The ATLANTIC (Arterial Grafting International Consortium) Alliance (2017). Mechanisms, Consequences, and Prevention of Coronary Graft Failure. *Circulation*, *136*(18), 1749-1764. https://doi.org/10.1161/CIRCULATIONAHA.117.027597

Mechanisms, consequences, and prevention of coronary graft failure.

Mario Gaudino[a] MD, Umberto Benedetto[b] MD, Charalambos Antoniades[c] MD, Saswata Deb[d] MD, Antonino Di Franco[a] MD, Gabriele Di Giammarco[e], Stephen Fremes[d] MD, David Glineur[f] MD, Juan Grau[f] MD, Guo-Wei He[g] MD, Daniele Marinelli[e] MD, Lucas B Ohmes[a] MD, Carlo Patrono[h] MD, John Puskas[i] MD, Robert Tranbaugh[a] MD, Leonard N Girardi[a] MD, David P Taggart[c] MD.

The ATLANTIC (Arterial Grafting International Consortium) Alliance

[a]*Weill Cornell Medicine, Department of Cardio-Thoracic Surgery, New York City, NY, USA*

[b]*Bristol Heart Institute, University of Bristol, School of Clinical Sciences, Bristol, United Kingdom*

[c]*University of Oxford, United Kingdom*

[d]*Schulich Heart Centre, Sunnybrook Health Science, University of Toronto, Toronto, Canada*

[e]*University "G. D'Annunzio", Chieti, Italy*

[f]*Division of Cardiac Surgery, Ottawa Heart Institute, Ottawa, Canada*

[g]*TEDA International Cardiovascular Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin, China*

[h]*Catholic University School of Medicine, Department of Pharmacology, Rome, Italy*

[i]*Icahn School of Medicine at Mount Sinai, Department of Cardiovascular Surgery, New York City, NY, USA*

Brief title: Coronary graft failure

Word Count: 6525

Corresponding Author

Mario Gaudino, MD, Department of Cardio-Thoracic Surgery, Weill Cornell Medicine

525 E 68th St, New York, NY 10065. Email: mfg9004@med.cornell.edu

Tel. +1 212 746 9440 Fax. +1 212 746 8080.

Abstract

Graft failure occurs in a sizeable proportion of coronary artery bypass conduits. We review the current evidence in order to give an overview of the incidence, pathophysiology, and clinical consequences of this multifactorial phenomenon. Thrombosis, endothelial dysfunction, vasospasm, and oxidative stress are different mechanisms associated with graft failure. Intrinsic morphologic and functional features of the bypass conduits play a role in determining of graft failure. Characteristics of the target coronary vessel such as the severity of stenosis, the diameter, the extent of atherosclerotic burden, and previous endovascular interventions are important determinants of graft failure and must be taken into account at the time of surgery. Technical factors such as the method used to harvest the conduits, the vasodilatory protocol, and the storage solution as well as the anastomotic technique also play a major role. Systemic vascular risk factors such as age, gender, diabetes, hypertension, and dyslipidemia have been variably associated with graft failure. The correlation between graft failure and clinical events is less strict than commonly believed and varies according to the type and location of the failed graft. Intraoperative flow verification and secondary prevention using antiplatelet and lipid-lowering agents can help reducing the incidence of graft failure.

Long-term graft patency is the primary aim of coronary artery bypass surgery (CABG).

Graft failure is a complex, multifactorial event that occurs in a substantial proportion of CABG conduits.

With the aim of contributing to a better understanding of this phenomenon, we present a review of the current evidence on the biological, technical, and local factors that predispose a graft to failure. In addition, we review the published evidence on the clinical implications of graft failure and discuss possible preventive strategies.

Literature Search

The *ATLANTIC (ArTeriaL grAftiNg inTernatIonal Consortium)* Alliance is an international group of experts in CABG with a particular focus on the use of arterial grafts. In November 2016, the members of ATLANTIC searched PubMed using the terms “graft patency”, “graft failure” coupled with “coronary surgery”, “myocardial revascularization”, “coronary artery bypass”, “CABG”, “morphology”, “vascular biology”, “intraoperative detection” and “prevention”. Relevant abstracts were reviewed and the related articles function used for all included manuscripts. References from selected studies were cross-checked. After collegial discussion, the most important papers were selected and form the basis of the present review.

Patency of Different Conduits

The incidence of graft failure is different for the various types of conduits used in CABG (Table 1).

Great Saphenous Vein

The patency of saphenous vein grafts (SVGs) at 1-year has been reported to range from 81 to 98%.[1–3] It is worth noting that one modern trial, the Project of Ex Vivo Vein Graft Engineering via Transfection IV, (PREVENT IV), reported a SVG patency of only 75% at 12-18 months.[4] Mid-term patency of SVGs, between 5 to 7 years, was reported to be 75-86%.[1,2,5,6] Late SVG patency is severely reduced at ≥10-year

follow-up with studies reporting patency rates of 55-60% .[1,7,8] A large Veteran Affair (VA) trial assessed SVG and left internal thoracic artery (LITA) graft patency in 1,074 and 457 patients, respectively. The 10-year patency was 61% for veins and 85% for arterial grafts (p<0.001). If a graft was patent at 1 week, that graft had a 68% (SVG) and 88% (LITA) chance of being patent at 10 years (p<0.001).[8] A network meta-analysis comparing all conduits used for CABG has shown that compared to the RA and the RITA SVGs have a 3- to 4-fold higher risk of occlusion after 4-years.[5] The attrition rate of SVG is 1-2%/year between 1 to 6 years and 4%/year between 6 to 10 years.[9] However, some groups have reported substantially superior SVG angiographic outcomes using an atraumatic harvesting method or a composite graft technique.[10,11]

Internal Thoracic Artery

Since the mid-1980s the use of the LITA for left anterior descending artery (LAD) grafting has been a cornerstone of CABG surgery. The patency of the LITA at 1 year has been reported to be 93-96%[3,8,12], at 5 years 88-94%,[2,8,12] and ≥10 years 85-90%.[8,12] Tatoulis et al.[13] reported patency rates for the LITA and right internal thoracic artery (RITA) at 5, 10, and 15 years to be 98% and 96%, 95% and 81%, 88% and 65%, respectively. In this study, the LITA was predominantly targeted to the LAD while the RITA was commonly grafted to the right coronary artery (RCA) followed by the circumflex territory. The lower patency of the RITA was likely due to the poor patency of the RITA-RCA/posterior descending artery (PDA) target (overall conduit/target, patency: LITA/LAD, 97%; RITA/LAD, 95%; RITA/RCA or PDA, 83%).[13] Internal thoracic arteries (ITAs), left or right, seem to have the best patency rates when targeted to the LAD, followed by diagonal, circumflex, and the RCA territory.[13] The leading mechanistic explanation is competitive flow between the graft and the native coronary circulation. Given that dominant RCAs are usually larger diameter vessels than the LAD or circumflex, a bigger RCA without a high-grade proximal stenosis may continue to have substantial flow. In addition, the LAD is technically an easier target with more outflow, which are all factors contributing to excellent ITA to LAD patency.[12] The RITA may be

used as a free graft without compromising patency; either as an aorto-coronary graft or as a composite graft based on the LITA[13]

Radial Artery

The 1-year patency of the radial artery (RA) has been reported to be 89-92%[2,3], with the mid-term patency (≥5 years) being 90-98%.[2,6,14] A meta-analysis reported radial patency beyond 4 years to be 90%.[5] Achouh et al.[15] reported a 20-year angiographic patency of 83% and attrition rate of 0.4%/year after the first year up to 20 years. Gaudino and colleagues[16] reported 85% patency rate at 20 years and 25±0.2% probability of graft failure at 20 years for the RA compared to 19.0±0.2% for the LITA and 55.0±0.2% for SVG (p=0.002 for RA vs. SVG, 0.11 for RA vs. ITA, and p<0.001 for ITA vs. SVG). The Radial Artery Patency and Clinical Outcomes randomized trial (RAPCO)[17] presented their late results at the 2016 American Association of Thoracic Surgery meeting ; 10-year patency of the RA was reported to be 89-91%. Similar to ITAs, an important predictor of early and late patency for the RA is the severity of proximal native disease.[18]

Right Gastroepiploic Artery

There is limited data regarding right gastroepiploic artery (RGEA) patency. Early 1-year patency was reported to be 92-97%,[19] 80-90% at 5 years,[20] and 62% at 10 years.[20] These relatively low long-term patency rates are improved by using skeletonization and more restrictive criteria for target vessel stenosis (95% and 90% cumulative patency rates at 5 and 8 years, respectively).[19]

In conclusion the incidence of graft failure varies with the type of conduits used for CABG. Arterial grafts have higher patency rates compared to SVGs, especially at long-term follow-up.

Biological mechanisms underlying graft failure.

Graft failure being significantly more common in venous than arterial grafts, most of the known mechanisms have been described in SVGs. Even though graft failure is a single term describing graft stenosis and occlusion, the underlying mechanisms can vary, particularly in the early vs. late stages following implantation. The pathophysiology of vein graft failure has been attributed to acute thrombosis within the first month, intimal hyperplasia up to 1 year, and atherosclerosis beyond 1 year[21] (Figure 1). Different mechanisms are associated for each time frame, however, all contribute to graft occlusion.

Mechanisms of Acute Thrombosis

Early graft failure is caused by acute thrombosis, secondary to either direct endothelial injury or endothelial activation leading to a pro-thrombotic phenotype.[22] De-endothelialization as a result of mechanical forces is predominantly seen in free grafts, such as SVGs.[23] This results in exposure of the underlying extracellular matrix, local release of tissue factors as well as reduced bioavailability of prostacyclin and nitric oxide (NO), all of which contribute to platelet aggregation, deposition of fibrin, and ultimately thrombus formation.[24] At the same time, activated platelets express several pro-thrombotic molecules on their surface, such as P-selectin, and secrete substances with potent paracrine effects, such as platelet-derived growth factor, von-Willebrand factor, and the CD40 ligand, all promoting thrombosis as well as local inflammation through leukocyte chemotaxis and vascular wall infiltration.[22] Intact endothelial cells may also be activated due to stress experienced during the operation, transient ischemia, or systemic triggers, such as diabetes. Expression of a series of pro-thrombotic molecules on the luminal surface as well as impaired mechanisms of endothelial-dependent vasorelaxation combined with a shift towards the production of pro-thrombotic molecules (e.g. thromboxane A_2 (TXA_2), plasminogen activator inhibitor-1) all promote the interaction of the activated endothelial cells with circulating platelets and leukocytes, which initiate the inflammatory and thrombotic cascade responsible for graft thrombosis and failure.[25]

Impaired endothelial function

The vascular endothelium is a source of a number of molecules with either vasorelaxant (e.g. NO) or vasoconstrictive properties (e.g., endothelin); the balance of which ultimately regulates the vascular tone.[26,27] However, NO exerts pleiotropic effects by not only regulating the vascular tone through activation of guanyl-cyclase in the underlying vascular smooth muscle cells (VSMCs) but also by suppressing local inflammation, thrombosis, and protecting against oxidative injury.[27] Interestingly, NO bioavailability appears to be greater in arterial compared to venous grafts, providing a possible explanation for the better outcome rates observed with arterial grafts.[28] However, endothelial function varies even between different arterial types,[26] with higher endothelial NO synthase (eNOS) expression partly explaining the greater NO-mediated vasorelaxations in ITA compared to RA grafts.[29] Nevertheless, recent evidence suggests that high eNOS expression is not necessarily beneficial, given that in the presence of high levels of oxidative stress, depletion of the eNOS cofactor tetrahydrobiopterin can result in eNOS uncoupling and an increased production of superoxide ($O_2^{\cdot-}$) anions resulting in endothelial dysfunction.[30]

