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STATE OF THE ART REVIEW
Ischaemic heart disease

The association between coronary graft patency and clinical status in patients with coronary artery disease

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The concept of a direct association between coronary graft patency and clinical status is generally accepted. However, the relationship is more complex and variable than usually thought. Key issues are the lack of a common definition of graft occlusion and of a standardized imaging protocol for patients undergoing coronary bypass surgery. Factors like the type of graft, the timing of the occlusion, and the amount of myocardium at risk, as well as baseline patients' characteristics, modulate the patency-to-clinical status association. Available evidence suggests that graft occlusion is more often associated with non-fatal events rather than death. Also, graft failure due to competitive flow is generally a benign event, while graft occlusion in a graft-dependent circulation is associated with clinical symptoms. In this systematic review, we summarize the evidence on the association between graft status and clinical outcomes.

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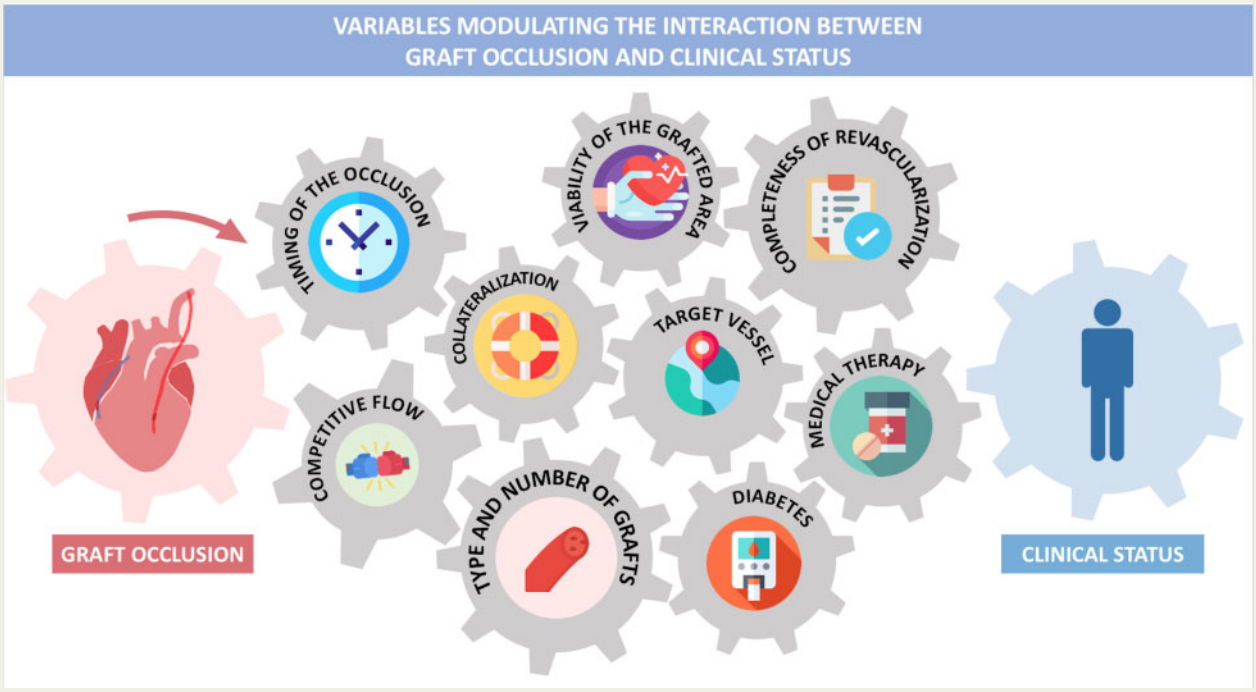
Graphical Abstract



Variables modulating the interaction between graft occlusion and clinical status.

Keywords Patency • CABG • Graft failure

Introduction

The classic concept of a direct and close association between coronary artery graft patency and clinical status is intuitive and biologically plausible. However, the relationship is more complex and variable than generally thought. In this review, we summarize the evidence of the association between coronary graft patency and clinical status in patients with coronary artery disease. A systematic review of the literature was performed by a medical librarian; the search strategy, study selection methods, and the PRISMA flowchart are provided in the Supplementary material online (Supplementary material online, *Table S1* and *Figure S1*).

