, there was no significant difference in SVG patency or cardiovascular events, neither was there a difference in the incidence of major bleeding between the 2 treatment groups at 1 year. Moreover, the superiority of clopidogrel over aspirin for optimising graft patency after CABG has not been established and thus aspirin should be regarded as the drug of first choice, however, clopidogrel is an acceptable alternative to aspirin. [90]

In patients whom underwent CABG for ACS subgroup analyses of the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) and CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) study provides supportive evidence to prescribe clopidogrel for 9 to 12 months in addition to aspirin. [100,101] In patients undergoing coronary bypass surgery with a coronary stent in situ implanted within 1 year, clopidogrel should be continued if the stented vessel has not been grafted. Finally, in patients with SVG failure treated

with PCI, prehospital use of antiplatelet therapy compared with patients not using antiplatelets was associated with lower occurrence of major adverse cardiac events after SVG intervention. [102] Also, DAPT did not improved outcomes when compared to single antiplatelet therapy.

Warfarin – Conflicting evidence is reported whether warfarin in addition to aspirin is beneficial in patients post CABG. In an extended follow-up of 7.5 years of the post CABG trial, low-dose anticoagulation compared with placebo reduced the rate of death by 35%, deaths or myocardial infarction (MI) by 31%, and the composite clinical endpoint of death, MI, stroke, CABG, or angioplasty by 17%. [103] However, in a smaller randomized trial, moderate-intensity oral anticoagulation alone or combined with low-dose aspirin was not superior to low-dose aspirin in the prevention of recurrent ischemic events in patients with non-ST-elevation ACS and previous CABG. [104] Currently, the American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines recommended that oral anticoagulation in addition to aspirin can be considered only when it is indicated for other reasons. [105]

Lipid lowering therapy – Clinical trials have shown that lipid lowering therapy (in particular statins) is beneficial in patients who have undergone CABG. [103,106-110] Besides the lipid lowering effect, statins also exert a number of pleiotropic effects on the vascular wall which may effect SVG in a similar way. In SVG, statins have shown to reduce vascular oxidative stress, improve NO bioavailability and reduce vascular inflammation, all critical components of SVG failure. [111] Subsequently, statins have systemic antithrombotic and anti-inflammatory effects and their administration may prevent acute SVG failure post CABG. [112] Aggressive lipid lowering therapy may be beneficial for long-term patency of grafts. In the randomized Post CABG trial, patients who had undergone bypass surgery 1 to 11 years before base line with elevated serum LDL-cholesterol concentrations (130 to 175 mg/dL / 3.4 to 4.5 mmol/L) were assigned to receive either aggressive lipid lowering therapy with lovastatin and, if needed, cholestyramine (target LDL-cholesterol <100 mg/dL / 2.6 mmol/L) or to moderate therapy (target LDL-cholesterol of approximately 134 mg/dL / 3.5 mmol/L). [106] Compared to a moderate strategy, aggressive lipid lowering therapy was associated with a delay in the progression of graft disease at an average of 4.3 years as assessed by angiography. Moreover, after clinical follow-up of 7.5 years, a 30% reduction in revascularization procedures and a 24% reduction in the composite endpoint of cardiovascular death, MI, stroke, CABG, or angioplasty were seen. [103] Similar findings were observed in a post hoc analysis from the TNT trial. In patients with previous CABG, simvastatine 80 mg compared to simvastatine 10 mg, was significantly more effective in reducing the rate of a combined cardiovascular endpoint at a median follow-up of 4.9 years (9.7% versus 13.0%). [110] Repeat revascularization with either CABG or PCI was also significantly reduced in patients assigned to the higher dose (11.3% versus 15.9%).

Antiplatelet agents and statin therapy are the only modalities with proven efficacy for the prevention of SVG stenosis. The routine use of beta blockers, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, or nitrates post CABG is not supported by data, however, many of these patients require beta blockers and ACE inhibitors for preexistent heart failure or MI according to the ACC/AHA guideline recommendations. [113,114]

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The PREVENT IV trial, including almost 3,000 patients that underwent CABG, demonstrated that rates of use of secondary prevention medications in patients with ideal indications for these therapies are high for antiplatelet agents and lipid-lowering therapy, but suboptimal for beta-blockers and ACE inhibitors or ARBs. [115] The study demonstrated that the use of multiple secondary prevention medications after CABG was associated with significant improve in clinical outcome death or MI at 2 years (4.2% in patients taking all indicated medications versus 9.0% in patients taking half or fewer of the indicated medications). No association was found between the use of most individual medications and subsequent outcomes, thus underscoring the importance of ensuring appropriate secondary prevention measures after CABG.

9. Guidelines on revascularization in patients with prior CABG

In the European Society of Cardiology (ESC)/ European Association for Cardio-Thoracic Surgery (EACTS) guidelines on myocardial revascularization [116] published in 2010 states that in acute post-operative graft failure PCI may be an alternative to re-operation with acceptable results and fewer complications. [117] The target for PCI is the body of the coronary artery of the arterial graft while freshly occluded SVG or the anastomosis itself should be targeted due to the risk of embolization or perforation. When multiple grafts are occluded or the graft or native coronary artery appears unsuitable for PCI, surgery should be favoured. In asymptomatic patients, redo CABG or PCI should only be considered if the graft or coronary artery is of good size, severely narrowed and supplies a large territory of myocardium. Redo CABG or PCI should be decided by the Heart Team.

Repeat revascularization in patients with late graft failure is indicated in the presence of severe anginal symptoms despite anti-anginal medication. In patients with mild or no symptoms repeat revascularization is dependent on risk stratification by non-invasive testing. [118,119] In patients with previous CABG, PCI has worse acute and long-term outcomes than in patients without prior CABG. Redo CABG has a two- to four-fold higher mortality than the first procedure which is mainly driven by comorbidity and less by the re-operation itself. [120,121] There is limited data comparing the efficacy of PCI with redo CABG in patients with previous CABG. In a propensity analysis of long-term survival after redo CABG or PCI in patients with multivessel disease and high-risk features, short-term outcome was very favourable, with nearly identical survival at 1 and 5 years. [118] However, in the AWESOME RCT and registry the overall in-hospital mortality was higher in the redo CABG group compared to the PCI group. [17,122] Because of the initial higher mortality of redo CABG and comparable long-term mortality, the guidelines state that PCI is the preferred revascularization strategy in patients with LIMA or amenable anatomy. Redo CABG is preferred in patients with more diseased or occluded grafts, reduced systolic function, total occlusions of native coronary arteries or in the absence of a patent arterial graft. [118] If possible, the IMA is the conduit of choice when performing redo CABG. [123]

In the 2012 appropriateness criteria for coronary revascularization focussed update of the American College of Cardiology Foundation Appropriateness Criteria Task Force (ACCF),

Society for Cardiovascular Angiography and Interventions (SCAI), Society of Thoracic Surgeons (STS), American Association for Thoracic Surgery (AATS), American Heart Association (AHA), and the American Society of Nuclear Cardiology (ASNC) it is stated that in patients with prior CABG, the presence of high-risk findings on noninvasive testing, higher severity of symptoms, or an increasing burden of disease in either the bypass grafts or native coronaries tended to increase the likelihood of an appropriate rating. [119] In patients with prior CABG receiving no or minimal anti-ischemic therapy or having low-risk findings on noninvasive testing revascularization was considered inappropriate. No specific recommendations are provided on the strategy for revascularization, performing redo CABG or PCI.