Vasoconstriction and spasm

Both arterial and vein grafts are susceptible to the effects of vasoactive substances, such as endothelin, TXA_2, serotonin, and α1-agonists.[31] These vasoconstrictors come either from the systemic circulation or are generated inside the vascular wall by endothelial cells, VSMCs, or infiltrating inflammatory cells.[26] However, the response of different conduits to vasoconstrictors varies, highlighting the biological heterogeneity of the different conduits used in CABG.[26] For example, variations in the presence and relative dominance of adrenergic receptors in VSMCs may explain why certain conduits (i.e., RA) are more prone to vasospasm than others.[26]

Other biological factors: the role of oxidative stress and morphological characteristics

Effects of the vascular redox state on vascular disease are well-documented and several studies have implicated the production of reactive oxygen species (ROS) in disease progression in both arterial and vein grafts.[32] ROS possess both direct deleterious effects on the vascular wall and also upregulate vascular inflammation through the activation of redox-sensitive pro-inflammatory pathways.[33] In addition, the relative absence of endogenous antioxidant protective mechanisms in SVGs compared to ITAs might contribute to their worse patency rates.[32]

In addition, structural characteristics of arterial and venous conduits have also been linked to their susceptibility to graft failure. For example, the relative absence of an internal elastic lamina in combination with high intercellular junction permeability in SVGs accelerates atherosclerosis through infiltration by circulating leukocytes and lipoprotein deposition.[23] In addition, exposure to the high pressure of arterial circulation results in early, diffuse intimal thickening as a compensatory response, termed "arterialization".[35] On the other hand, variations in the wall structure of arterial grafts (e.g. muscular wall phenotype in RA grafts compared to a more elastic phenotype in ITA) might also explain differences in patency rates with different graft types.[36]

Systemic Risk Factors

Most systemic risk factors have deleterious effects on local vascular biology and promote a pro-atherogenic phenotype. In addition, other systemic factors (e.g. platelet reactivity, age) might affect the individual response to post-CABG medical therapy, therefore increasing the risk for early or late graft failure.[37]

Diabetes mellitus is associated with persistent platelet activation, endothelial dysfunction, increased VSMC reactivity to vasoconstriction, and accelerated intimal hyperplasia in SVG.[34,38] The impact of diabetes on arterial and venous grafts has been investigated by several authors with most[2,12,39], but not all[40,41], showing a detrimental effect on graft patency. In a sub-analysis of the Radial Artery Patency

Study (RAPS), Desai and colleagues evaluated 440 RA grafts and 440 SVG. For all grafts, diabetes was demonstrated to be a predictor of graft occlusion at 1 year (Relative risk (RR):1.45, 95% confidence interval (CI) 1.03-2.05; p=0.03).[39] Diabetes plays a different role depending on the type of graft used. In another sub-analysis of the same trial, Deb et al.[18] showed that in diabetic patients the proportion of complete graft occlusion was significantly lower for RA grafts than for SVGs (p=0.0004), whereas this was not true for non-diabetic patients (p=0.19). Of note, interaction between diabetic status and conduit type was also statistically significant (p=0.02), suggesting that SVG do poorly in diabetics when compared to arterial grafts.

Harskamp and colleagues recently evaluated the determinants of ITA graft failure in a cohort of 1,539 CABG patients undergoing angiographic follow-up from the PREVENT-IV trial.[41] Surprisingly, the only patient-specific predictor of ITA graft failure was the absence of diabetes (Odds Ratio (OR):1.86, CI 1.22-2.81; p=0.004).

Shah and colleagues[40] in a study involving 3,715 angiograms, failed to show a predictive value of diabetes on graft failure (OR:1.12, CI 0.81-1.55; p=0.5).

As most of the clinical trials on CABG mainly enrolled men, the role of gender is difficult to evaluate.[42] However, the influence of gender on patency based on the type of conduit used has been suggested. In the quoted sub-analysis of the RAPS trial, RA graft occlusion at 1 year occurred in similar proportions of men (8.6%) and women (5.3%) (p= 0.6), whereas occlusion rates for the SVG were 12.0% and 23.3%, respectively (p=0.02).[39]

In the same study, traditional cardiovascular risk factors like age, preoperative myocardial infarction, hypertension, elevated lipids, smoking status, and peripheral vascular disease were not predictive of 1-year graft failure. Of note, however, in the more recent 5-year report of the same trial, female sex

(OR:2.23, CI 1.14-4.38; p=0.02), smoking history (OR:1.49, CI 1.01-2.21; p=0.047) and elevated creatinine levels (OR:1.17, CI 1.02-1.35; p=0.03) were found to be independent predictors of graft failure.[39]

A large angiographic series found no association between the classical vascular risk factors and graft patency.[40] However, in the 10-year VA angiographic study, age (acceleration factor (AF):1.28; CI 1.04-1.58; p=0.02), cholesterol levels (AF:0.76; CI 0.60-0.96; p=0.02) and Canadian Functional Class II-IV (AF:0.64; CI 0.40-1.02; p=0.05) were predictors of long-term graft status.[8] Finally, in a sub-analysis of the PREVENT-IV trial, cerebrovascular disease was the only systemic predictor of graft patency (OR:1.35; CI 1.04-1.77; p=0.03).[4]

In conclusion the classical vascular risk factors, particularly diabetes, seems to play a role in determining graft failure, although the correlation between individual risk factors and graft outcome needs further investigation.

Clinical Consequences of Graft Failure

The association between graft failure and clinical outcome has not been as clearly proven as commonly believed. Different studies have in fact reported discordant results.

Lytle et al. compared long-term survival of a cohort of 1,296 patients with (723) and without (573) SVGs stenosis.[43] At a mean follow-up of 6.9 years, patients with vein graft stenosis occurring within 5 years and patients with no vein graft stenosis had similar outcomes. However, patients with significant stenosis in SVGs to the LAD had higher rates of death and cardiac events.

In a large angiographic study on more than 5,000 grafts vein graft patency and occlusion were closely correlated with need for reoperation and survival.[1]

An analysis from the Duke Cardiovascular Databank reported the clinical impact of early vein graft failure in 1,243 patients who underwent angiography after CABG.[44] The investigators found that SVG graft failure was associated with death, myocardial infarction, or revascularization ($p<0.0001$ for all).

The results of the long-term follow-up study of the PREVENT IV trial showed that SVG failure was associated with an increase in revascularization but not with death and/or myocardial infarction.[45]

In a large angiographic study, Shavadia et al. found that LITA-to-LAD graft failure but not GSV graft failure was associated with a worse long-term prognosis.[46] In the PREVENT IV trial, LITA-to-LAD graft failure was also associated with a significantly higher incidence of acute clinical events, mostly as a result of a higher rate of repeat revascularization (HR:3.92, CI, 2.30-6.68; $p<0.0001$).[41]

In an analysis of the RAPS trial examining late angiographic follow-up, Yamasaki and co-authors found that the incidence of adverse clinical events and need for revascularization was significantly higher in patients with graft stenosis ($p<0.0001$ and $p<0.0009$, respectively).[47]

The lack of a constant correlation between graft failure and clinical event is likely related to the different amount of myocardium supplied by the failed graft.

Other possible explanations are the high rate of non-flow limiting stenosis bypassed when using standard angiography for planning the grafting strategy[48] and the possible development of a collateral network from other patent grafts.

In conclusion the clinical consequences of graft failure seem to vary according to the location of the distal anastomosis, with graft to the LAD more closely related to clinical events. Further investigation is required to clarify the correlation between graft occlusion and clinical outcome and to elucidate the pathophysiologic mechanisms of this correlation.

Pharmacological Preparation and Graft Storage

Almost all vasodilator agents have been used to prevent graft spasm before usage.[48] Papaverine, nitrates, calcium antagonists, phosphodyesterase inhibitors, phenoxybenzamine, and iloprost have been proposed. Less frequently used vasodilators include Rho-kinase inhibitors, angiotensin receptor antagonists, potassium channel openers, heme-oxygenases, C-type natriuretic peptides, TXA_2 antagonists, and antiplatelet agents.[48] Drugs acting through different mechanisms used in antispastic protocols include L-carnitine, botulinum toxin, and NO-independent guanylate cyclaseactivator YC-1 or NO-nucleophile adduct diethylamine/NO.[48]

Vasodilator drugs relax the vessel through a very specific mechanism(s) (Figure 2) and, due to the complex and variable physiopathology of graft spasm, there is no "perfect" vasodilator. For this reason a common approach is to combine agents that target different mechanisms of spasm. The most used combinations is a calcium channel blocker (usually verapamil or nicardipine) combined with a NO-releasing drug such as nitroglycerin.[49–51] The addition of a systemic calcium channel antagonist is of questionable benefit.[50,52]

The antispastic protocol should also include an atraumatic harvesting technique that protects the endothelium and smooth muscle cells of the media.

Few studies have correlated the vasodilatory protocol used for graft preparation with patency.

Yoshizaki and coworkers reviewed angiographic results among 116 CABG patients who had RA grafts and were treated either with verapamil-nitroglycerin or papaverine.[53] Results showed that papaverine was significantly associated with RA graft occlusion. Among patients randomized to either continue or suspend diltiazem therapy 1 year after RA grafting, Gaudino and colleagues showed that at 5-year follow-up there was no difference in angiographic patency rates between groups.[54]

The solutions in which grafts are stored before use also plays a crucial role. Storage solutions include normal saline, blood-based, heparinized, and buffered solutions. Numerous studies demonstrate the

detrimental effect of normal saline solutions on endothelial function and clinical outcomes. Wise and colleagues showed that grafts stored in normal saline have significantly reduced endothelial-dependent and -independent vasodilation ($p=0.005$ and $p=0.002$, respectively).[55] Follow-up data from the PREVENT IV trial showed that 1-year vein graft failure rates were significantly lower when buffered saline, instead of saline or blood, was used (OR:0.63, CI 0.49-0.79; $p<0.001$ and OR:0.63, CI 0.48-0.81; $p<0.001$, respectively).[56]

For arterial grafts the addition of pharmacologic agents to the storage solution has the potential to prevent graft spasm.[50,51]

In the PREVENT IV trial ex vivo treatment with edifoligide (E2F decoy, regulates expression of genes controlling SMC proliferation) has been shown to be ineffective in the prevention of early vein graft failure.[57]

Preoperative pharmacologic treatment with vitamin-C and cerivastatin has been proposed in order to achieve maximal vasodilatation and endothelial preservation of the RA.[52] Adenoviral transfer of the eNOS gene also has been described.[58]

To summarize the pharmacological protocol used for graft preparation and storage has the potential to influence the graft's outcome. Buffered storage solutions seems to lead to better patency rates, but further investigation is required.

Technical Factors

As in every surgical procedure, technical factors play a major role during CABG and have the potential to affect the patency rate of bypass conduits.

Harvesting techniques have the potential to affect graft patency. Current angiographic evidence suggests that endoscopic harvesting is associated with reduced SVG patency. A post-hoc analysis of the

PREVENT IV showed that endoscopic harvesting was associated with a significantly higher risk of vein graft failure at 12-18 months compared to the open technique (OR:1.41; CI 1.16-1.71, p=0.0001).[4] Similarly, in a planned sub-analysis of the Randomized ON/OFF Bypass (ROOBY) Trial the 1-year patency rate of endoscopically harvested SVG was significantly lower than that of veins harvested using the open technique (74.5% vs. 85.2%, p<0.001).[59] A meta-analysis of the angiographic data of 5 trials examining 6,504 grafts showed a significantly higher incidence and risk of graft failure in the endoscopic harvesting group (26.9% vs. 20.3%, p<0.0001; OR:1.38, CI 1.01-1.88).[60] Another meta-analysis including angiographic results from 7,929 patients described a significantly higher incidence of graft stenosis and occlusion for endoscopically harvested saphenous veins (log-rate ratio (RR):1.19, CI 1.05-1.34, p=0.005 for graft stenosis and RR:1.39, CI 1.11–1.75, p=0.004 for graft occlusion).[61] Although in both studies these differences lost statistical significance when analyses were limited to the randomized trials, this could be related to the reduction in statistical power as a trend toward higher graft failure in the endoscopic group was present even when pooling together randomized trials. The most plausible explanation for the reported difference is the higher degree of damage to the vascular wall induced by endoscopic harvesting, although not all the studies are concordant on this issue.[62] Of note, studies have reported equivalent clinical outcomes between patients operated using endoscopic vs. open saphenous vein harvesting technique.[63] However, in view of the discussed lack of strict correlation between clinical outcomes and graft patency, the angiographic data seems more relevant to clarify this issue.