Incidence, mechanisms, and timing of graft failure

The incidence of graft failure varies for the different types of conduits. At 5 years, failure rates of 17.5% for the saphenous vein graft (SVG), 2.3% and 13.5% for the left and right internal thoracic artery (LITA and RITA), respectively, and 9.4% for the radial artery (RA) have been reported.[1,2] Ten-year failure rates are 39% for SVG, 15% for LITA, 20–25% for RITA, and 11–15% for the RA.[3,4]

The pathophysiology of graft failure varies in different postoperative periods, being mainly due to acute thrombosis within the first postoperative month, intimal hyperplasia in the 1st year, and atherosclerosis thereafter (*Figure 1*).[1]

Early failure is predominantly due to technical factors (anastomotic defect, kinking), competitive flow, haemodynamic factors,[5] or hypercoagulability.[6] Intimal hyperplasia is an adaptive process that starts at the anastomotic site and is generally self-limited, but in some cases, can become generalized and lead to graft occlusion.[7] Atherosclerosis in bypass grafts is accelerated compared with native coronary arteries and has distinctive morphologic features such as a concentric and diffuse pattern and a poorly defined fibrous cap at high risk for rupture.[8]

The different mechanisms lead to failure with different time courses: technical failure and thrombosis usually cause acute occlusion, while failure due to intimal hyperplasia and atherosclerosis occurs over a longer period of time.

Different types of bypass conduits have different histologic characteristics of failure, with fibrous hyperplasia being more common in arterial grafts and atherosclerosis in SVGs. Sex and other baseline clinical characteristics,[9] pharmacological interventions, such as the use of anti-platelets and lipid-lowering therapy,[10,11] and even genetic variants[12] may affect the risk of graft failure.