Both the ESC/EACTS guidelines on myocardial revascularization and the ACCF/SCAI/STS/AATS/AHA/ASNC/HFSA/SCCT 2012 appropriate use criteria for coronary revascularization focused update do not provide recommendations for patients with prior CABG presenting with (non) ST segment elevation myocardial infarction (STEMI) or ACS.

10. Percutaneous coronary intervention

Implantation of coronary stents has become the preferred revascularization strategy for treatment of graft lesions, because redo CABG is associated with an increased morbidity and mortality. [17,124-129] Compared to native vessel stenting, stenting of graft lesions is associated with higher rates of periprocedural events as well as cardiac events at follow-up, due to distal embolization and subsequent no-reflow and higher percentages of restenosis. [124,125, 130,131] This increased risk is mainly attributed to the friable, degenerated atheromatous and thrombotic debris that develop when SVGs deteriorate. [132] Moreover, patients with graft intervention often have a higher generalized atherosclerotic burden and more comorbidities. [130,131] To date, SVG graft intervention accounts approximately for 5% to 10% of all PCI.

Early graft failure - The incidence of early graft failure within 24 h after CABG is about 1% to 3%. [133] Perioperative graft failure following CABG may result in acute myocardial ischemia which may necessitate acute secondary revascularization procedure to salvage myocardium, preserve left ventricular function and improve patient outcome. Perioperative MI and rise in cardiac markers after CABG is associated with a substantially increased in-hospital morbidity and mortality. [134-136] The most common graft-related causes of myocardial ischemia after CABG are graft occlusion due to acute graft thrombosis, graft kinking or overstretching, postoperative graft spasm and subtotal or hemodynamic relevant anastomotic stenosis. [137,138] Nongraft-related causes for myocardial ischemia after CABG are surgery-related possibly due to surgical manipulation on pre-existing microembolizing and disintegrating unstable plaque and include inadequate cardioplegic perfusion and myocardial protection, incomplete revascularization, or distal coronary microembolization. [139-141] Rapid identification of early graft failure after CABG and diagnostic discrimination from other causes enables an adequate reintervention strategy for re-revascularization, i.e. redo CABG or PCI, and may prevent irreversible myocardial ischemia. Thus far, limited non-randomized data is available showing that in patients with acute perioperative myocardial ischemia due to early

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graft failure following CABG, emergency PCI may limit the extent of myocardial cellular damage compared with redo CABG. [133] A nonsignifiant numerical difference was observed in in-hospital and 1-year mortality between the PCI group or redo CABG (12.0% and 20.0% in PCI group versus 20.0% and 27% in redo CABG group). Moreover, compared to acute redo-CABG, emergency PCI is quicker and less invasive. Importantly, in this study patent grafts were observed in 25% to 34% of the patients, therefore repeat coronary angiography should be applied when myocardial ischemia due to acute graft failure is suspected. Regarding the type of bypass graft, LIMA graft failure may be responsible for acute ischemic complications after CABG in at least a third up to half of the cases. [133,138,142]

Recurrent angina during the early postoperative period is usually due to a technical problem with a graft or with early graft closure and there is an indication for prompt coronary angiography with percutaneous revascularization. The feasibility of PCI in patients presenting with clinical evidence of ischemia within 90 days of CABG was evaluated in 2 registries. Most patients presented with ACS and the most common cause of graft failure was occlusion or thrombosis. Both registries showed that patients with graft failure can undergo PCI with a relatively low risk for in-hospital mortality or nonfatal major complications. [143,144]

SVG failure - Recurrent angina after the first few months after CABG is caused by both graft disease and by progression of atherosclerosis in non-bypassed vessels. Percutaneous intervention in SVG lesions was evaluated in several randomized studies. The SAVED (Saphenous Vein de Novo) study randomized 200 patients with SVG lesions to placement of Palmaz-Schatz bare metal stent (BMS) or standard balloon angioplasty (BA) and demonstrated that compared to BA, bare metal stents (BMS) were associated with a higher procedural success (92% vs. 69%, $p<0.001$) but they had more frequent hemorrhagic complications (17% vs. 5 %, $p<0.01$). [145] At 6 months, a non-significant reduction in angiographic restenosis was observed (36% vs. 47%, $p=0.11$) and clinical follow-up at 9 months showed that freedom from death, MI, repeated bypass surgery, or revascularization of the target lesion was significantly better in the stent group (73% vs. 58 %, $P = 0.03$). Based on the results of the SAVED study, the majority of patients with SVG stenosis are treated with stenting. To prevent distal embolization form friable atheroemboli, and in addition may serve as a smooth-muscle cell barrier to decrease restenosis, stents covered with a mesh, most commonly polytetrafluorethylene (PTFE), were evaluated. However, 3 prospective randomized trails have not shown benefit with covered stents with respect to major adverse cardiac events nor in preventing restenosis. [146-148]