The ongoing Randomized Endo-vein Graft Prospective (REGROUP) trial[64] will provide new important insights on this topic.

A no-touch technique of SVG harvesting, that reduces endothelial injury[10] has shown superior long-term patency of 83% at 16 years when compared with conventional harvesting.[11] The results from a multi-center randomized trial investigating whether the no-touch vs. conventional harvesting is associated with superior early SVG patency are pending.[65]

Skeletonized ITA and RA conduits have been reported to be non-inferior to pedicled with respect to patency.[52,66]

The anastomotic technique is another important technical factor in determining patency of grafts. Controversy still exists on the effect of on- vs. off-pump surgery on patency rates. The ROOBY trial randomized 2,203 patients to on- or off-pump CABG. At 1-year follow-up, angiographic patency rates of the off-pump group was significantly lower than that of the on-pump (82.6% vs. 87.8%, $p<0.01$).[67] A smaller European randomized trial reported similar results.[68] However, two other small randomized trials and a post-hoc sub-analysis of the PREVENT IV study found no difference in patency rate between the two techniques.[69–71] All the meta-analysis on the subject showed a significantly higher incidence of graft failure among the off-pump cases. The most recent meta-analysis of CRTs pooled angiographic data on 7,011 grafts and reported a OR of 1.51 for graft failure in the off-pump series (CI 1.21-1.88, $p=0.002$).[72] It is plausible that differences in operator experience, study design, and enrollment criteria are the reasons for the discrepancies.

Several studies compared the clinical outcomes of on- vs. off-pump CABG.[73] As for the endoscopic vs. open harvesting comparison, due to the lack of a direct correlation between graft patency and clinical status, it is unlikely that the results of clinical outcome studies can be extrapolated to graft patency.

To summarize technical factors are important in determining graft outcome. Endoscopic saphenous vein harvesting and off-pump technique have been correlated with lower patency rates.

Target Vessel Factors

Different quantitative and qualitative characteristics of the target coronary vessel have the potential to influence the long-term patency of bypass grafts.

The grafting of a vessel that is not significantly stenosed creates a situation where the flow through the conduit and the native coronary artery are in competition. Arterial grafts are living conduits with high vasoactive capacity and tend to react to this situation with a reduction in graft flow. Low endothelial stress due to reduced flow is associated with reduced NO bioavailability, upregulation of several pro-atherogenic genes in the vascular wall, and high risk of thrombosis.[74] This is also a putative mechanism of arterial graft string sign.

The radial and gastroepiploic arteries are the most affected by competitive flow due to their higher degree of contractility and vasospastic characteristics. Studies have demonstrated that radial graft patency is higher in patients with severe proximal stenosis. In a report by Gaudino and colleagues,[16] 80% of very-long-term RA occlusion or string sign cases occurred in patients in whom the artery was anastomosed to coronary arteries with stenosis ≤90%, irrespective of distal anastomosis location. This also applies to the gastroepiploic artery. As stated before, Suzuki and coauthors[19] reported patency rates of 97.8%, 94.7% and 90.2% at early, 5, and 8-year follow-up when the gastroepiploic artery was anastomosed to a target vessels with >90% stenosis. This is in contrast to a 66.5% patency at 10-year follow-up when the gastroepiploic artery was anastomosed to a target vessel with <90% stenosis.[75]

The ITA are also sensitive to competitive flow, although to a lesser degree. Many[76] but not all[77] published studies have found that the patency of ITA grafts is directly correlated with the degree of proximal stenosis in the coronary target. Of note, even when chronic native competitive flow does not affect midterm graft patency, it influences ITA diameter.[78]

The resistance of SVG appears negligible and therefore the pressure at the distal graft anastomosis is nearly equal to the aortic pressure, with minimal risk of developing competitive flow. Also SVG's lack the ability to regulate the blood flow to the coronary territory and exhibit reduced variations in graft flow.

For this reason, competitive flow is a significant issue for arterial bypass, but less for venous conduits.[79,80]

This concern is recognized in the 2011 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline for Coronary Artery Bypass, in which arterial grafting is contraindicated in patients with less than sub-occlusive stenosis of the native vessel.

Another crucial factor determining long-term patency of the graft is target vessel diameter. Goldman and colleagues examined the 10-year patency rates of SVG and found that if the target vessel diameter was >2.0mm, SVG patency was 88% as compared to a patency rate of 55% if the target vessel diameter was ≤2.0mm ($p<0.001$).[8] In a report by Shah and coworkers that explored determinants of SVG failure, smaller target coronary vessel diameter (1.0-1.4mm, $p<0.001$) significantly affected graft patency.[81] In a small randomized controlled trial, Souza and coauthors found that target vessel diameter ≥2.0mm impacted patency rates (OR:4.7, CI 1.4-15.4; $p=0.011$).[39,82]

Studies have demonstrated that diffuse coronary artery disease is associated more with lower graft patency than focal disease. One study using fractional flow reserve (FFR) to characterize diffuse vs. focal lesions found that the former were associated with an increased risk of graft failure within 6 months of CABG (26% vs. 7%, $p=0.021$).[83] Diffuse atherosclerosis affects vasomotor regulation of the coronary target and also limits the availability of adequate landing zones for the bypass conduit.

Prior coronary artery stenting has a similar effect as diffuse atherosclerosis, by reducing the vasomotor properties of the coronary vessel and limiting the areas available for anastomoses. Graft patency rates are significantly lower in stented coronary arteries compared with those that have not been previously instrumented.[84]

Extensive calcification of the coronary target has even worse implications for graft failure. In addition to the effect on vasomotor properties and the limited areas for anastomosis described above, severely

calcified plaques are not amenable to suturing without performing extensive endarterectomies that significantly alter the architecture of the coronary artery.

In conclusion target vessel factors can significantly impact graft patency. Competitive flow is particularly important for arterial grafts. Target vessel diameter, extent of atherosclerotic burden, calcification and previous endovascular interventions have the potential to influence graft patency.

Intraoperative Graft Assessment and Patency

Transit-Time Flow Measurement (TTFM) is the most commonly used method for intraoperative graft verification in coronary surgery.

The area under the modulated flow trace corresponds to the mean graft flow (MGF, ml/min). The pulsatility index (PI), the percentage backward flow through the anastomosis (%BF) and diastolic filling (DF) are other important flow variables for evaluating graft function.

Current ACC/AHA guidelines recommend TTFM for direct intraoperative quality control in CABG surgery (IC).

According to the recommendations of the Joint Task Force on Myocardial Revascularization of the European Association of Cardiothoracic Surgery and the European Society of Cardiology, the MGF cut-off value to detect graft malfunction should be 20 mL/min, but different values have been reported by other authors (Table 2).

The PI is obtained by dividing the difference between the maximum and minimum flow by the value of the mean flow. Any factor that increase the resistance to graft flow increases the PI value. According to the quoted European recommendations, a PI cut-off of 5 has to be used to detect graft malfunction. However, PI cut-off values from 3 to 5 have been reported.[85]

The %BF expresses the percentage of blood flow directed backward across the anastomotic site compared to the total forward flow during one cardiac cycle. The cut-off values for %BF is generally accepted at 3% and this index is considered particularly important in diagnosing a competition of flow or functional graft occlusion.[85] Anyhow it has to be considered as proof of anastomosis patency.

The DF expresses the proportion of diastolic graft flow during the entire graft flow. It is known that the graft flow on the right coronary artery shows a systolic prevalence and a diastolic filling by 50% compared to the left coronary system where it should be above 60%. Although the correlation of the DF with patency is poorly known, it is a possible field of future investigations on the systolic function of the right ventricle.

TTFM is characterized by a fairly high specificity with a poor sensitivity that leads to a low positive predictive value and high negative predictive value.[86] Standardization of factors such as the systemic arterial pressure at which measurements are taken and the position of the probe is extremely important to increase TTFM sensitivity.[86]

Limited evidence exists on the correlation between TTFM values and graft patency, as most of the published studies have clear selection bias, used different definitions and cut-off values, and had different follow-up. All published series are probably underpowered to detect moderate correlations. A small randomized study on the subject showed that routine TTFM does not improve 1-year graft patency but did find a significant correlation between low TTFM flow and graft occlusion at 1 year.[87] A retrospective angiographic analysis of two randomized controlled trials, the Best Bypass Surgery trial and the Copenhagen Arterial Revascularization Randomized Patency and Outcome trial on 982 grafts found a 4% decrease in graft failure odds for every 1 mL/min increase in MGF (OR:0.96, CI 0.93-0.99; p=0.005).[88]

The lack of sensitivity of the method may be partially overcome by increasing the myocardial oxygen demand by injecting a bolus of 20 mcg/Kg of dobutamine.[89] The dobutamine test can be helpful in evaluating a reversal of a flow competition between two branches of a composite conduit produced by an unbalanced severity of the native stenosis. It is additionally useful in predicting patency of a single ITA at risk of functional occlusion (very high PI and very low MGF and very high % BF).[85]

Integration with intraoperative imaging (Figure 3) in order to visualize the anastomosis morphology is another mean of increasing TTFM sensitivity. It has been demonstrated that when TTFM is coupled with high-resolution ultrasound imaging the diagnostic accuracy can increase to 100%.[90]

Fluorescence coronary angiograms using indocyanine green is another imaging method for intraoperative evaluation of graft function that can potentially be coupled with TTFM, but very few data have been reported to date.[91]

Finally, it must be noted that most of the published TTFM data refers to the ITA and the saphenous vein. A recent comparative analysis showed that those two types of grafts have fairly overlapping TTFM results.[85] Very few data exist for the other conduits.

To summarize TTFM is an important tool to intraoperatively evaluate graft function and can potentially predict long-term graft patency. However, concomitant use of imaging techniques or of pharmacological tests is necessary in order to improve TTFM accuracy.

Secondary Prevention

Post-operative antiplatelet and lipid-lowering agents continue to be the mainstay of secondary prevention after CABG surgery. Inhibition of platelet activation after CABG helps maintain graft patency and prevent atherothrombotic complications. According to a recent AHA scientific statement on secondary prevention after CABG surgery, aspirin should be administered pre-operatively and within 6

hours after CABG in doses of 81-325mg daily. It should then be continued indefinitely to reduce graft occlusion and major vascular events (Class I, Level of Evidence A; IA). For aspirin-treated patients, current guidelines recommend continuing antiplatelet therapy prior to surgery, except for patients at high bleeding risk. However, there is limited randomized evidence to support one strategy over the other,[92] and the recently published Aspirin and Tranexamic Acid for Coronary Artery Surgery (ATACAS) trial,[93] enrolling 2,100 patients did not resolve this uncertainty. Notably, patients were enrolled into the study if they had not been taking aspirin regularly before the trial or had stopped taking aspirin at least four days before CABG surgery.[93]

There is a discrepancy among current US and European guidelines on the recommended dose of aspirin for long-term treatment after CABG: while the former suggest considering a higher (325mg daily) rather than a lower (81mg daily) aspirin dose, "presumably to prevent aspirin resistance" (IIaA), the latter recommend a low-dose (75-100mg daily) aspirin in all patients (IA). Aspirin "resistance" is an ill-defined phenomenon, largely explained by non-compliance, a pharmacodynamic interaction of some nonsteroidal anti-inflammatory drugs with low-dose aspirin, or reduced systemic bioavailability of some enteric-coated formulations.[94] A more likely explanation for the impaired efficacy of low-dose aspirin in the early post-operative period following CABG surgery is represented by a transient increase in platelet turnover[95] that may limit the duration of platelet TXA_2 inhibition because of accelerated renewal of the drug target. Consistent with this hypothesis, two independent groups have shown that multiple daily doses of aspirin (81mg qid or 100mg bid) overcome impaired platelet inhibition in response to a conventional once-daily regimen, and are more effective in suppressing platelet TXA_2 production than higher od doses (200 to 325mg) four to seven days after CABG surgery. Clearly, a randomized clinical trial is needed to test the hypothesis that more frequent aspirin dosing reduces premature graft occlusion and prevents major vascular events. The high rate of death and thrombotic complications in the recent ATACAS trial, particularly non-fatal myocardial infarction, detected within the first 30 days

after CABG (13.8% vs. 15.8% in the aspirin vs. the placebo group, respectively (RR:0.87, CI, 0.71-1.07; p=0.20)[93] outlines the limitations of current antithrombotic strategies in this setting and emphasizes the need for additional clinical studies.