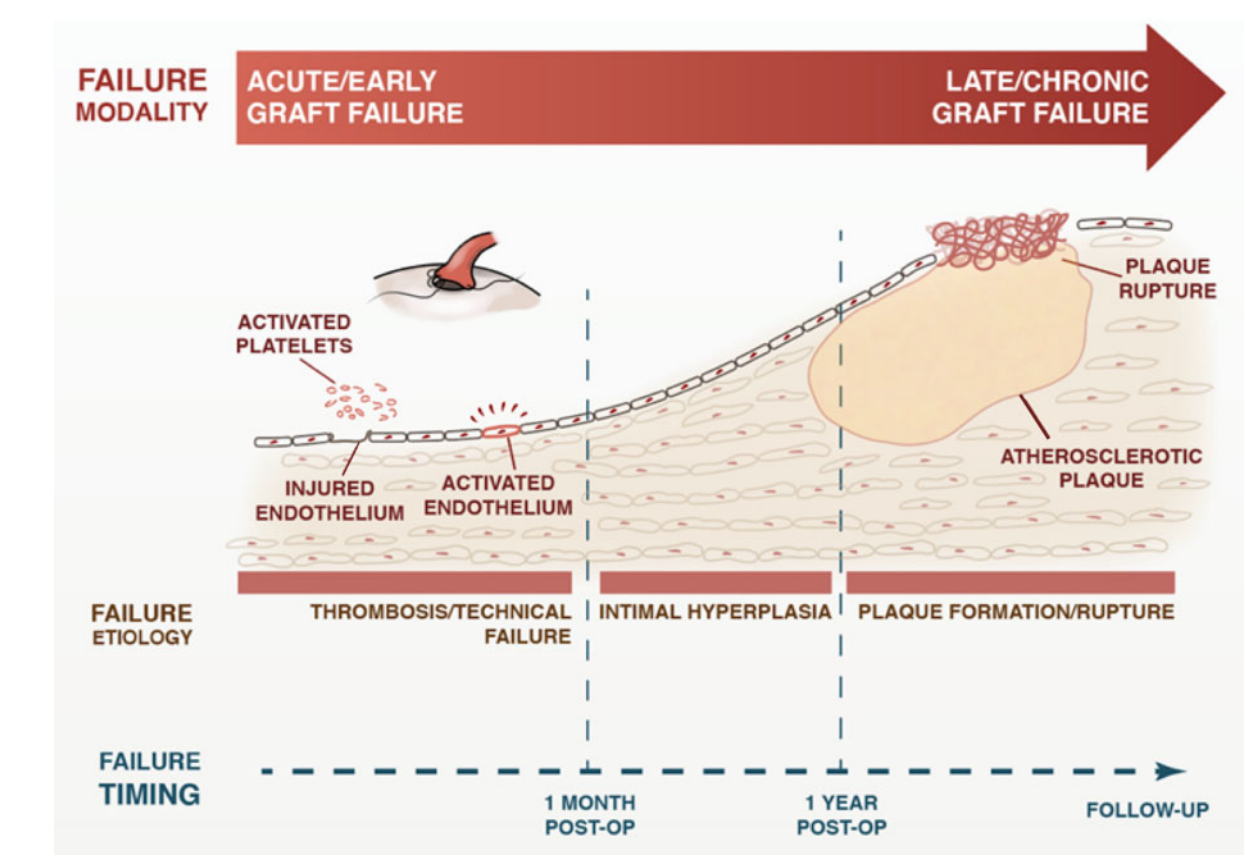


Figure 1 Pathophysiology of graft failure in different postoperative periods.

Current guidelines recommend that early graft failure is treated by either percutaneous interventions or reoperation, based on the Heart Team decision, while percutaneous interventions are preferred to treat late graft failure.[13]

The issues with graft patency studies

Invasive angiography has traditionally been used for patency studies, but we now have evidence that computed tomography angiography has very high sensitivity and specificity in assessing coronary grafts[14] and will likely become the new standard. The use of intravascular imaging techniques adds important anatomic information and may help in identifying the mechanism responsible for graft failure.[15]

A key factor complicating the analysis of graft patency studies is the lack of a universal definition of graft failure and of graft patency. Although in recent years, the three-level Fitzgibbon classification (grade A: excellent graft with unimpaired runoff; grade B: stenosis reducing calibre of proximal or distal anastomoses or trunk to <50% of the grafted coronary artery; grade O: occlusion)[16] has been adopted by several groups, many investigators have used different scales with heterogeneous definitions.[17]

Another key issue is that from graft patency studies one can determine only when graft occlusion was visualized, but not when occlusion occurred. In trying to establish a causal relationship between graft failure and clinical events, it is key to know that graft failure came first and the event thereafter.

Other important complicating factors are differences in the completeness and timing of follow-up in the published series.[17] Graft patency studies inherently suffer from survivor bias. In most observational series, imaging of grafts is reserved for symptomatic patients introducing a major selection bias. It has been shown that reported graft failure rates are higher in studies including only symptomatic patients.[18] Even in randomized controlled trials, incomplete follow-up is common because of new medical complications or consent withdrawal. It has been shown that patients who decline late angiography have different baseline risk profiles than patients with imaging follow-up.[19] While analytic options to address incomplete follow-up exist,[20] they have not been consistently applied.

When femoral access and use of angiography were the norm, the selection criteria for graft patency studies excluded patients with

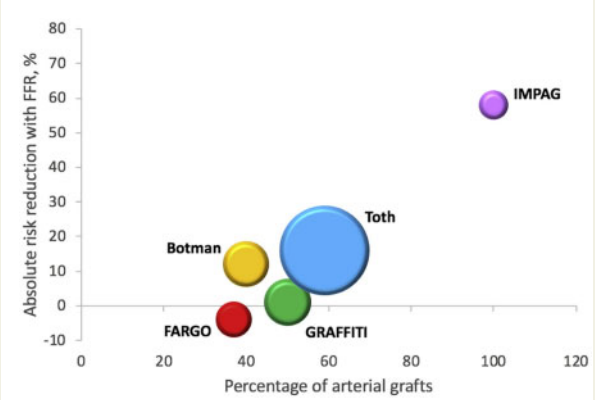


Figure 2 Reduction in graft failure using fractional flow reserve for coronary artery bypass grafting. Reproduced with permission from Spadaccio *et al.*[25]

vascular and renal disease. This limitation is less relevant today, but it applies to most of the published evidence. An important consideration is patient age—older patients represent a large proportion of patients undergoing surgical revascularization but because of their shorter survival and higher comorbidities are under-represented in patency studies.