In native coronary arteries, drug-eluting stents (DES) have demonstrated a marked reduction in in-stent restenosis compared to BMS in the treatment of coronary artery disease. Several DES with different stent platforms, polymers or drugs are available. In the RRISC (Reduction of Restenosis in Saphenous Vein Grafts With Cypher Sirolimus-Eluting Stent) trial, 75 patients were randomized to sirolimus-eluting stent (SES) or BMS. [149] At 6 months follow-up, in-stent late loss was significantly reduced in SES (0.38 ± 0.51 mm vs. 0.79 ± 0.66 mm in BMS). Target lesion revascularization rate was also significantly reduced (5.3% vs. 21.6%) but no difference in death and MI was observed. Howbeit, a post hoc analysis of RRISC trial at 3 years reported similar rates of target vessel revascularization and while statistically underpowered for clinical outcomes, significantly higher all-cause mortality was reported with SES compared

with BMS. [150] The SOS (Stenting of Saphenous Vein Grafts) trial randomized 80 patients to either paclitaxel-eluting stent (PES) or BMS and showed significant reduction in primary end point, binary angiographic restenosis at 12 months (9% vs. 51%). [151] At 1.5 years clinical follow-up the PES patients had a significant reduction in target lesion revascularization (5% vs. 28%), target vessel failure (22% vs. 46%) and a trend towards less MI (15% vs. 31%) but increased mortality (12% vs. 5%). In contrast to the long-term results of the RRISC study, at a median follow-up of 35 months PES treated-patients had a significantly lower incidence of MI (17% vs. 46%), target lesion revascularization (10% vs. 41%), and target vessel failure (34% vs. 72%) as well as a trend toward less definite or probable stent thrombosis (2% vs. 15%). All-cause mortality (24% vs. 13%) and cardiac mortality (7% vs. 13%) did not differ between groups. [152] More evidence was provided in the ISAR-CABG (Prospective, Randomized Trial of Drug-Eluting Stents Versus Bare Metal Stents for the Reduction of Restenosis in Bypass Grafts). In this study, 610 patients with diseased SVGs were randomized to DES and BMS and the combined incidence of death, MI, and target lesion revascularisation at 1 year was significantly lower in the DES group than in the BMS group (15.4% vs. 22.1%) which was mainly driven by a nearly 50% relative reduction in the risk of target lesion revascularization (7.2% vs. 13.1%), with non-significant differences in mortality. [153] Consistent results of improved efficacy with DES and no significant safety hazard were reported in different meta-analyses which also included non randomized trails. [154-157] The RRISC, SOS and ISAR CABG all compared first-generation DES to BMS. The SOS-Xience V (Stenting of Saphenous Grafts-Xience V) prospectively examined the frequency of angiographic in-stent restenosis in SVG lesions 12 months after implantation of everolimus-eluting stent (EES), a second generation DES. Use of EES in SVGs is associated with high rates of stent strut coverage and high malapposition rates at 12 months post implantation as assessed by optical coherence tomography, however, clinical results are to be waited. [158] Finally, in a multicenter analysis no difference was observed in real-world patients comparing first-generation DES to BMS. [159] In a meta-analysis including 29 studies (3 randomized controlled trials (RCT)) involving over 7500 patients, the authors stated that DES may decrease TVR rate in treatment of SVG stenoses but no differences in reinfarction rate, stent thrombosis or mortality was found between the DES and BMS groups in the RCT's. [160] In contrast, the observational data showed lower risk for MI, stent thrombosis and death in the DES group. This may be a result of patient selection bias in the observational studies or represent a true finding that was not detected in the RCT analysis due to limited statistical power.

Stents are effective as treatment for focal lesions, however, the optimal treatment strategy for a diffusely degenerated SVG is uncertain. Endoluminal reconstruction with stent omplantation has been suggested as a treatment for diffuse lesions. This was evaluated in a study including 126 patients with diffusely degenerated stenosed or occluded SVG treated with stents. [161] At 3 year follow-up, survival free of death, infarction, or revascularization was only 43%.

Regarding stenting technique in SVG lesions, it has been suggested that direct stenting, compared to predilatation with balloon angioplasty, may be beneficial as trapping of debris could decrease distal embolization that may occur from repeated balloon inflations. Registry data showed that in unselected patients who underwent SVG intervention direct stenting was

associated with a lower CK-MB release and fewer non-Q-wave MI. [162] These results needs to be confirmed in a prospective randomized trial.

After PCI of SVG, progression of disease outside the stented segment can lead to high rates of restenosis. Therefore, treatment of native coronary artery lesions is preferred to treatment of degenerated SVG if feasible. In addition, in patients with prior CABG, early diagnostic angiography can be important as there is a high success rate of percutaneous coronary intervention (PCI) at the time of subtotal occlusion; and the substantial consequences of the loss of a bypass graft through total occlusion (e.g, low success and high complication rates of PCI for totally occluded SVG, and difficult to control angina).

A numerous of predictors for worse outcome after percutaneous SVG intervention have been identified. Multivariate analysis revealed that major CK-MB release after SVG intervention and renal insufficiency are powerful independent predictor of all-cause mortality. [163-165] Lesion length, greater angiographic degeneration of SVG, and larger estimated plaque volume which may result in a greater likelihood of distal embolization and myocardial necrosis after intervention, have been identified as predictors of 30-day major adverse cardiac events after SVG intervention. [166,167] Sexe also appeared to be a predictor as women have a significantly higher 30-day cumulative mortality rate compared with men (4.4% vs. 1.9%), a higher incidence of vascular complications (12% vs. 7.3%), and postprocedural acute renal failure (8.1% vs. 4%). [168] Whether specific stent platforms, polymers or drugs are more appropriate in SVG and arterial graft lesions has not been addressed at this time.

Arterial graft failure - Due to the superior long-term patency of arterial grafts, in specific the IMA, they are the vascular conduit of choice for patients undergoing CABG and the increasing frequency of their use has resulted in a small but increasing need for revascularization. In arterial graft failure, ostial stenoses are the least common and the pathogenesis of ostial stenoses may be affected by its proximity to the aorta and potential extension of atherosclerosis from that vessel.

Anastomosis of IMA to the native coronary is the most frequent site of a target lesion. The particular anatomical feature of the IMA-to-LAD anastomosis is subjected to continuous mechanical stress, owing to the asynchronous motion of heart, lungs and bypass. Moreover, it has been suggested that this predilection reflects scar tissue induced by injury during surgical manipulation. [169]

Published reports have demonstrated that BA of the IMA can be performed safely with high procedural success and a low incidence of clinical restenosis. [170-175] The use of BMS compared to BA alone for percutaneous revascularization of the IMA graft was investigated in several studies. In a large cohort of 174 patients who underwent BA or BMS placement, anastomotic lesions were more evident, 63% of al cases. [169] These lesions were more commonly treated with BA (91%), whereas lesions located at the ostium (8%) were more frequently treated with stents (69%). Patients who underwent stenting had a target lesion revascularization rate of 15.4% and those who underwent BA had a rate of 5.4%. In a retrospective analysis patients undergoing BMS implantation for the treatment of IMA graft stenosis were compared to patients treated with BA. [176] The minority of patients were treated

with BMS (26.4%) and received at least either ticlopidine or clopidogrel for 4 weeks post PCI. Angiographic success after stenting was high, 92%. At 1 year follow-up, target lesion revascularization rates were significantly higher in the stented lesions than lesions treated with BA alone (19.2% vs. 4.9%) and the higher rate in stented lesions was most apparent at the anastomotic site (25.0% vs. 4.2%). Moreover, a significant difference was observed between 1-year all-cause mortality between stented lesions and lesions treated with BA alone (13.6% vs. 4.4%), no difference was observed for MI. In a multivariate analysis including all available baseline factors contributing to target lesion revascularization, indicated that stent use was an independent predictor. In this observational study selection bias may have resulted in more lesions at high risk of restenosis being chosen for stenting, as stenting was at the discretion of the operator.