Following off-pump CABG, dual antiplatelet therapy is recommended for 1 year with low-dose aspirin (81-162mg daily) and clopidogrel (75mg daily) to reduce graft occlusion (IA). Dual antiplatelet therapy for 1 year after on-pump CABG may be considered in patients without recent acute coronary syndrome (ACS), but the benefits are not well established (IIbA). After completion of the Platelet Inhibition and Patient Outcomes (PLATO) study, a phase-3 trial of ticagrelor vs. clopidogrel in aspirin treated ACS patients[96], the investigators performed a post-hoc analysis of the 1,261 patients who underwent CABG within 7 day of receiving treatment.[97] In this sub-group, ticagrelor was associated with a non-significant reduction in the primary end-point at 1-year compared with clopidogrel (10.6% with ticagrelor vs. 13.1% with clopidogrel; HR:0.84, CI, 0.60-1.16; p=0.29), and a significant reduction in cardiovascular mortality (4.1% vs. 7.9%, respectively; HR:0.52, CI, 0.32-0.85; p<0.01), with no significant difference in CABG-related major bleeding between the two $P2Y_{12}$ blockers (81.2% vs. 80.1%, respectively; HR:1.01, CI 0.90-1.15; p=0.84).[97] However, no additional studies have examined prospectively the potential superiority of ticagrelor or prasugrel vs. clopidogrel in a representative population of patients undergoing CABG.

Elevated low-density lipoprotein (LDL)-cholesterol levels accelerate the process of SVG disease after CABG, by favoring the development of intimal hyperplasia and atheromatous plaques. Statins are highly effective in reducing plasma LDL-cholesterol concentrations independently of the baseline level. Moreover, their efficacy and safety in reducing important vascular outcomes has been convincingly established by numerous randomized clinical trials in approximately 174,000 coronary artery disease patients participants and a meta-analysis of their individual data.[98] Overall, in this meta-analysis, among the 27 trials included, statins reduced the risk of major vascular events by 21% for each mmol/L reduction in LDL-cholesterol (RR:0.79, CI 0.77-0.81; p<0.0001), with significant reductions in both

women and men. Moreover, similar proportional reductions in risks of major vascular events per mmol/L LDL-cholesterol reduction independently of the baseline characteristics of the randomized participants, including pre-treatment LDL cholesterol level, history of CHD, and estimated 5-year risk of major vascular events were demonstrated.[98]

Statins have been shown to reduce the development of SVG disease by inhibiting neo-intimal formation and VSMC proliferation. Thus, the Post-CABG trial demonstrated that lowering LDL-cholesterol levels to <100 mg/dL reduced both cardiovascular events and the progression of atherosclerosis in native coronary arteries and SVG (27% vs. 39% aggressive vs. moderate cholesterol-lowering treatment, respectively; $p<0.001$).[99] Although the benefits of more aggressive lipid lowering by high-intensity statin therapy to LDL levels <70 mg/dL in further reducing the risk of major vascular events are well established[98], specific data on patients undergoing CABG are sparse and further research is needed.

Despite the remarkable database supporting the efficacy and safety of long-term statin therapy,[98] it remains underused after CABG with declining patient adherence. According to the recent AHA statement, essentially all CABG patients should receive long-term statin therapy, starting in the pre-operative period and restarting early after surgery in the absence of contraindications such as liver disease (IA). High-intensity statin therapy (e.g., atorvastatin 40-80mg, rosuvastatin 20-40mg daily) should be administered after CABG surgery to all patients <75-years of age (IA). Moderate-intensity statin therapy should be prescribed to those patients who are intolerant of high-intensity therapy and to those at greater risk of drug-drug interactions, such as CABG patients >75-years of age (IA).

The recent IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial) found a 8.8% (CI 3.1–14.6) lower absolute risk of cardiovascular death, major coronary event or stroke at 6 years by adding ezetimibe to statin therapy in patients with prior CABG.[100]

Although CABG using arterial grafts might be associated with a lesser degree of downstream coronary and conduit disease progression, there is no evidence that this may dictate a different approach to secondary prevention.

To summarize post-operative therapy with antiplatelet and lipid-lowering agents remain the cornerstone of secondary prevention after CABG surgery. The role of dual antiplatelet therapy and of ezetimibe remain to be determined.

Conclusion

Graft failure is a complex phenomenon that occurs in a substantial proportion of CABG conduits. Biological mechanisms, target vessel characteristics, as well as surgical technique, and type of graft used all play a role in determining failure. The correlation between vascular risk factors and graft patency needs further investigation. The clinical consequences of graft failure seem to be dependent on the type and location of the failed graft and are still poorly characterized. Pharmacological prevention with antiplatelet and lipid-lowering agents is associated with better clinical outcome after CABG and has the potential to reduce the incidence of graft occlusion. Finally, further studies are need on the possibility that intraoperative assessment of graft flow by TTFM and imaging techniques can reduce the incidence of graft failure.

Sources of Funding

Prof Antoniades is supported by the British Heart Foundation (FS/16/15/32047 and PG/13/56/30383) and the National Institute for Health Research - Oxford Biomedical Research Centre.

Dr Fremes is supported in part by the Bernard S Goldman Chair in Cardiovascular Surgery.

Dr Taggart has research funding provided by Medistim to investigate transit time flow measurement.

Disclosures

There are no disclosures for this manuscript.

References

1. Fitzgibbon GM, Kafka HP, Leach AJ, Keon WJ, Hooper GD, Burton JR. Coronary bypass graft fate and patient outcome: angiographic follow-up of 5,065 grafts related to survival and reoperation in 1,388 patients during 25 years. *J Am Coll Cardiol*. 1996;28:616–626.

2. Deb S, Cohen EA, Singh SK, Une D, Laupacis A, Fremes SE, RAPS Investigators. Radial artery and saphenous vein patency more than 5 years after coronary artery bypass surgery: results from RAPS (Radial Artery Patency Study). *J Am Coll Cardiol*. 2012;60:28–35.

3. Goldman S, Sethi GK, Holman W, Thai H, McFalls E, Ward HB, Kelly RF, Rhenman B, Tobler GH, Bakaeen FG, Huh J, Soltero E, Moursi M, Haime M, Crittenden M, Kasirajan V, Ratliff M, Pett S, Irimpen A, Gunnar W, Thomas D, Fremes S, Moritz T, Reda D, Harrison L, Wagner TH, Wang Y, Planting L, Miller M, Rodriguez Y, Juneman E, Morrison D, Pierce MK, Kreamer S, Shih M-C, Lee K. Radial artery grafts vs saphenous vein grafts in coronary artery bypass surgery: a randomized trial. *JAMA*. 2011;305:167–174.

4. Hess CN, Lopes RD, Gibson CM, Hager R, Wojdyla DM, Englum BR, Mack MJ, Califf RM, Kouchoukos NT, Peterson ED, Alexander JH. Saphenous vein graft failure after coronary artery bypass surgery: insights from PREVENT IV. *Circulation*. 2014;130:1445–1451.

5. Cao C, Manganas C, Horton M, Bannon P, Munkholm-Larsen S, Ang SC, Yan TD. Angiographic outcomes of radial artery versus saphenous vein in coronary artery bypass graft surgery: a meta-analysis of randomized controlled trials. *J Thorac Cardiovasc Surg*. 2013;146:255–261.

6. Collins P, Webb CM, Chong CF, Moat NE, Radial Artery Versus Saphenous Vein Patency (RSVP) Trial Investigators. Radial artery versus saphenous vein patency randomized trial: five-year angiographic follow-up. *Circulation*. 2008;117:2859–2864.

7. Lytle BW, Loop FD, Cosgrove DM, Ratliff NB, Easley K, Taylor PC. Long-term (5 to 12 years) serial studies of internal mammary artery and saphenous vein coronary bypass grafts. *J Thorac Cardiovasc Surg*. 1985;89:248–258.

8. Goldman S, Zadina K, Moritz T, Ovitt T, Sethi G, Copeland JG, Thottapurathu L, Krasnicka B, Ellis N, Anderson RJ, Henderson W, VA Cooperative Study Group #207/297/364. Long-term patency of saphenous vein and left internal mammary artery grafts after coronary artery bypass surgery: results from a Department of Veterans Affairs Cooperative Study. *J Am Coll Cardiol*. 2004;44:2149–2156.

9. Motwani JG, Topol EJ. Aortocoronary saphenous vein graft disease: pathogenesis, predisposition, and prevention. *Circulation*. 1998;97:916–931.

10. Dashwood MR, Tsui JC. “No-touch” saphenous vein harvesting improves graft performance in patients undergoing coronary artery bypass surgery: a journey from bedside to bench. *Vascul Pharmacol*. 2013;58:240–250.

11. Samano N, Geijer H, Liden M, Fremes S, Bodin L, Souza D. The no-touch saphenous vein for coronary artery bypass grafting maintains a patency, after 16 years, comparable to the left internal thoracic artery: A randomized trial. *J Thorac Cardiovasc Surg*. 2015;150:880–888.

12. Sabik JF, Lytle BW, Blackstone EH, Houghtaling PL, Cosgrove DM. Comparison of saphenous vein and internal thoracic artery graft patency by coronary system. *Ann Thorac Surg*. 2005;79:544-551-551.

13. Tatoulis J, Buxton BF, Fuller JA. Patencies of 2127 arterial to coronary conduits over 15 years. *Ann Thorac Surg*. 2004;77:93–101.

14. Hayward PAR, Gordon IR, Hare DL, Matalanis G, Horrigan ML, Rosalion A, Buxton BF. Comparable patencies of the radial artery and right internal thoracic artery or saphenous vein beyond 5 years: Results from the Radial Artery Patency and Clinical Outcomes trial. *J Thorac Cardiovasc Surg*. 2010;139:60–67.

15. Achouh P, Acar C. Twenty-year fate of the radial artery graft. *Ann Cardiothorac Surg*. 2013;2:481–484.

16. Gaudino M, Tondi P, Benedetto U, Milazzo V, Flore R, Glieca F, Ponziani FR, Luciani N, Girardi LN, Crea F, Massetti M. Radial Artery as a Coronary Artery Bypass Conduit: 20-Year Results. *J Am Coll Cardiol*. 2016;68:603–610.

17. Buxton BF, Hayward PA, Matalanis G, Monten S, Horrigan M, Rosalion A. 10-year Endpoint of RAPCO is Reached: Clinical and Angiographic Results of a Randomised Trial of Radial Artery Versus Right Internal Thoracic Artery or Saphenous Vein for the Second Graft. 2016;

18. Deb S, Singh SK, Moussa F, Tsubota H, Une D, Kiss A, Tomlinson G, Afshar M, Sless R, Cohen EA, Radhakrishnan S, Dubbin J, Schwartz L, Fremes SE, Radial Artery Patency Study Investigators. The long-term impact of diabetes on graft patency after coronary artery bypass grafting surgery: a substudy of the multicenter Radial Artery Patency Study. *J Thorac Cardiovasc Surg*. 2014;148:1246–1253; discussion 1253.