Another important confounding factor is related to the functional severity of the grafted coronary vessel.[21] Functional data have shown that when the indication to revascularization is based on angiography alone, up to 20% of the grafted target vessels do not have flow-limiting stenosis.[22,23] The consequent chronic native competitive flow is a strong risk factor for occlusion for arterial grafts, and among them the RA is more affected than the internal thoracic artery[24,25] (*Figure 2*). However, graft occlusion due to competitive flow is a different event than graft occlusion from other causes. In the IMPAG trial, arterial graft failure was mainly due to competitive flow and was not associated with clinical events.[24] SYNTAX-LE MANS was an angiographic sub-study of the SYNTAX trial evaluating the patency of bypass grafts in patients with left main disease, a situation at high risk of competitive flow: no correlation between adverse events at 15-month follow-up and graft failure was found.[26]

The likely reason behind this finding is that the implantation of a bypass graft creates a separate coronary inflow, parallel to the native circulation. If the latter is dominant and the graft fails from competitive flow, there is no reduction in distal perfusion and, thus, no clinical events associated with graft failure. In contrast, with percutaneous interventions and stent thrombosis, there is a sudden reduction of the only flow source that generally results in clinical events.

The completeness of revascularization and the number of grafts implanted, as well as the viability of the myocardial area served by the graft are other important modulators of the association of graft occlusion with clinical events (*Graphical abstract*).

In addition, some of the factors that affect graft patency, such as renal failure and diabetes, also affect progression of native coronary disease, and clinical outcomes may be driven by the latter rather than the former.

Finally, it must be noted that the majority of patency studies date back to the era of the introduction of coronary surgery and may not represent current surgical practice (*Table 1*).[16,26–38]

Studies supporting an association between graft patency and clinical outcomes

In one of the first angiographic series of coronary artery bypass graft surgery (CABG), Winer *et al.*[39] performed postoperative angiography in 67 patients and found that angina improvement and graft patency were highly correlated. Bourassa *et al.*[28] described a close association between graft patency and survival in 600 CABG cases and Knatterud *et al.*[33] in a sub-analysis of the POST CABG study showed that SVG failure was associated with adverse clinical events, including death.

Fitzgibbon *et al.*[16] in a study of more than 5000 grafts found that graft patency was inversely associated with the need for reoperation and directly associated with survival. In an analysis from the Duke Cardiovascular Databank on 1243 patients, graft failure was associated with death, myocardial infarction (MI), or repeat revascularization.[34]

In a study of 1296 CABG patients, Lytle *et al.*[31] found that at 7-year follow-up, patients with SVG stenosis occurring within 5 years of surgery and patients with no SVG stenosis had similar outcomes, but when the stenosis occurred in the SVG to the left anterior descending artery (LAD), survival was significantly reduced and the adverse event rate increased.

Shavadia *et al.*[36] in a provincial angiographic database from Alberta found that LITA-to-LAD failure, but not SVG failure to non-LAD targets was associated with reduced long-term survival.

Loop *et al.*[40] found a significant association of decreased mortality and all cardiac endpoints with the use of the LITA compared with the SVG to graft the LAD, and postoperative angiography revealed significantly higher patency of the arterial conduit. A small randomized trial found similar results: improved cardiac event-free survival at 10 years in patients who received LITA vs. the SVG to graft the LAD, and improved patency of the arterial graft.[41]

In the PREVENT IV trial, graft failure was associated with an increased risk of revascularization, but not of death or MI and the association was consistent for venous and arterial grafts.[35] Of note, most of the revascularizations were performed within 2 weeks of the protocol-mandated angiography, suggesting that the event rate may have been inflated due to the imaging protocol.

In the RAPS trial, the risk of adverse events was significantly higher in patients with graft stenosis.[38] An individual patient-level meta-analysis of six angiographic trials comparing RA with SVG found a reduction in graft occlusion and in the composite of death, MI, or repeat revascularization at 5 years in the RA arm.[42] An association between graft patency and stress test performance was reported by Korpilahti *et al.*[43] in 1999.

The use of cholesterol-lowering medications and of antithrombotic or anti-platelet therapy reduced SVG occlusion and

Table I Overview of selected studies examining the relationship between graft patency and clinical outcomes after coronary artery bypass grafting