Comparison of BMS and DES for percutaneous revascularization of IMA Grafts, have reported conflicting results. In a retrospective study, outomes after BMS and DES treatment in IMA grafts were evaluated. [177] Baseline characteristics were comparable between the 2 groups, except for a trend toward longer stent lengths in the DES group (DES 20.2±7.7 mm vs. BMS 14.8±3.5 mm). No significant differences were present in in-hospital and 1- or 6-month outcomes between the 2 groups, including target lesion revascularization with DES (DES 3.33% vs. BMS 10%). Contrastingly, 2 small studies did not show improved clinical impact of DES compared to BMS. At 1-year clinical follow-up, no differences were detected in target lesion revascularization rates after treatment with BMS and PES (26.6% vs. 25%). [178] In the PES group, 2 late stent thromboses were observed. In addition, in a small study the long-term outcomes of 41 patients undergoing PCI of the IMA anastomosis BMS or SES were compared. [179] At a median follow-up of 29.2 months (interquartile range, 11.1-77.7 months) target lesion revascularization was 47.8% with SES and 7.1% with BMS. Patients who underwent repeat revascularization were more likely to have longer stents than those who did not (18.2 mm vs 14.2 mm).

The favourable results of BA compared to stenting in IMA graft intervention is in contrast with native coronary artery intervention. This might be explained by the fact that: 1) the proliferative response to BA in IMA may be less aggressive than that in native coronary arteries; 2) in native coronary arteries as compared to BA, stenting leads to more pronounced arterial injury, greater inflammatory response, and enhanced neointimal formation; 3) in small native coronary arteries, the high stent-to-wall ratio might predispose restenosis more frequently; and 4) stents are known to be thrombogenic and lead to neointimal formation and restenosis. [180-183]

Percutaneous treatment of ostial stenosis, presents technical challenges for the interventionalist whereas lesions in the shaft are most similar to routine intervention in a native coronary arteries. Stenting of the anastomotic site takes carefully positioning of the stent to achieve apposition to the arterial wall given the acute angle at which IMA meets the native coronary artery. In one observational study a difference in 1-year target lesion revascularization rates was present at the ostial, shaft, and anastomotic sites (30.8%, 5.0%, and 7.2%, respectively). [176] The anastomosis experiences a bending of the stent with strut shrinkage and might cause stent fracture or in DES might limit elution of drug to vessel wall.

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Failure of the RA graft is most frequently a complete occlusion and less often a string-like appearance. However, on rare occasions, focal stenoses of the RA graft can occur.

RA graft stenosis treated by percutaneous intervention was evaluated in a small study including 18 patients. [184] The location of the RA stenosis was proximal (n = 2), shaft (n = 11) or distal anastomosis (n = 5). BA alone was performed on nine RA grafts at 1.7 years after surgery and stenting (3 BMS, 6 DES) of nine RA grafts was achieved at 9.2 years after surgery. At 5.8 years, clinical follow-up showed heart failure (n = 2) and recurrent angina (n = 3), all after balloon dilatation. At 4.5 years, 1 RA graft was occluded due to competitive flow from the native coronary vessel and 2 RA restenoses following BA were treated by stenting. Intra-stent RA stenosis was noted in 1 patient. PCI with BA should be restricted to the early postoperative period during which spasm is difficult to exclude. Stenting showed excellent and durable results and is preferred in most cases. There are no large studies on other arterial grafts to draw definite conclusions for the treatment with PCI by BA, BMS or DES.

Antithrombotic therapy during graft intervention - The preferred parenteral antithrombotic therapy during graft intervention remains to be explored. The role of glycoprotein IIb/IIIa antagonists in graft intervention is limited as they failed to demonstrate a reduction in periprocedural MI. [185-187] Similarly, no reduction in MACE at 30 days was observed in a post hoc analysis when glycoprotein IIb/IIIa antagonists were used in conjunction with filter-based embolic protection, although there was a trend toward improved procedural success. [188] In contrast, bivalirudin as compared with unfractionated heparin may have beneficial effects on biochemical and clinical outcomes as it was associated with a significant reduction in CK-MB elevation and a trend toward lower in-hospital non–Q-wave MI, repeat revascularization, and vascular complications. [189] Moreover, bivalirudin may offer a safety advantage over heparin plus a glycoprotein IIb/IIIa anatagonist as minor bleeding complications were lower with bivalirudin alone (26% vs. 38%) with equal or greater suppression of adverse ischemic events. [190] Pharmacological treatment of slow or no-reflow is targeted at microvascular flow with intragraft administration of vasodilators and delivery of pharmaceutical agents to the distal microvasculature and can be maximized with a microcatheter like an aspiration thrombectomy catheter. Adenosine is an endogenous purine nucleoside, a vasodilator of arteries and arterioles, and inhibits platelet activation and aggregation. A high dose of intragraft adenosine (≥5 boluses of 24 μg each) can result in reversal of slow or no-reflow and improve final Thrombolysis In Myocardial Infarction (TIMI) flow grade. However, the use of adenosine is limited because severe bradycardia may occur due to its effect on sinoatrial and atrioventricular nodal conduction and the half-life of adenosine is very short. Intracoronary administration of nitroprusside, a direct donor of NO, results in a rapid improvement in both angiographic flow and blood flow velocity. Caution is warranted in patients who are volume depleted or hypotensive at baseline because profound hypotension may occur. Prophylactic intragraft administration of verapamil (100 to 500 μg) can reduce the occurrence of no-reflow and improve TIMI myocardial perfusion grade. Prophylactic intragraft administration of nicardipine, a potent arteriolar vasodilator, may reduce CK-MB elevation. Independent predictors for slow flow or no-reflow are probable patients treated for ACS, stent thrombosis, diseased SVG, and lesion ulceration.