19. Suzuki T, Asai T, Nota H, Kuroyanagi S, Kinoshita T, Takashima N, Hayakawa M. Early and Long-Term Patency of In Situ Skeletonized Gastroepiploic Artery After Off-Pump Coronary Artery Bypass Graft Surgery. *Ann Thorac Surg*. 2013;96:90–95.

20. Malvindi PG, Jacob S, Kallikourdis A, Vitale N. What is the patency of the gastroepiploic artery when used for coronary artery bypass grafting? *Interact Cardiovasc Thorac Surg*. 2007;6:397–402.

21. Harskamp RE, Lopes RD, Baisden CE, de Winter RJ, Alexander JH. Saphenous vein graft failure after coronary artery bypass surgery: pathophysiology, management, and future directions. *Ann Surg*. 2013;257:824–833.

22. Storey RF. Exploring mechanisms of graft occlusion toward improved outcomes in coronary artery bypass graft surgery. *J Am Coll Cardiol*. 2011;57:1078–1080.

23. Sabik JF. Understanding saphenous vein graft patency. *Circulation*. 2011;124:273–275.

24. Manchio JV, Gu J, Romar L, Brown J, Gammie J, Pierson RN, Griffith B, Poston RS. Disruption of graft endothelium correlates with early failure after off-pump coronary artery bypass surgery. *Ann Thorac Surg*. 2005;79:1991–1998.

25. Yahagi K, Kolodgie FD, Otsuka F, Finn AV, Davis HR, Joner M, Virmani R. Pathophysiology of native coronary, vein graft, and in-stent atherosclerosis. *Nat Rev Cardiol*. 2016;13:79–98.

26. He GW, Yang CQ, Starr A. Overview of the nature of vasoconstriction in arterial grafts for coronary operations. *Ann Thorac Surg*. 1995;59:676–683.

27. Tousoulis D, Antoniades C, Stefanadis C. Evaluating endothelial function in humans: a guide to invasive and non-invasive techniques. *Heart*. 2005;91:553–558.

28. Liu ZG, Ge ZD, He GW. Difference in endothelium-derived hyperpolarizing factor-mediated hyperpolarization and nitric oxide release between human internal mammary artery and saphenous vein. *Circulation*. 2000;102:III296-301.

29. He GW, Liu ZG. Comparison of nitric oxide release and endothelium-derived hyperpolarizing factor-mediated hyperpolarization between human radial and internal mammary arteries. *Circulation*. 2001;104:I344-349.

30. Antoniades C, Shirodaria C, Crabtree M, Rinze R, Alp N, Cunnington C, Diesch J, Tousoulis D, Stefanadis C, Leeson P, Ratnatunga C, Pillai R, Channon KM. Altered plasma versus vascular biopterins in human atherosclerosis reveal relationships between endothelial nitric oxide synthase coupling, endothelial function, and inflammation. *Circulation*. 2007;116:2851–2859.

31. He GW, Angus JA, Rosenfeldt FL. Reactivity of the canine isolated internal mammary artery, saphenous vein, and coronary artery to constrictor and dilator substances: relevance to coronary bypass graft surgery. *J Cardiovasc Pharmacol*. 1988;12:12–22.

32. Shi Y, Patel S, Davenpeck KL, Niculescu R, Rodriguez E, Magno MG, Ormont ML, Mannion JD, Zalewski A. Oxidative stress and lipid retention in vascular grafts: comparison between venous and arterial conduits. *Circulation*. 2001;103:2408–2413.

33. Lee R, Margaritis M, Channon KM, Antoniades C. Evaluating oxidative stress in human cardiovascular disease: methodological aspects and considerations. *Curr Med Chem*. 2012;19:2504–2520.

34. Davì G, Patrono C. Platelet activation and atherothrombosis. *N Engl J Med*. 2007;357:2482–2494.

35. Atkinson JB, Forman MB, Vaughn WK, Robinowitz M, McAllister HA, Virmani R. Morphologic changes in long-term saphenous vein bypass grafts. *Chest*. 1985;88:341–348.

36. He G-W. Arterial grafts: clinical classification and pharmacological management. *Ann Cardiothorac Surg*. 2013;2:507–518.

37. Gluckman TJ, McLean RC, Schulman SP, Kickler TS, Shapiro EP, Conte JV, McNicholas KW, Segal JB, Rade JJ. Effects of aspirin responsiveness and platelet reactivity on early vein graft thrombosis after coronary artery bypass graft surgery. *J Am Coll Cardiol*. 2011;57:1069–1077.

38. Choudhary BP, Antoniades C, Brading AF, Galione A, Channon K, Taggart DP. Diabetes mellitus as a predictor for radial artery vasoreactivity in patients undergoing coronary artery bypass grafting. *J Am Coll Cardiol*. 2007;50:1047–1053.

39. Desai ND, Naylor CD, Kiss A, Cohen EA, Feder-Elituv R, Miwa S, Radhakrishnan S, Dubbin J, Schwartz L, Fremes SE, Radial Artery Patency Study Investigators. Impact of patient and target-vessel characteristics on arterial and venous bypass graft patency: insight from a randomized trial. *Circulation*. 2007;115:684–691.

40. Shah PJ, Gordon I, Fuller J, Seevanayagam S, Rosalion A, Tatoulis J, Raman JS, Buxton BF. Factors affecting saphenous vein graft patency: clinical and angiographic study in 1402 symptomatic patients operated on between 1977 and 1999. *J Thorac Cardiovasc Surg*. 2003;126:1972–1977.

41. Harskamp RE, Alexander JH, Ferguson TB, Hager R, Mack MJ, Englum B, Wojdyla D, Schulte PJ, Kouchoukos NT, de Winter RJ, Gibson CM, Peterson ED, Harrington RA, Smith PK, Lopes RD. Frequency and Predictors of Internal Mammary Artery Graft Failure and Subsequent Clinical Outcomes: Insights From the Project of Ex-vivo Vein Graft Engineering via Transfection (PREVENT) IV Trial. *Circulation*. 2016;133:131–138.

42. Domanski MJ, Borkowf CB, Campeau L, Knatterud GL, White C, Hoogwerf B, Rosenberg Y, Geller NL. Prognostic factors for atherosclerosis progression in saphenous vein grafts: the postcoronary artery bypass graft (Post-CABG) trial. Post-CABG Trial Investigators. *J Am Coll Cardiol*. 2000;36:1877–1883.

43. Lytle BW, Loop FD, Taylor PC, Simpfendorfer C, Kramer JR, Ratliff NB, Goormastic M, Cosgrove DM. Vein graft disease: the clinical impact of stenoses in saphenous vein bypass grafts to coronary arteries. *J Thorac Cardiovasc Surg*. 1992;103:831–840.

44. Halabi AR, Alexander JH, Shaw LK, Lorenz TJ, Liao L, Kong DF, Milano CA, Harrington RA, Smith PK. Relation of early saphenous vein graft failure to outcomes following coronary artery bypass surgery. *Am J Cardiol*. 2005;96:1254–1259.

45. Lopes RD, Mehta RH, Hafley GE, Williams JB, Mack MJ, Peterson ED, Allen KB, Harrington RA, Gibson CM, Califf RM, Kouchoukos NT, Ferguson TB, Alexander JH, Project of Ex Vivo Vein Graft Engineering via Transfection IV (PREVENT IV) Investigators. Relationship between vein graft failure and subsequent clinical outcomes after coronary artery bypass surgery. *Circulation*. 2012;125:749–756.

46. Shavadia J, Norris CM, Graham MM, Verma S, Ali I, Bainey KR. Symptomatic graft failure and impact on clinical outcome after coronary artery bypass grafting surgery: Results from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease registry. *Am Heart J*. 2015;169:833–840.

47. Yamasaki M, Deb S, Tsubota H, Moussa F, Kiss A, Cohen EA, Radhakrishnan S, Dubbin J, Ko D, Schwartz L, Fremes SE, Radial Artery Patency Study Investigators. Comparison of Radial Artery and Saphenous Vein Graft Stenosis More Than 5 Years After Coronary Artery Bypass Grafting. *Ann Thorac Surg*. 2016;102:712–719.

48. He G-W, Taggart DP. Antispastic Management in Arterial Grafts in Coronary Artery Bypass Grafting Surgery. *Ann Thorac Surg*. 2016;102:659–668.

49. He G-W, Fan L, Furnary A, Yang Q. A new antispastic solution for arterial grafting: nicardipine and nitroglycerin cocktail in preparation of internal thoracic and radial arteries for coronary surgery. *J Thorac Cardiovasc Surg*. 2008;136:673–680, 680–2.

50. He GW. Verapamil plus nitroglycerin solution maximally preserves endothelial function of the radial artery: comparison with papaverine solution. *J Thorac Cardiovasc Surg*. 1998;115:1321–1327.

51. He GW, Yang CQ. Use of verapamil and nitroglycerin solution in preparation of radial artery for coronary grafting. *Ann Thorac Surg*. 1996;61:610–614.

52. Gaudino M, Crea F, Cammertoni F, Mazza A, Toesca A, Massetti M. Technical issues in the use of the radial artery as a coronary artery bypass conduit. *Ann Thorac Surg*. 2014;98:2247–2254.

53. Yoshizaki T, Tabuchi N, Toyama M. Verapamil and nitroglycerin improves the patency rate of radial artery grafts. *Asian Cardiovasc Thorac Ann*. 2008;16:396–400.

54. Gaudino M, Glieca F, Luciani N, Alessandrini F, Possati G. Clinical and angiographic effects of chronic calcium channel blocker therapy continued beyond first postoperative year in patients with radial artery grafts: results of a prospective randomized investigation. *Circulation*. 2001;104:I64-67.

55. Wise ES, Hocking KM, Eagle S, Absi T, Komalavilas P, Cheung-Flynn J, Brophy CM. Preservation solution impacts physiologic function and cellular viability of human saphenous vein graft. *Surgery*. 2015;158:537–546.

56. Harskamp RE, Alexander JH, Schulte PJ, Brophy CM, Mack MJ, Peterson ED, Williams JB, Gibson CM, Califf RM, Kouchoukos NT, Harrington RA, Ferguson TB, Lopes RD. Vein graft preservation

solutions, patency, and outcomes after coronary artery bypass graft surgery: follow-up from the PREVENT IV randomized clinical trial. *JAMA Surg*. 2014;149:798–805.

57. Alexander JH, Hafley G, Harrington RA, Peterson ED, Ferguson TB, Lorenz TJ, Goyal A, Gibson M, Mack MJ, Gennevois D, Califf RM, Kouchoukos NT, PREVENT IV Investigators. Efficacy and safety of edifoligide, an E2F transcription factor decoy, for prevention of vein graft failure following coronary artery bypass graft surgery: PREVENT IV: a randomized controlled trial. *JAMA*. 2005;294:2446–2454.

58. Cable DG, Caccitolo JA, Pearson PJ, O'Brien T, Mullany CJ, Daly RC, Orszulak TA, Schaff HV. New approaches to prevention and treatment of radial artery graft vasospasm. *Circulation*. 1998;98:II15-21; discussion II21-22.

59. Zenati MA, Shroyer AL, Collins JF, Hattler B, Ota T, Almassi GH, Amidi M, Novitzky D, Grover FL, Sonel AF. Impact of endoscopic versus open saphenous vein harvest technique on late coronary artery bypass grafting patient outcomes in the ROOBY (Randomized On/Off Bypass) Trial. *J Thorac Cardiovasc Surg*. 2011;141:338–344.

60. Deppe A-C, Liakopoulos OJ, Choi Y-H, Slottosch I, Kuhn EW, Scherner M, Stange S, Wahlers T. Endoscopic vein harvesting for coronary artery bypass grafting: a systematic review with meta-analysis of 27,789 patients. *J Surg Res*. 2013;180:114–124.