Study (first author, year)	Type of study	Total no. of CABG patients	No. of CABG patients who underwent imaging follow-up	Indication for imaging follow-up	Completeness of imaging follow-up	Follow-up time (mean/ median, years)	Type of graft studied	Key findings
Studies showing an association between graft patency and clinical outcomes								
Bourassa, 1982[28]	Prospective	600	108	Per-protocol angiography	18.0%	6	SVG	Graft occlusion was significantly associated with recurrence of angina. Graft patency was significantly associated with survival.
Laird-Meeter, 1983[29]	Prospective	1041	169	Per-protocol angiography	16.2%	3.5	SVG	Graft occlusion was significantly associated with recurrence of angina.
Lytle, 1992[31]	Retrospective	NR	1296	Clinically driven angiography	NR	6.9	SVG	Late (≥5 years after CABG) stenosis in grafts to the LAD was associated with decreased survival, decreased reoperation-free survival, and decreased event-free survival ($P < 0.001$ for all), whereas early (<5 years after CABG) graft stenosis did not influence outcome.
Fitzgibbon, 1996[16]	Prospective	1388	NR	Per-protocol angiography	NR (of the total 5284 original grafts, 1987 were studied at 5 years)	Up to 22.5	SVG	Vein graft failure was associated with increased reoperation rate and decreased survival.
Knatterud, 2003[33]	Substudy—the POST CABG trial	1351	961	Per-protocol angiography	71.1%	3.4	SVG	Progression of atherosclerosis in ≥1 graft was associated with an increased risk of adverse cardiac outcomes (RR 2.4, 95% CI 1.7–3.5), cardiovascular death or MI (RR 2.2, 95% CI 1.3–3.8), and revascularization (RR 3.3, 95% CI 2.0–5.3) ($P < 0.001$ for all).
Halabi, 2005[34]	Retrospective	6745	1243	Clinically driven angiography	18.4%	6.7 (IQR 3.0–11.5)	SVG	Critical, non-occlusive (75–99%) graft stenosis was the strongest predictor of the composite of death/MI/revascularization (HR 2.36, 95% CI 2.00–2.79, $P < 0.0001$).
Lopes, 2012[35]	*Post hoc* analysis—PREVENT IV trial	2400	1829	Per-protocol angiography	76.2%	4	SVG	Vein graft failure was associated with the composite of death/MI/revascularization (HR 1.58, 95% CI 1.21–2.06, $P = 0.008$), but not with death (HR 1.04, 95% CI 0.71–1.52, $P = 0.85$), or death/MI (HR 1.08, 95% CI 0.77–1.53, $P = 0.65$).

Continued

Table 1 *Continued*

Study (first author, year)	Type of study	Total no. of CABG patients	No. of CABG patients who underwent imaging follow-up	Indication for imaging follow-up	Completeness of imaging follow-up	Follow-up time (mean/ median, years)	Type of graft studied	Key findings
Shavadia, 2015[36]	Retrospective	5276	281	Clinically driven angiography	5.3%	5.4	SVG and arterial grafts	Patients with ≥70% ITA stenosis had a strong trend towards worse long-term survival compared with patients with vein graft failure (adjusted HR 2.2, 95% CI 0.98–5.0, $P = 0.056$).
Harskamp, 2016[37]	*Post hoc* analysis—PREVENT IV trial	2400	1539	Per-protocol angiography	64.1%	5.0 ± 0.7	ITA	ITA failure was associated with the composite of death/MI/revascularization (HR 3.92, 95% CI 2.30–6.68, $P < 0.0001$), but not with death (HR 1.10, 95% CI 0.50–2.39, $P = 0.82$), or death/MI (HR 1.29, 95% CI 0.66–2.50, $P = 0.46$).
Yamasaki, 2016[38]	*Post hoc* analysis—RAPS trial	529	234	Both per-protocol and clinically driven angiography	44.2%	7.5 ± 1.3	SVG and RA	Patients with significant (≥50%) graft stenosis had higher rates of the composite of death/MI/revascularization ($P < 0.0001$), and revascularization ($P < 0.0009$).
Studies showing no association between graft patency and clinical outcomes								
Robert, 1978[27]	Prospective	117	19	Per-protocol angiography	16.2%	6	SVG	Progression of native coronary artery disease, but not graft occlusion, was significantly associated with recurrence of angina.
Brindis, 1984[30]	Prospective	NR	18	Per-protocol CT scan	NR	4 to 9 days post-operatively	SVG	Perioperative MI was not associated with graft occlusion.
Huikuri, 1992[32]	Prospective	NR	339	Per-protocol angiography	NR	5	SVG	The presence of ≥1 occluded graft at 3 months after CABG was not associated with 5-year mortality.
Morice, 2011[26]	Substudy—SYNTAX-LE MANS	348	115	Per-protocol angiography	33.0%	1.3	SVG and arterial grafts	In patients with left main disease the composite of death/MI/stroke/revascularization was not significantly associated with graft occlusion ($P = 0.85$).