Embolic protection Devices - Graft intervention, in particular SVG, can be complicated by distal embolization of atheroembolic debris leading to decreased epicardial and microvascular perfusion due to capillary plugging and vasospasm from the release of neurohumoral factors. Distal embolization may result in the slow or no-reflow and is associated with periprocedural myocardial necrosis and increased in-hospital mortality. However, distal embolization remains difficult to predict. Several embolic protection devices are available to prevent distal embolization and in SVG intervention it is recommended a class I according to the ACC/AHA guideline. [191] Distal balloon systems provide occlusion beyond the lesion securing the blood and may prevent plaque embolization into the myocardial bed. Hereafter, the blood with contained debris can be aspirated before occlusive balloon deflation. Advantages are the low crossing profile and entrapment of debris of all sizes as well as neurohumoral mediators such as serotonin and thromboxane that may have an adverse effect on the distal microvasculature. However, disadvantages are: 1) the need to cross the lesion before adequate protection, possibly liberating friable material before balloon occlusion; 2) temporary cessation of blood flow leading to ischemia and possible hemodynamic instability, as well as limiting visualization making accurate stent placement difficult; 3) inability to obtain full evacuation, especially near the occlusion balloon; 4) possible traumatic injury to the SVG during balloon occlusion, and 5) the need for a relatively disease-free landing zone of approximately 3 cm distal to the lesion for placement of the occlusion balloon. [192] The PercuSurge GuardWire (Medtronic, Minneapolis, Minnesota) and the TriActiv embolic protection system (Kensey Nash Corporation, Exton, Pennsylvania) both demonstrated a significant decrease the incidence of no-reflow and improved 30-day clinical outcome but the latter was associated with more vascular complications and the need for blood transfusion. [193,194]

Distal filter systems, composed of a tightly wrapped filter attached to a guidewire and sheathed within a delivery catheter for placement distal to the target lesion, can trap debris that embolize while the intervention is performed over the guidewire. After the intervention, a retrieval catheter is advanced over the guidewire to collapse the filter and remove it along with retained contents. It is ease-of-use and antegrade blood flow during intervention is maintained to avoid ischemia allowing the ability to inject contrast media to facilitate accurate balloon inflation or stent placement. Distal filter systems may be preferred in high-risk patients who are at increased risk for hemodynamic instability such as patients with severe left ventricular dysfunction or last remaining conduit. These systems do need a high crossing profile (large diameter sheath approximately 3- to 4-F) and the maneuverability is poor. Moreover, the inability to completely entrap microparticles, possible occlusion of the filter due to large amounts of debris, and inability to use in very distal lesions because of the need for a landing zone to deploy the filter are some other disadvanteges. The FilterWire EX (Boston Scientific) and the FilterWire EX (Boston Scientific) both showed noninferiority to distal balloon occlusion devices. [195]

The Proxis embolic protection system (St. Jude Medical, Maple Groves, Minnesota), a proximal balloon occlusion device, employs a distal balloon to seals the SVG while a proximal balloon seals the inside of the guiding catheter. This secures the blood with debris from embolizing

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downstream into the microvasculature. After the intervention, the blood with the debris can be aspirated with a suction catheter before deflating the balloon. The advantages are that protection from distal embolization of atheromatous debris can be established before crossing the lesion, side branches can be protected, and distal lesions that are not amenable to distal embolic protection because of lack of a landing zone can be treated. The device can not be used in ostial or very proximal lesions as approximately 15 mm of landing zone is required, and the device causes cessation of antegrade perfusion resulting in myocardial ischemia. The multicenter prospective randomized PROXIMAL trial determined outcomes of the Proxis embolic protection device compared to distal protection devices during stenting of degenerated SVG. [196] In a subset of 410 patients with lesions amenable to treatment with either proximal or distal protection devices the primary composite end point, death, MI, or target vessel revascularization at 30 days, occurred in 12.2% of distal protection patients and 7.4% of proximal protection patients.

The decision regarding whether or not to intervene in a diseased graft should be guided by the patient's symptoms, angiographic evidence of a significant stenosis, and noninvasive evidence of myocardial ischemia in the region subtended by the bypass graft. Fractional flow reserve (FFR) measurement to assess the significance of stenosis in a bypass graft can be performed in a similar fashion as in a native coronary vessel and guide decision making.

Moreover, risk-scoring models are considered to be valuable in predicting outcomes and guiding to appropriate treatment strategies for patients undergoing PCI. Although, the SYNTAX score, developed to characterize angiographic complexity, has been proposed to predict outcomes and select an optimal treatment strategy for patients with coronary artery disease, the score is complex and does not take into account patients with coronary bypass graft lesions. [197-199] The Duke myocardial jeopardy score was developed in the 1980s as a simple method to estimate the amount of myocardium at risk for ischemia on the basis of the location of a coronary lesion in non-surgically managed patients with coronary artery disease. [200] Recently, an adjustment was suggested to this score to include left main disease as well as the protective properties of patent bypass grafts, the modified Duke jeopardy score (Figure 1). [201] The same assumptions are used as in the original score, assigning greater prognostic significance to more proximal lesions than more distal lesions in the same vessel. Noteworthy, the modified Duke jeopardy score has not been validated yet.

Acute coronary syndrome - After CABG, progression of atherosclerosis occurs both in grafts and native coronary arteries, resulting in significant morbidity and mortality, especially in patients who present with acute ACS. Estimates from the Coronary Artery Surgery Study and Veteran's Affairs Cooperative Study of Coronary Bypass indicate a rate of MI of approximately 2% to 3% per year over the first 5 years after CABG, with recurrent infarction in as many as 36% of patients at 10 years and even higher rates of hospitalization for recurrent ischemia. [202-204] Although primary PCI is the preferred strategy for STEMI patients, current guidelines do not provide specific recommendations on the optimal reperfusion strategy in patients with prior CABG. [205] Compared to patient without prior CABG, patients with prior CABG presenting with ACS are older, have more cardiovascular risk factors, more frequent comorbidities, higher