61. Sastry P, Rivinius R, Harvey R, Parker RA, Rahm A-K, Thomas D, Nair S, Large SR. The influence of endoscopic vein harvesting on outcomes after coronary bypass grafting: a meta-analysis of 267,525 patients. *Eur J Cardio-Thorac Surg Off J Eur Assoc Cardio-Thorac Surg*. 2013;44:980–989.

62. Rousou LJ, Taylor KB, Lu X-G, Healey N, Crittenden MD, Khuri SF, Thatte HS. Saphenous vein conduits harvested by endoscopic technique exhibit structural and functional damage. *Ann Thorac Surg*. 2009;87:62–70.

63. Williams JB, Peterson ED, Brennan JM, Sedrakyan A, Tavris D, Alexander JH, Lopes RD, Dokholyan RS, Zhao Y, O'Brien SM, Michler RE, Thourani VH, Edwards FH, Duggirala H, Gross T, Marinac-Dabic D, Smith PK. Association between endoscopic vs open vein-graft harvesting and mortality, wound complications, and cardiovascular events in patients undergoing CABG surgery. *JAMA*. 2012;308:475–484.

64. Zenati MA, Gaziano JM, Collins JF, Biswas K, Gabany JM, Quin JA, Bitondo JM, Bakaeen FG, Kelly RF, Shroyer AL, Bhatt DL. Choice of vein-harvest technique for coronary artery bypass grafting: rationale and design of the REGROUP trial. *Clin Cardiol*. 2014;37:325–330.

65. Fremes SE. Improving the Results of Heart Bypass Surgery Using New Approaches to Surgery and Medication (SUPERIORSVG) [Internet]. Sunnybrook Health Sciences Centre, Hamilton Health Sciences Corporation; 2010 [cited 2017 Jan 6]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT01047449

66. Sá MPB de O, Ferraz PE, Escobar RR, Nunes EO, Lustosa P, Vasconcelos FP, Lima RC. Patency of skeletonized versus pedicled internal thoracic artery in coronary bypass graft surgery: a systematic review, meta-analysis and meta-regression. *Int J Surg Lond Engl*. 2014;12:666–672.

67. Shroyer AL, Grover FL, Hattler B, Collins JF, McDonald GO, Kozora E, Lucke JC, Baltz JH, Novitzky D, Veterans Affairs Randomized On/Off Bypass (ROOBY) Study Group. On-pump versus off-pump coronary-artery bypass surgery. *N Engl J Med*. 2009;361:1827–1837.

68. Uva MS, Cavaco S, Oliveira AG, Matias F, Silva C, Mesquita A, Aguiar P, Bau J, Pedro A, Magalhães MP. Early graft patency after off-pump and on-pump coronary bypass surgery: a prospective randomized study. *Eur Heart J*. 2010;ehq210.

69. Puskas JD, Williams WH, O'Donnell R, Patterson RE, Sigman SR, Smith AS, Baio KT, Kilgo PD, Guyton RA. Off-pump and on-pump coronary artery bypass grafting are associated with similar graft patency, myocardial ischemia, and freedom from reintervention: long-term follow-up of a randomized trial. *Ann Thorac Surg*. 2011;91:1836-1842-1843.

70. Kobayashi J, Tashiro T, Ochi M, Yaku H, Watanabe G, Satoh T, Tagusari O, Nakajima H, Kitamura S, Japanese Off-Pump Coronary Revascularization Investigation (JOCRI) Study Group. Early outcome of a randomized comparison of off-pump and on-pump multiple arterial coronary revascularization. *Circulation*. 2005;112:I338-343.

71. Magee MJ, Alexander JH, Hafley G, Ferguson TB, Gibson CM, Harrington RA, Peterson ED, Califf RM, Kouchoukos NT, Herbert MA, Mack MJ, PREVENT IV Investigators. Coronary artery bypass graft failure after on-pump and off-pump coronary artery bypass: findings from PREVENT IV. *Ann Thorac Surg*. 2008;85:494-499-500.

72. Deppe A-C, Arbash W, Kuhn EW, Slottosch I, Scherner M, Liakopoulos OJ, Choi Y-H, Wahlers T. Current evidence of coronary artery bypass grafting off-pump versus on-pump: a systematic review with meta-analysis of over 16,900 patients investigated in randomized controlled trials†. *Eur J Cardio-Thorac Surg Off J Eur Assoc Cardio-Thorac Surg*. 2016;49:1031–1041; discussion 1041.

73. Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Straka Z, Piegas LS, Avezum A, Akar AR, Lanas Zanetti F, Jain AR, Noiseux N, Padmanabhan C, Bahamondes J-C, Novick RJ, Tao L, Olavegogeascoechea PA, Airan B, Sulling T-A, Whitlock RP, Ou Y, Gao P, Pettit S, Yusuf S. Five-Year

Outcomes after Off-Pump or On-Pump Coronary-Artery Bypass Grafting. *N Engl J Med*. 2016;375:2359–2368.

74. Davies PF. Hemodynamic shear stress and the endothelium in cardiovascular pathophysiology. *Nat Clin Pract Cardiovasc Med*. 2009;6:16–26.

75. Suma H, Tanabe H, Takahashi A, Horii T, Isomura T, Hirose H, Amano A. Twenty years experience with the gastroepiploic artery graft for CABG. *Circulation*. 2007;116:I188-191.

76. Berger A, MacCarthy PA, Siebert U, Carlier S, Wijns W, Heyndrickx G, Bartunek J, Vanermen H, De Bruyne B. Long-term patency of internal mammary artery bypass grafts: relationship with preoperative severity of the native coronary artery stenosis. *Circulation*. 2004;110:II36-40.

77. Honda K, Okamura Y, Nishimura Y, Uchita S, Yuzaki M, Kaneko M, Yamamoto N, Kubo T, Akasaka T. Graft flow assessment using a transit time flow meter in fractional flow reserve-guided coronary artery bypass surgery. *J Thorac Cardiovasc Surg*. 2015;149:1622–1628.

78. Gaudino M, Alessandrini F, Nasso G, Bruno P, Manzoli A, Possati G. Severity of coronary artery stenosis at preoperative angiography and midterm mammary graft status. *Ann Thorac Surg*. 2002;74:119–121.

79. Glineur D, Poncelet A, El Khoury G, D'hoore W, Astarci P, Zech F, Noirhomme P, Hanet C. Fractional flow reserve of pedicled internal thoracic artery and saphenous vein grafts 6 months after bypass surgery. *Eur J Cardio-Thorac Surg Off J Eur Assoc Cardio-Thorac Surg*. 2007;31:376–381.

80. Glineur D, D'hoore W, de Kerchove L, Noirhomme P, Price J, Hanet C, El Khoury G. Angiographic predictors of 3-year patency of bypass grafts implanted on the right coronary artery system: a

prospective randomized comparison of gastroepiploic artery, saphenous vein, and right internal thoracic artery grafts. *J Thorac Cardiovasc Surg*. 2011;142:980–988.

81. Shah PJ, Gordon I, Fuller J, Seevanayagam S, Rosalion A, Tatoulis J, Raman JS, Buxton BF. Factors affecting saphenous vein graft patency: clinical and angiographic study in 1402 symptomatic patients operated on between 1977 and 1999. *J Thorac Cardiovasc Surg*. 2003;126:1972–1977.

82. Souza DSR, Dashwood MR, Tsui JCS, Filbey D, Bodin L, Johansson B, Borowiec J. Improved patency in vein grafts harvested with surrounding tissue: results of a randomized study using three harvesting techniques. *Ann Thorac Surg*. 2002;73:1189–1195.

83. Shiono Y, Kubo T, Honda K, Katayama Y, Aoki H, Satogami K, Kashiyama K, Taruya A, Nishiguchi T, Kuroi A, Orii M, Kameyama T, Yamano T, Yamaguchi T, Matsuo Y, Ino Y, Tanaka A, Hozumi T, Nishimura Y, Okamura Y, Akasaka T. Impact of functional focal versus diffuse coronary artery disease on bypass graft patency. *Int J Cardiol*. 2016;222:16–21.

84. Songur MÇ, Özyalçin S, Özen A, Şimşek E, Kervan Ü, Taşoğlu İ, Kaplan S, Köse K, Ulus AT. Does really previous stenting affect graft patency following CABG? A 5-year follow-up: The effect of PCI on graft survival. *Heart Vessels*. 2016;31:457–464.

85. Di Giammarco G, Pano M, Cirmeni S, Pelini P, Vitolla G, Di Mauro M. Predictive value of intraoperative transit-time flow measurement for short-term graft patency in coronary surgery. *J Thorac Cardiovasc Surg*. 2006;132:468–474.

86. Niclauss L. Techniques and standards in intraoperative graft verification by transit time flow measurement after coronary artery bypass graft surgery: a critical review. *Eur J Cardio-Thorac Surg Off J Eur Assoc Cardio-Thorac Surg*. 2016;

87. Singh SK, Desai ND, Chikazawa G, Tsuneyoshi H, Vincent J, Zagorski BM, Pen V, Moussa F, Cohen GN, Christakis GT, Fremes SE. The Graft Imaging to Improve Patency (GRIIP) clinical trial results. *J Thorac Cardiovasc Surg*. 2010;139:294–301, 301.e1.

88. Lehnert P, Møller CH, Damgaard S, Gerds TA, Steinbrüchel DA. Transit-time flow measurement as a predictor of coronary bypass graft failure at one year angiographic follow-up. *J Card Surg*. 2015;30:47–52.

89. Gaudino M, Di Mauro M, Iacò AL, Canosa C, Vitolla G, Calafiore AM. Immediate flow reserve of Y thoracic artery grafts: an intraoperative flowmetric study. *J Thorac Cardiovasc Surg*. 2003;126:1076–1079.

90. Di Giammarco G, Canosa C, Foschi M, Rabozzi R, Marinelli D, Masuyama S, Ibrahim BM, Ranalletta RA, Penco M, Di Mauro M. Intraoperative graft verification in coronary surgery: increased diagnostic accuracy adding high-resolution epicardial ultrasonography to transit-time flow measurement. *Eur J Cardio-Thorac Surg Off J Eur Assoc Cardio-Thorac Surg*. 2014;45:e41-45.

91. Kuroyanagi S, Asai T, Suzuki T. Intraoperative fluorescence imaging after transit-time flow measurement during coronary artery bypass grafting. *Innov Phila Pa*. 2012;7:435–440.

92. Hastings S, Myles P, McIlroy D. Aspirin and coronary artery surgery: a systematic review and meta-analysis. *Br J Anaesth*. 2015;115:376–385.

93. Myles PS, Smith JA, Forbes A, Silbert B, Jayarajah M, Painter T, Cooper DJ, Marasco S, McNeil J, Bussières JS, Wallace S, ATACAS Investigators of the ANZCA Clinical Trials Network. Stopping vs. Continuing Aspirin before Coronary Artery Surgery. *N Engl J Med*. 2016;374:728–737.

94. Patrono C. The Multifaceted Clinical Readouts of Platelet Inhibition by Low-Dose Aspirin. *J Am Coll Cardiol*. 2015;66:74–85.

95. Paikin JS, Hirsh J, Ginsberg JS, Weitz JI, Chan NC, Whitlock RP, Pare G, Johnston M, Eikelboom JW. Multiple daily doses of acetyl-salicylic acid (ASA) overcome reduced platelet response to once-daily ASA after coronary artery bypass graft surgery: a pilot randomized controlled trial. *J Thromb Haemost JTH*. 2015;13:448–456.

96. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA, PLATO Investigators, Freij A, Thorsén M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361:1045–1057.

97. Held C, Asenblad N, Bassand JP, Becker RC, Cannon CP, Claeys MJ, Harrington RA, Horrow J, Husted S, James SK, Mahaffey KW, Nicolau JC, Scirica BM, Storey RF, Vintila M, Ycas J, Wallentin L. Ticagrelor versus clopidogrel in patients with acute coronary syndromes undergoing coronary artery bypass surgery: results from the PLATO (Platelet Inhibition and Patient Outcomes) trial. *J Am Coll Cardiol*. 2011;57:672–684.

98. Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, Blumenthal R, Danesh J, Smith GD, DeMets D, Evans S, Law M, MacMahon S, Martin S, Neal B, Poulter N, Preiss D, Ridker P, Roberts I, Rodgers A, Sandercock P, Schulz K, Sever P, Simes J, Smeeth L, Wald N, Yusuf S, Peto R. Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet Lond Engl*. 2016;388:2532–2561.

99. Post Coronary Artery Bypass Graft Trial Investigators. The effect of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation on obstructive changes in saphenous-vein coronary-artery bypass grafts. *N Engl J Med*. 1997;336:153–162.

100. Eisen A, Cannon CP, Blazing MA, Bohula EA, Park J-G, Murphy SA, White JA, Giugliano RP, Braunwald E, IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial) Investigators. The benefit of adding ezetimibe to statin therapy in patients with prior coronary artery bypass graft surgery and acute coronary syndrome in the IMPROVE-IT trial. *Eur Heart J*. 2016;37:3576–3584.

Figure Legends

Figure 1: Pathophysiology of early and late graft failure.

Different biological mechanisms contribute to the pathophysiology of vascular graft failure. While early failure is linked to technical factors resulting in endothelial injury and activation with subsequent thrombosis, late failure is more commonly the result of atherogenesis and plaque rupture. In the early stages following graft implantation, endothelial injury due to surgical manipulations and endothelial cell activation (e.g., due to hemodynamic stress or transient ischemia) can result in the release of pro-thrombotic and pro-inflammatory molecules (e.g. vWF, CD40L, tissue factor) that trigger the thrombotic cascade resulting in acute occlusion. Impaired endothelial function (characterized by poor NO bioavailability) also promotes a pro-inflammatory and pro-thrombotic phenotype, whereas local release of cytokines such as PDGF promotes cell migration and neo-intima formation. On the contrary, late failure (months to years after surgery) is associated with atherosclerotic vascular disease. Systemic biological factors (e.g., diabetes, smoking, hypercholesterolemia) and local biological mechanisms (e.g., increased oxidative stress, vascular inflammation, endothelial dysfunction) all contribute to the initial plaque formation and subsequent progression until the advanced disease stages of significant luminal stenosis or plaque rupture which results in thrombosis and occlusion to blood flow.

CD40L: cluster of differentiation 40 ligand, LDL: low-density lipoprotein, NO: nitric oxide, PAI-1: plasminogen activator inhibitor 1, PDGF: platelet-derived growth factor, ROS: reactive oxygen species,

TxA2: Thromboxane A2, VCAM-1: Vascular cell adhesion molecule 1, VSMC: vascular smooth muscle cells, vWF: von Willebrand factor.

Figure 2: Schema of molecular mechanisms of smooth muscle contraction and the relaxation in the coronary artery bypass grafts (Reproduced from He GW, Taggart DP. Ann Thorac Surg. 2016;102:659-68 with permission).

Contraction: Contraction is the summation of myosin light chain kinase (MLCK) and myosin light chain phosphatase (MLCP) activity. Ca^{2+} influx via calcium channels in the membrane (voltage-operated channel [VOC] and receptor-operated channel [ROC]) and Ca^{2+} release from intracellular stores in the sarcoplasmic reticulum (SR) via phospholipase C (PLC)-mediated hydrolysis of phosphotidyl inositol bisphosphate, yielding inositol triphosphate (IP3) result an increase in intracellular Ca^{2+}. The Ca^{2+} interacts with calmodulin, forming a Ca^{2+}-calmodulin complex which activates MLCK that phosphorylates myosin light chain, allowing for force generation. Vasoconstrictors such as the agonists of α-adrenoceptor (α), thromboxane A2 (TxA_2), endothelin-1 (ET), etc., stimulate G-protein coupled receptors (GPCRs) directly opening the ROC causing Ca^{2+} influx, or through the production of second messengers such as IP3 causing release of the stored Ca^{2+}. Contraction can also be mediated in Ca^{2+}-sensitization mechanism. Rho-kinase becomes activated via the activated RhoA protein, which subsequently phosphorylates MLCP, rendering the enzyme inactive and incapable of de-phosphorylating MLC.

Relaxation: Relaxation occurs with MLCP dephosphorylating MLC. This can be accomplished through various mechanisms. For example, it can be via blockage of Ca^{2+} influx by calcium channel blocker (CCB) to decrease the intracellular Ca^{2+}. The antagosists of specific vasoconstrictors such as the antagonists ofα-adrenoceptor, TxA_2, ET, etc, inhibit the ROC associated with GPCRs. Nitrovasodilators via releasing nitric oxide (NO) stimulates soluble guanylate cyclose (sGCs), which increases synthesis of cGMP from GTP. Increased cGMP level inhibits VOC and ROC through protein kinase G (PKG) pathways. NO-cGMP also interacts with Rho Kinase pathway via cGMP regulated protein kinases (cGK), interferes the MLC and phospho-MLC acitivity, and finally relaxes the smooth muscle. The Rho Kinase inhibitor inhibits Rho Kinase pathway and the phosphodiesterase (PDE) inhibitors increase cGMP level via inhibiting cGMP—

5'GMP activity, relaxing the vessel. Potassium channel openers (K^+ openers) open the potassium channels such as calcium-sensitive potassium channels (KCa), cause efflux of K^+ and hyperpolarizes the membrane potential (Em). The membrane hyperpolarization decreases intracellular Ca^{2+} levels by inhibiting Ca^{2+} influx through VOC and favors the re-uptake of Ca^{2+} into intracellular stores and extrusion of Ca^{2+} from the cell, resulting in relaxation. Prostacyclin (PGI2) raises cAMP levels in the cytosol and via activation of the protein kinase A pathway leads to relaxation.

This schema also shows that each vasodilator relaxes blood vessel in a specific pathway, although there are some interactions between the pathways. A possible protocol for relaxation of coronary artery bypass grafts is to combine two vasodilators that relax the vessel in different pathways.

Figure 3: Intraoperative graft verification on a 72 year-old male, previous PCI on LAD; recent ACS with occluded LAD. (Courtesy Prof. G. Di Giammarco)

(A): 2-D image of LIMA to LAD grafting; (B): Color Flow Mapping of the same graft; (C): MGF of LIMA to LAD below cut-off value (15ml/min); (D): dobutamine test of the same graft with three-fold increase of MGF at double product of 14900.

PCI: percutaneous coronary intervention; LAD: Left anterior descending artery; ACS: acute coronary syndrome; LIMA: left internal mammary artery; MGF: mean graft flow

Tables

Table 1. Coronary artery bypass graft patency rates

Conduit	Early patency (1-year)	Mid-term patency (5-7 years)	Late patency (≥10 years)
Saphenous Vein Graft	81-97.9%	75-86%	50-60%
Internal Thoracic Artery	93-96%	88-98%	85-95%
Radial Artery	89-92%	90-98%	89-91%
Right Gastroepiploic Artery	92-97%	80-90%	62%

Table 2. Major series on intraoperative graft verification

Author, year, journal, study type	Patient group	Study Aim	Results	Comments
D'Ancona et al. 2000, European J Thorac Cardiovasc Surg Retrospective Study	409 off- pump CABG patients via median sternotomy with 1,145 grafts tested using TTFM	Clinical application of TTFM for the detection of anastomotic failure	41 grafts revised in 33 patients 34 (91.9%) were revised for both low flow and abnormal flow curve patterns	No information about mid-term angiographic patency in the three conduits with altered flow and no technical problems at the revision.
Gaudino et al. 2003, J Thorac Cardiovasc Surg Prospective Study	21 composite arterial conduits evaluated with intra-operative dobutamine bolus injection after coronary grafting	Intraoperative evaluation of coronary flow reserve	Double product after test 12087±2395 (range); Flow reserve: Main stem of the composite conduit: 2.1±0.6, LIMA branch: 2.2±0.9, RIMA branch: 2.1±0.9	Intraoperative injection of dobutamine increases the flow in the Y thoracic graft by more than two times, not only in the main stem but also in each branch. This finding attests to the large flow reserve of Y thoracic conduits.
Kim et al. 2005, Ann Thorac Surg Retrospective study	58 arterial off-pump CABG patients evaluated with intraoperative TTFM and postoperative angiography	Validity of intraoperative TTFM for the prediction of graft flow abnormalities	Criteria to predict abnormal grafts as systolic dominant flow curve: MGF <15 ml/min; PI>3 in the left coronary territories, and >5 in the right coronary territories and %BF >2%. Sensitivity and specificity of TTFM to detect graft flow abnormality were 96.2% and 76.9%, respectively	Small sample size and diagnostic accuracy evaluated without multivariate and ROC analysis.
Di Giammarco et al. 2006, J Thorac Cardiovasc Surg Retrospective study	157 patients evaluated with intraoperative TTFM and angiography	Predict postoperative graft patency in coronary surgery by means of TTFM	Group A: 266 grafts patent; Group B: 38 grafts failed MGF (OR, 0.86; P=0.002), PI (OR, 1.3; P=0.031), %BF (OR, 1.1; P=0.041) values were confirmed to be predictive parameters of graft failure, even in case of venous grafts. Cut-off, sensitivity, specificity and PPV for MGF: 15, 0.87, 0.87, 0.95; PI: 3:0, 0.66, 0.67, 0.66; %BF3: 1 0, 0.67, 0.53, respectively	The retrospective nature of the study is a limiting factor.
Tokuda et al. 2008, Ann Thorac Surg Retrospective study	123 patients with postoperative angiography were divided into two groups: A (occluded grafts) and B (patent grafts)	TTFM's ability to predict mid-term graft failure	*Group A vs. Group B* MGF: 26.5±14.7 vs. 47.7±30.2, P=0.01; %BF: 6.13±9.47 vs. 2.30±5.02, P<0.05. *Odds Ratio (OR) of midterm graft failure* MGF: OR:0.96 (0.93-0.98), P<0.01; PI: OR:1.14 (0.98-1.40) P=0.12; %BF: OR:1.08 (1.01-1.17) P=0.15; Time to angiography: OR:1.06 (1.01-1.13) P<0.05	Small sample size limited the ability of logistic regression analysis to detect risk factors. Postoperative angiography was not performed in all patients.
Kieser et al. 2010, European J Thorac Cardiovasc Surg Prospective study	336 patients evaluated with TTRM including 990 arterial grafts	TTFM parameters' ability to predict MACE in the postoperative period	25 (7.4%) patients suffered MACEs postoperatively: recurrent angina: 6/336 (1.8%), perioperative myocardial infarction: 9/336 (2.7%), PCI: 6/336	ROC analysis was not performed to establish cut-off values.

			(1.8%), early re-operation 4/336 (1.2%) and/or perioperative death: 16/336 (4.8%). The variables PI >5, age, and admission status were all significant predictor variables of MACE ($P < 0.05$).	
Di Giammarco et al. 2014, European J Thorac Cardiovasc Surg Retrospective study	333 CABG with a total of 717 grafts being verified by means of both TTFM and HR-ECUS	Compare TTFM combined with HR-ECUS vs. TTFM alone for diagnostic accuracy of intraoperative graft evaluation	Among 678 grafts considered to be functioning at TTFM, 3 (0.4%) were failing at HR-ECUS. HR-ECUS confirmed the functional status of the remaining 675 grafts already demonstrated by TTFM. Among them, 8 showed high TnI release, whereas the remaining 667 had no high TnI release. In 2 of 39 grafts malfunctioning at TTFM, HR-ECUS confirmed the graft failure. Surgical inspection of the anastomosis during redo procedure showed a technical error leading to define those 2 grafts as 'true positive' on the basis of either direct vision and improved post-redo TTFM parameters. Finally, in 35 cases, HR-ECUS did not confirm a TTFM diagnosis demonstrating full patency of the anastomosis; these grafts had an uneventful clinical course. PPV, NPV, and diagnostic accuracy of combined TTFM and HR-ECUS intraoperative graft verification procedure: 100%, 99%, and 100%, respectively.	Lack of angiographic controls.