CABG, coronary artery bypass grafting; CI, confidence interval; CT, computed tomography; HR, hazard ratio; ITA, internal thoracic artery; LAD, left anterior descending artery; MI, myocardial infarction; NR, not reported; POST CABG, Post Coronary Artery Bypass Graft trial; PREVENT IV, Project of Ex-vivo Vein Graft Engineering via Transfection trial; RA, radial artery; RAPS, Radial Artery Patency Study; RR, relative risk; SVG, saphenous vein graft; SYNTAX-LE MANS, Synergy between PCI with TAXUS express and cardiac surgery left main angiographic sub-study.

improved outcomes in several trials, but the causal relation between patency and outcomes is unclear due to the effect of the medications on the native coronary circulation.[11,44,45]

Studies showing no association between graft patency and clinical outcomes

Robert *et al.*[27] in a study of 72 CABG patients found that at long-term follow-up, angina recurrence was mainly due to progression of native disease rather than graft occlusion. Achuff *et al.*[46] described symptomatic and functional improvement in 7 out of 12 patients with all grafts occluded and Benchimol *et al.*[47] did not find any association between clinical status and graft patency in a small series of 32 patients.

Hoel *et al.*[48] in a study of 90 patients found no association between graft patency and MI and Huikuri *et al.*[32] in a study of 339 patients showed that graft patency was not associated with survival at 5-year follow-up.

In the ROOBY trial, LAD status, but not graft patency, was associated with patient-reported angina 1 year after CABG.[49]

In the acute postoperative setting, Brindis *et al.*[30] showed that the majority of the cases of perioperative MI after CABG were not associated with graft occlusion and Aintablian *et al.*[50] did not find an association between graft status after surgery and postoperative appearance of new Q waves. A systematic review of the results of emergency angiography in patients with perioperative MI following CABG found that graft failure was not the cause of the acute event in 37.9% of the cases.[51]

Possible reasons for the described discrepancy among studies

While there is no clear-cut explanation for the reported discrepancy among studies, several factors need to be taken into account. Many

Table 2 Overview of selected studies examining the effect of CABG graft type on disease progression in the native coronary circulation

Study (first author, year)	Type of study	No. of patients included	Follow-up (mean/median, years)	Comparators	Key finding
Alderman, 1993[57]	*Post hoc* analysis—CASS study	314	5	LITA vs. SVG	A significant increase in native coronary artery disease progression in the LAD territory was observed in patients who received an SVG instead of an LITA graft.
Dimitrova, 2012[55]	Observational	772	5.5 ± 3.5	LITA vs. RA vs. SVG	RA and LITA grafting had a strong protective effect against progression of native coronary artery disease. Native vessel disease progression at 1, 5, and 10 years after CABG was 0.01%, 4%, and 8% in territories with patent LITA grafts; 0.01%, 6%, and 11% with patent RA grafts ($P = 0.157$); and 3%, 19%, and 43% with patent SVG ($P < 0.0001$).
Zhu, 2014[58]	*Post hoc* analysis—RAPCO trial	405	6.2 ± 3.1	Arterial graft vs. SVG	The use of arterial grafts was an independent predictor of disease regression in the native vessel.
Zhang, 2016[56]	Observational	468	5.4 ± 3.4 (CABG) 5.3 ± 3.4 (PCI)	CABG vs. PCI	Patients receiving LITA-to-LAD CABG had a significantly lower incidence of downstream disease progression compared with those receiving LAD PCI with BMS or DES (LITA 12.4% vs. BMS 85.9%, HR 0.34, 95% CI 0.20–0.59; vs. DES 24.1%, HR 0.39, 95% CI 0.20–0.79).
Yoon, 2017[52]	Observational	911	4.7	Arterial graft vs. SVG vs. No graft	The new occlusion rate of vessels after CABG was highest with SVG, followed by arterial grafts, and lowest in non-bypassed vessels, irrespective of baseline vessel stenosis degree (intermediate stenosis, 11.1% vs. 5.2% vs. 1.7%, $P < 0.001$; severe stenosis, 23.7% vs. 15.9% vs. 9.9%, $P < 0.001$).

BMS, bare metal stent; CABG, coronary artery bypass grafting; DES, drug-eluting stent; HR, hazard ratio; LAD, left anterior descending artery; LITA, left internal thoracic artery; PCI, percutaneous coronary intervention; RA, radial artery; SVG, saphenous vein graft.