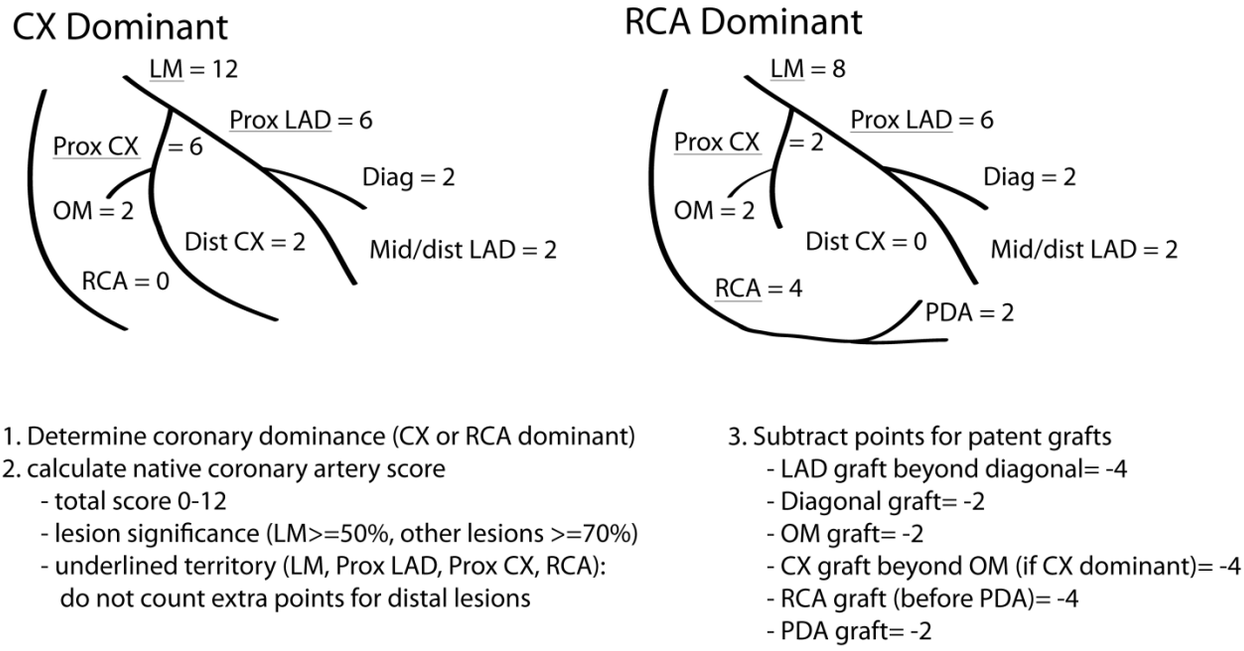

Figure 1. Modified Duke Jeopardy Score

TIMI risk score, lower left ventricular ejection fraction, had higher prevalence of previous treatment with evidence-based medications, were less likely to have ST-segment deviation or positive cardiac biomarker on presentation. [206-209] During hospitalization prior CABG patients experienced larger infarct size, were less likely to receive reperfusion therapy, early invasive therapy and were more likely to be managed medically when compared to non-CABG patients. [207,209] However, the efficacy of reperfusion therapy in patients with previous CABG is less well characterized. Given the large amount of atherosclerotic material and thrombus burden with limited runoff found in occluded SVG, it is suggested that reperfusion success rate is reduced. In the GUSTO-1 (Global Utilization of Streptokinase and TPA for Occluded Arteries I) trial a significantly increase in 30-day mortality was observed following reperfusion with tissue-type plasminogen activator in prior CABG patients compared to those without prior CABG (10.7% vs. 6.7%). [210] In addition, the prior CABG group also suffered more pulmonary edema, hypotension, or cardiogenic shock and a lower TIMI flow grade 3 rate was achieved (31% vs. 49.2%). In the PERSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy) trial the efficacy of eptifibatide, a Glycoprotein IIb/IIIa antagonist, in patients with ACS was compared in patients with or without prior CABG. [88] After adjusting for differences in baseline characteristics and treatment, patients with prior CABG had a significantly higher mortality rates at 6 months. At 30 days, there was a similar effect on the primary end point of death or MI in the eptifibatide group versus the placebo group in prior CABG patients and in patients without a history of CABG. Finally, in the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) Trial patients with prior CABG presenting with ACS were randomized to bivalirudin or heparin plus a glycoprotein IIb/IIIa inhibitor. [209] Bivalirudin monotherapy did not

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improve short-term or long-term prognoses in ACS patients with prior CABG. Currently, the optimal antithrombotic therapy for patients with prior CABG presenting with ACS is not known, and existing data are conflicting.

As the non-invasive treatment did not significantly improve outcomes in patients with prior CABG presenting with ACS a percutaneous strategy was investigated. Invasive versus non-invasive treatment in ACS and prior CABG was evaluated in the GRACE (Global Registry of Acute Coronary Events), and 6-month mortality was lower in patients revascularized versus those treated medically by univariate but not by multivariable analysis. [211] Similarly, in a large Swedish registry of 10,837 patients with previous CABG, 1-year adjusted mortality was reduced with 50% with revascularization compared with medical management. [212]

Long-term clinical follow-up of ACS patients with prior CABG treated with PCI has been assessed in several studies. In a small study, 34 consecutive patients with ACS who underwent PCI with DES for occluded SVG, showed a procedural success rate of 81%. [213] At 3-year follow-up mortality was 42%, recurrent ACS was 41% and repeat intervention was 38%. In a recently published retrospective analysis, the outcomes after PCI with BMS or DES for ACS due to graft failure were evaluated. [214] Although the majority of the 92 patients included were treated with BMS (84%), the groups were comparable for baseline clinical and angiographic characteristics. Graft failure occurred mainly in the SVG (90%), but also arterial grafts (LIMA and RIMA) were treated (8.7%). The initial restoration of normal blood flow was approximately 80%. The primary endpoint of death, MI, target vessel revascularization at 5-year follow-up was 65.9% in the BMS group and 43.4% in the DES group, this difference did not reach statistical significance. Individual endpoints at 5 years were also comparable between BMS and DES groups (death 46% vs. 43%, MI 36% vs. 33%, target lesion revascularization 26% vs. 15%, respectively). Predictors for the composite endpoint were cardiac shock (HR= 6.13; 95%-CI:3.12-12.01), creatinin (HR=1.006; 95%-CI:1.001-1.011), and multi-vessel disease (HR= 4.64; 95%-CI:1.40-15.41). Cardiac shock and creatinin also predicted for death.