CABG: coronary artery bypass graft, HR-ECUS: high-resolution epicardial ultrasonography, LAD: left anterior descending, LIMA: left internal mammary artery, MACE: major adverse cardiac events, MGF: mean graft flow, NPV: negative predicted value, PCI: percutaneous coronary intervention, %BF: percentage backward flow, PI: pulsatility index, PPV: positive predicted value, RIMA: right internal mammary artery, ROC: receiver operating characteristic, TnI: troponin I; TTFM: TransitTime flow measurement.

Figures

Figure 1

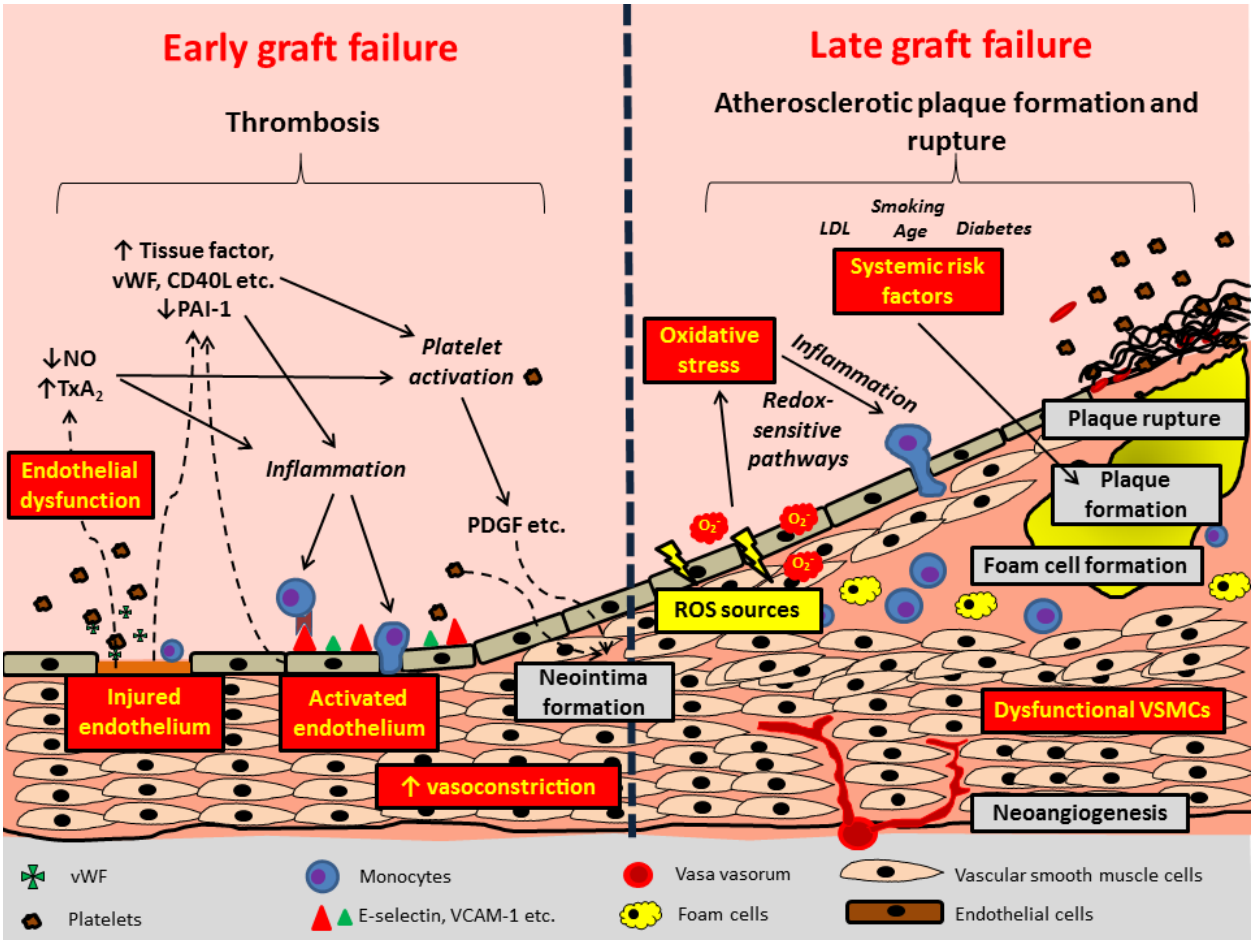


Figure 2

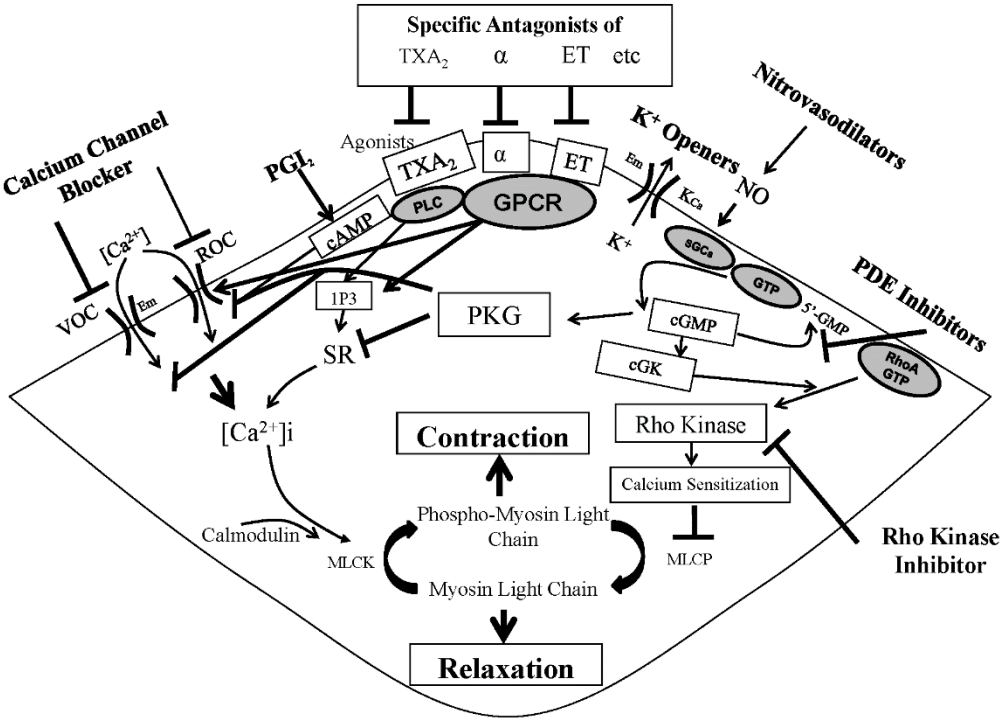
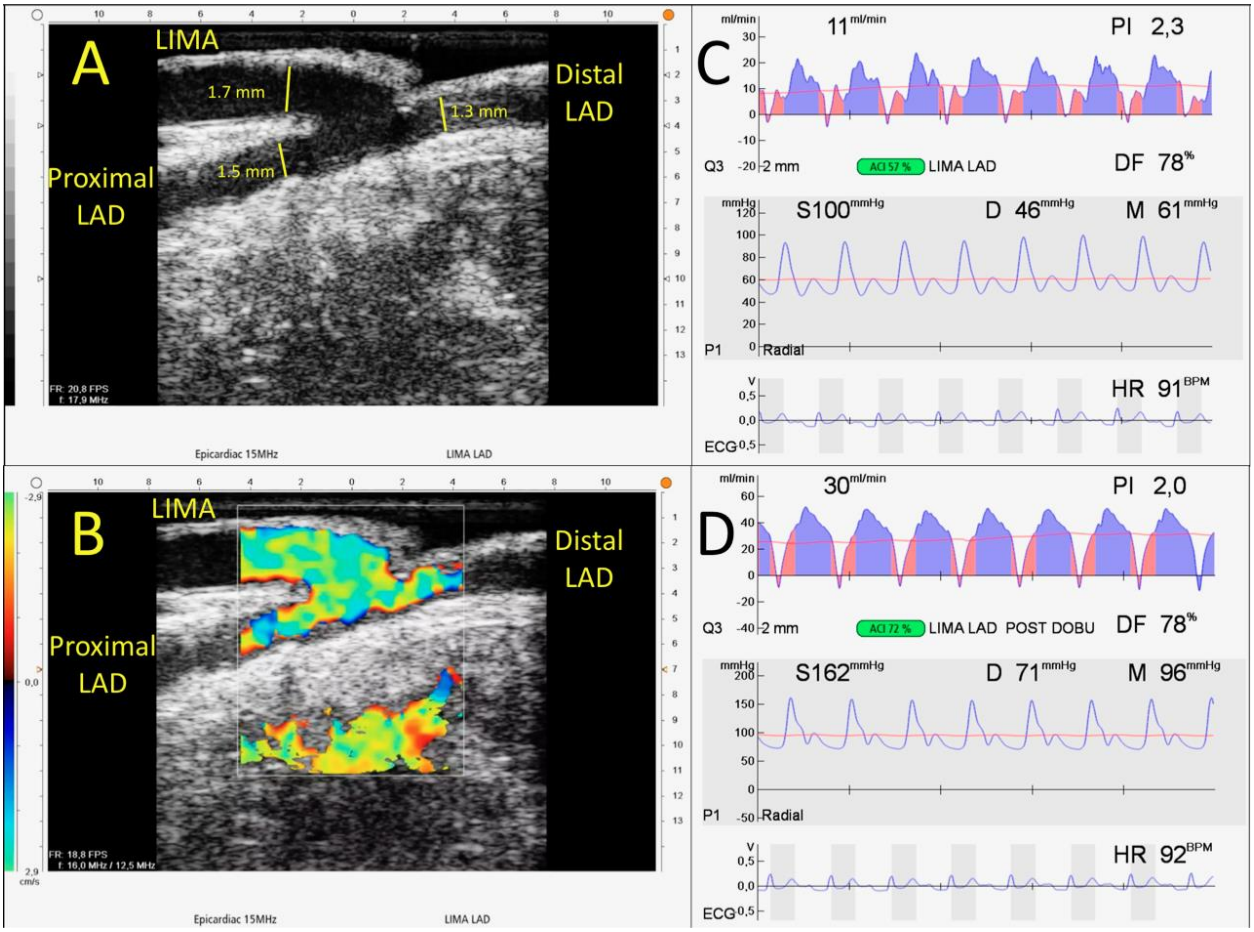

Specific Antagonists of
TXA2 α ET etc
Agonists
TXA2
α
ET
Calcium Channel Blocker
PGI2
Nitrovasodilators
K+ Openers
NO
Em
Kca
K+
[Ca2+]
ROC
VOC
Em
cAMP
PLC
GPCR
1P3
PKG
SR
sGCa
GTP
5'-GMP
cGMP
cGK
PDE Inhibitors
RhoA GTP
[Ca2+]i
Contraction
Rho Kinase
Calcium Sensitization
Calmodulin
MLCK
Phospho-Myosin Light Chain
Myosin Light Chain
MLCP
Rho Kinase Inhibitor
Relaxation

Figure 3


A
LIMA
1.7 mm
1.3 mm
1.5 mm
Distal
LAD
Proximal
LAD
Epicardiac 15MHz
LIMA LAD
B
LIMA
Distal
LAD
Proximal
LAD
Epicardiac 15MHz
LIMA LAD
C
11 ml/min
PI 2,3
Q3
2 mm
LIMA LAD
DF 78%
S100 mmHg
D 46 mmHg
M 61 mmHg
Radial
HR 91 BPM
ECG
D
30 ml/min
PI 2,0
Q3
2 mm
LIMA LAD POST DOBU
DF 78%
S162 mmHg
D 71 mmHg
M 96 mmHg
Radial
HR 92 BPM
ECG