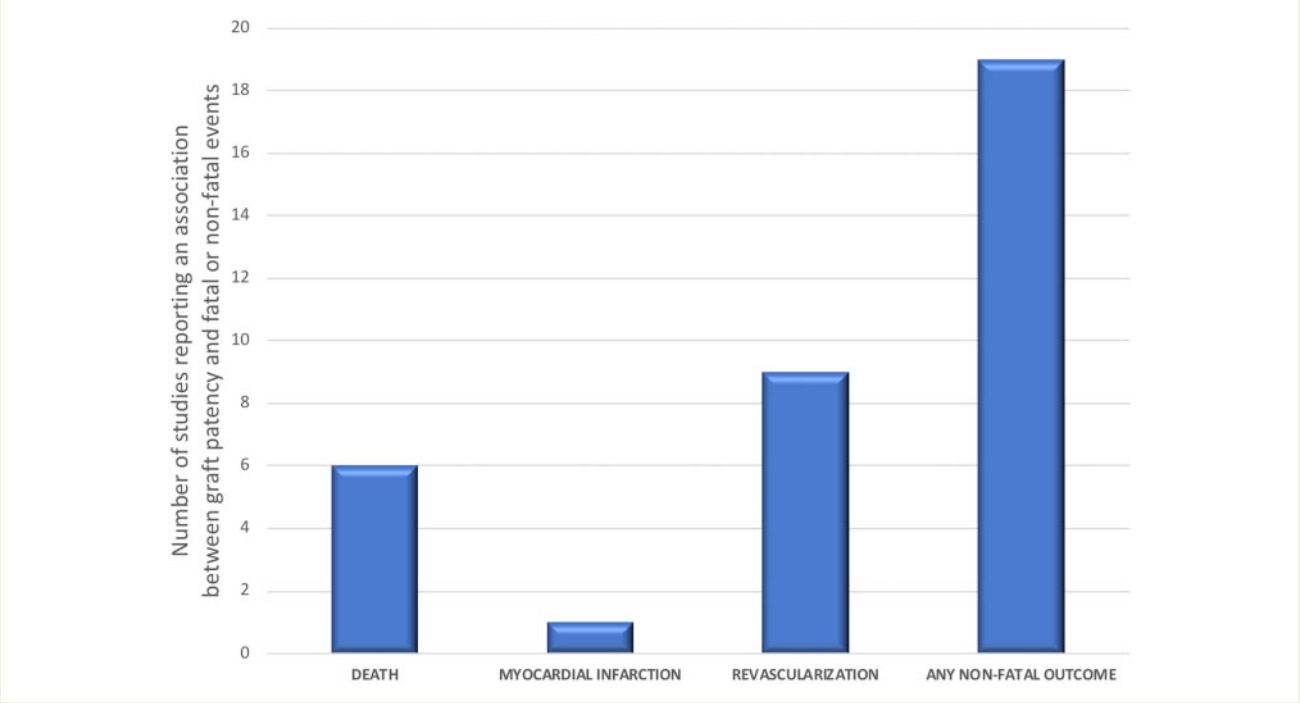


Figure 3 Number of published studies reporting an association between graft patency and fatal or non-fatal events. As shown, graft occlusion is generally associated with non-fatal events rather than death.

of the series that show no association between graft failure and symptoms are from an era when it was common to graft any stenosis >50% in any target vessel; graft failure due to flow competition or limited run-off in small target vessels (both situations at low risk of clinical events) were likely more common in these series. In addition, routine postoperative imaging was used more commonly in the older series, while the more contemporary studies may suffer from a higher selection bias, with only symptomatic patients referred for imaging.

Effect of surgical grafting on native coronary circulation

Saphenous vein graft grafting has been shown to accelerate progression of the proximal native stenosis to occlusion in many studies.[52–54] However, the use of arterial grafts is not associated with native stenosis progression and seems to have a protective effect on the distal coronary circulation (*Table 2*).[52,55–58] While the mechanisms of this effect are speculative, it is possible that the local anti-inflammatory and antithrombotic molecules that prevent atherosclerosis in arterial grafts may exert a protective effect on the native coronary bed.

Conclusions and practical implications

The association between graft patency and clinical status is complex and highly variable (*Graphical abstract*).