The beneficial effect of redo CABG over PCI was examined in the randomized AWESOME (Angina With Extremely Serious Operative Mortality Evaluation) trial in which 3-year survival and freedom from recurrent ACS was similar among patients with prior CABG and refractory myocardial ischemia, although patients favoured PCI. [215]

Patients with an acute MI / STEMI from a SVG culprit undergoing PCI are a high-risk subset of an already high-risk population. In the PAMI-2 (Second Primary Angioplasty in Myocardial Infarction) trial demonstrated lower angiographic success rates and higher mortality rates after BA in 58 patients with prior CABG compared with the 1068 patients without prior CABG. Primary PCI in patients with acute MI and prior CABG showed that patients treated with BA or BMS in SVG grafts compared to patients in whom a native vessel was treated had more no-reflow at initial treatment (8.9% vs. 1.6%) and significantly more MI at 1 year follow-up (26% vs. 11%). [130] In another study, outcomes of 192 patients with acute MI from a SVG culprit undergoing PCI were compared to patients with a native culprit. [216] After multivariable adjustment, SVG culprit remained significantly associated with lower levels of peak troponin. The likelihood of MACE was higher in SVG vs. native culprits in patients with small to modest

troponin elevations. Patients with a SVG culprit also suffered higher rates of mortality at 30 days (14.3% vs. 8.4%) and MACE at 1 year (36.8% vs. 24.5%). Finally, in the APEX-AMI trial, STEMI patients with prior CABG exhibited a smaller baseline territory at risk as measured by 12-lead ECG and had less myocardial necrosis. Moreover, in these patients receiving primary PCI, TIMI flow grade 3 was less frequently achieved and ST-segment resolution was less common but they have more frequent clinical comorbidities and increased 90-day clinical events including mortality. Risk factors for mortality were prior heart failure and age.

In conclusion, in patients with prior CABG presenting with ACS, PCI improves clinical outcomes compared to medical therapy alone. Redo CABG does not seem to further improve clinical outcomes.

11. Redo CABG for graft failure

Redo CABG is considered when revascularization of the LAD or a large area of the myocardium is required. Redo CABG is also preferred in patients with prior CABG with no patent grafts present but left main disease or 3-vessel disease, and in those with disabling angina, despite optimal non-surgical therapy, including lesions unsuitable for PCI. [217]

Surgeons are posed with a number of challenges in patients requiring redo CABG, including a higher likelihood of technical complications, incomplete revascularization, inadequate myocardial preservation, lack of suitable conduits, neurologic complications including major disabling stroke, renal failure, peri-operative bleeding and ischemia. [218,219] To help decrease the risks associated with redo CABG, a number of technical advances have been introduced in the surgical arena. The first challenge, safe sternal re-entry without damaging coronary bypass grafts and other retrosternal structures, has been described to be safely performed when using an oscillating or micro-oscillating saw. [220,221] Periodic deflating of the lungs will help prevent injury to the pulmonary parenchyme during re-entry. When a mammary artery was used in the first surgery, there are generally four types of mammary artery to sternal relationships that can be encountered. [219] The first: LIMA and RIMA are both used with the LIMA supplying the LAD and the RIMA reaching to the RCA or its branches. In this case, the risk of injury is relatively low, because the IMA grafts are parallel to the body of the sternum at a deeper plane and go through the pericardium (which is therefore open) directly away from the midline toward the target vessels. In a second situation, a pedicle LIMA graft crosses in front of the pleura, curves around and goes back laterally to reach the LAD, which is typically seen as a C-shaped curve on the angiogram. This type of LIMA grafting is particularly prone to injury during sternotomy because of its close proximity to the sternal body. In the third scenario, the RIMA graft is used and comes in front of the aorta across the midline and reaches the LAD. Although the graft crosses the midline the risk of injury is relatively low due to the close proximity to the aorta which lies deeper in the thorax and can be easily identified. Finally, the RIMA may go behind the aorta through the transverse sinus to reach the marginal branches of the Cx artery, which is very far away from the sternal re-entry area and poses therefore minimal risk for potential injury. The proximity of vein grafts to the sternum varies signifi-

cantly due to the large number of options for proximal as well as distal anastomosis sites. Careful review of the coronary angiogram or even cardiac/thoracic imaging to assess the relationship to the sternum and other anatomic structures is therefore warranted. Other structures at risk for injury during sternal re-entry include perforation of the right ventricle, and innominate vein. This is particularly true in patients where the pericardium was not closed. After sternal access, subsequent exposure of the heart can be completed by fibrosis which can be significant especially after pericarditis or radiation exposure. In patients requiring posterior vessel bypass, the entire heart should be cleared of fibrosis to allow surgical manipulation.

After sternal entry and inspection of the coronary vessels and branches, the second challenge is to assure adequate revascularization. Diffuse coronary artery disease poses a major problem in finding a suitable and satisfactory area for anastomosis. Thick plaque build-up and calcified coronary artery branches as well as calcification of the aortic arch make distal and proximal anastomosis of coronary bypass grafts hard and increase the chances of graft failure. [219] Additionally, the lack of satisfactory bypass conduits is common, because many patients undergoing redo CABG have very thin and dilated varicose veins, and small and calcified radial arteries. Risk factors for poor saphenous vein quality are age, obesity and diabetes, which are all more prominent in patients requiring redo CABG. In those patients the IMA may be small or even atherosclerotic.

Inadequate myocardial protection is an important cause of failure to wean patients off cardiopulmonary bypass. In the presence of degenerative old vein grafts, delivery of cardioplegia solution is considered safer through retrograde coronary sinus perfusion than anterograde delivery of cardioplegic solution because of the risk of atheromatous embolization from atherosclerotic vein grafts which can lead to acute occlusion of coronary artery branches. [222] Additional measures include a no touch approach regarding diseased vein grafts to minimalize the chance of distal embolization due to manipulation. [223] To assure a constant temperature in an attempt to minimize haematological abnormalities and tissue edema, some surgeons also occlude the IMA with a bulldog clamp to prevent the delivery of warm blood into the myocardium. In such a way, the entire myocardium is provided with continuous, cold cardioplegic solution through coronary sinus perfusion. [224,225] After placement of newly constructed coronary artery bypass grafts, anterograde cardioplegic solution can also be given.

Neurological complications and bleedings are common following redo CABG. Several techniques are used to decrease the risk of neurological complications. Most common are ischemic stroke or TIA due to cerebral embolization from a calcified ascending aorta, atheromatous plaques on the ascending aorta, and embolization from a jet phenomenon from aortic cannulation. Other causes for cerebral dysfunction are systemic inflammatory processes in response to cardiopulmonary bypass and gaseous microemboli. [226] Soft flow aortic cannulae, heparin-coated circuits, and administration of adenosine have proposed as techniques to lower neurological complications, but adequate studies and therefore evidence are lacking. [227-229] Bleeding is associated with an increased morbidity and mortality. Bleedings can be largely avoided by meticulous surgical dissection and careful catherization. Some studies using the application of fibrin glue suggest that this may help minimize peri-operative

bleeding. [230] Intraoperative blood loss is a major cause of post-operative bleeding from depleted coagulation factors and hemodilution. Consideration should be given to preoperative antiplatelet therapy including aspirin and clopidogrel. A low platelet count and other medical conditions that adversely affect the coagulation process should be carefully investigated.

Redo CABG for coronary bypass graft failure is not favoured by cardiologists and surgeons alike, due to the higher morbidity and mortality compared with primary CABG. Reported intraoperative mortality rates are 5.8-9.6%. [231] Other major complications include stroke (1.4-3.2%), non-fatal MI (3.0-9.6%), renal failure (2.4-11%) and post-operative bleeding (2.7-4.4%). [217,223] Following redo CABG, survival is 75–90% and 55–75% at 5- and 10-year follow-up, respectively. [231]

Redo CABG versus PCI - Available data comparing the outcomes of PCI to redo CABG in patients with prior CABG is limited. Initial studies evaluating BA versus CABG noted comparable long-term results except for a much higher rate of repeat revascularization in the BA group (BA 64% vs. redo CABG 8%). [232] Multivariate analysis identified age > 70 years, left ventricular ejection fraction < 40%, unstable angina, number of diseased vessels and diabetes mellitus as independent correlates of mortality for the entire group. Direct comparison between redo CABG and PCI was performed in the AWESOME trial. A total of 142 patients with refractory post-CABG ischemia and at least one of five high-risk features (i.e. prior open-heart surgery, age >70 years, left ventricular ejection fraction <35%, MI within seven days or intraaortic balloon pump required) amandable for either PCI or redo CABG were randomized. [17] Arterial grafts were used in 75% of redo CABG procedures and stents in 54% of PCI (approximately one-half with BMS). In-hospital mortality was higher after redo CABG (8% vs. 0%). At 3 years, there was no significant difference in overall patient survival (redo CABG 71% vs. PCI 77%), but there was a nonsignificant increase in survival free of unstable angina in the CABG group (65% vs. 48%). In the much larger retrospective observational study from the Cleveland Clinic of 2191 patients with prior CABG who underwent multivessel revascularization between 1995 and 2000 were evaluated. [233] A total of 1487 had redo CABG and 704 underwent PCI (77% with at least one stent). No difference was observed in 30-day mortality with redo CABG compared to PCI (2.8% vs. 1.7%) but as expected periprocedural Q wave MI occurred more often after redo CABG (1.4% vs. 0.3%). At 5-years follow-up, cumulative survival was similar with redo CABG and PCI (79.5% vs. 75.3%). After adjustment, PCI was associated with a nonsignificant increase in mortality risk (hazard ratio 1.47, 95% CI 0.94-2.28). The major predictors of mortality were higher age and lower LVEF, not the method of revascularization. Importantly, the choice of treatment strategy was largely determined by coronary anatomy wherein the most important factors to perform redo CABG were: 1) more diseased or occluded grafts, 2) absence of a prior MI, 3) lower left ventricular ejection fraction, 4) longer interval from first CABG (15 vs. 6 years), 5) more total occlusions in native coronary arteries, and 6) the absence of a patent mammary artery graft.

In diabetic patients with post-CABG angina, the outcomes after repeat revascularization were evaluated in an observational study in which 1123 such patients underwent PCI (75% BA, 25% stent palcement) and 598 underwent redo CABG. [234] Redo CABG was associated with increased in-hospital mortality (11.2% vs. 1.6%) and stroke (4.7% vs. 0.1%). At 10 years, there

was no significant difference in mortality between groups (redo CABG 74% vs. PCI 68%). Noteworthy, the available comparative studies were, however, conducted before the use of aggressive dual antiplatelet therapy with aspirin and clopidogrel after PCI with stenting and aggressive lipid-lowering with statins for secondary prevention.

In a recently published retrospective study, in which patients were prescribed aggressive dual antiplatelet therapy, 287 consecutive patients with graft failure were assigned by the heart-team to PCI or redo CABG. [235] A total of 243 patients underwent PCI (82% treated with BMS, 18% treated with DES) and 44 redo CABG. Patient selection was present as patients undergoing PCI more frequently presented with STEMI, multivessel disease, SVG failure, a history of MI, and shorter time-to-graft failure. At 5 year, the rate of composite all-cause death, MI or target vessel revascularization was comparable, 57.6% after PCI and 51% after redo CABG. Target lesion revascularization was 21.3% after PCI, and 3.2% following redo CABG. In the PCI group, BMS was associated with significantly higher rates of target lesion revascularization (24.8% vs. 7.6%), but the rate of death or MI compared with DES was similar. Independent predictors for the composite outcome were creatinine and peak creatine kinase MB. These results have to be confirmed in larger studies before definite conclusion can be drawn.

12. Conclusion

Patients with prior CABG remain at risk for future cardiac events, including graft failure. Stable patients with recurrence of angina following CABG can be treated medically for their symptoms and risk factor reduction. In all patients with coronary heart disease aggressive risk factor reduction is recommended which includes aspirin, treatment for hypertension and serum lipids, avoidance of smoking, and controlling serum glucose in diabetic patients. Evaluation for ischemia is as in other patients with stable angina without prior CABG. However, early diagnostic angiography is suggested as the different anatomic possibilities, i.e. graft stenosis or progression of native vessel disease in nonbypassed vessels can lead to recurrent ischemia. Revascularization of graft failure either by PCI or redo CABG is associated with worse acute and long-term outcomes compared to patients without prior CABG. The choice of treatment modality is influenced by clinical and angiographic characteristics. When multiple grafts are occluded or the graft or native coronary artery appears unsuitable for PCI, surgery should be favoured. The target for PCI is the body of the coronary artery of the arterial graft while freshly occluded SVG or the anastomosis itself should be targeted due to the risk of embolization or perforation. Whether specific stent platforms, polymers or drugs are more appropriate in SVG and arterial graft lesions has not been addressed at this time. Moreover, the role of various surgical techniques for graft revascularization, such as off-pump and minimal invasive CABG also remain unclear. Finally, factors including disease status of the native vessel, and patient characteristics such as left ventricular function, renal failure, diabetes and advanced age, as shown in our multivariate analysis are of influence on outcomes. Future prospective studies in the medical and invasive treatment of graft failure are therefore warranted. Those studies together with our growing understanding of the pathobiology of arterial and vein grafts will

ultimately result in practical patient-tailored therapeutic strategies to enhance graft function and control intimal hyperplasia and accelerated atherosclerosis.

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