Overall, the number of studies that support an association between graft occlusion and clinical events (mostly non-fatal) is higher than the number of studies that refute it (*Figure 3*). An important exception is graft failure from competitive flow that is usually asymptomatic.

Based on our data, one should conclude that the role of routine imaging follow-up after CABG appears limited. In addition, the incidental finding of asymptomatic graft failure in a CABG patient should not prompt re-intervention. Our finding of a variable association between graft status and clinical events has also implications for the design of future CABG trials: the assessment of clinical outcomes alone may underestimate the effect of interventions aimed at modifying graft patency and, for this reason, the use of patency as a surrogate or secondary outcome should be considered.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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References

1. Gaudino M, Antoniades C, Benedetto U, Deb S, Di Franco A, Di Giammarco G, Fremes S, Glineur D, Grau J, He G-W, Marinelli D, Ohmes LB, Patrono C, Puskas J, Tranbaugh R, Girardi LN, Taggart DP, Ruel M, Bakaeen FG, ATLANTIC (Arterial Grafting International Consortium) Alliance. Mechanisms, consequences, and prevention of coronary graft failure. *Circulation* 2017;**136**:1749–1764.
2. Gaudino M, Benedetto U, Fremes SE, Hare DL, Hayward P, Moat N, Moscarelli M, Di Franco A, Nasso G, Peric M, Petrovic I, Collins P, Webb CM, Puskas JD, Speziale G, Yoo KJ, Girardi LN, Taggart DP, RADIAL Investigators. Angiographic outcome of coronary artery bypass grafts: the radial artery database international alliance. *Ann Thorac Surg* 2020;**109**:688–694.
3. 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.
4. Buxton BF, Hayward PA, Raman J, Moten SC, Rosalion A, Gordon I, Seevanayagam S, Matalanis G, Benedetto U, Gaudino M, Hare DL, Gaer J, Negri J, Komeda M, Bellomo R, Doolan L, McNicol L, Brennan J, Chan R, Clark D, Dick R, Dortimer A, Ecclestone D, Farouque O, Fernando D, Horrigan M, Jackson A, Oliver L, Mehta N, Nadurata V, Nadarajah N, Proimos G, Rowe M, Sia B, Webb C, Anaveker N, Barlis P, Calafiore P, Chan B, Cotroneo J, Johns J, Jones E, Kertes P, O'Donnell D, Sylviris S, Tonkin A, Fabini R, Kearney L, Lim R, Molan M, Smith G, Wellman C, Eng J, Hameed I, Shaw M, Gerbo S, RAPCO Investigators. Long-term results of the RAPCO trials. *Circulation* 2020;**142**:1330–1338.
5. Ruiter MS, Pesce M. Mechanotransduction in coronary vein graft disease. *Front Cardiovasc Med* 2018;**5**:20.
6. Storey RF. Exploring mechanisms of graft occlusion toward improved outcomes in coronary artery bypass graft surgery. *J Am Coll Cardiol* 2011;**57**:1078–1080.
7. Harskamp RE, Lopes RD, Baisden CE, de Winter RJ, Alexander JH. Saphenous vein graft failure after coronary artery bypass surgery: pathophysiology, management, and future directions. *Ann Surg* 2013;**257**:824–833.
8. 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.
9. 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.
10. Agarwal N, Mahmoud AN, Patel NK, Jain A, Garg J, Mojadidi MK, Agrawal S, Qamar A, Golwala H, Gupta T, Bhatia N, Anderson RD, Bhatt DL. Meta-analysis of aspirin versus dual antiplatelet therapy following coronary artery bypass grafting. *Am J Cardiol* 2018;**121**:32–40.
11. 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.
12. Shah AA, Haynes C, Craig DM, Sebek J, Grass E, Abramson K, Hauser E, Gregory SG, Kraus WE, Smith PK, Shah SH. Genetic variants associated with vein graft stenosis after coronary artery bypass grafting. *Heart Surg Forum* 2015;**18**:E1–E5.
13. Neumann F-J, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet J-P, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferović PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO; ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J* 2019;**40**:87–165.
14. Hamon M, Lepage O, Malagutti P, Riddell JW, Morello R, Agostini D, Hamon M. Diagnostic performance of 16- and 64-section spiral CT for coronary artery bypass graft assessment: meta-analysis. *Radiology* 2008;**247**:679–686.
15. Murphy GJ, Angelini GD. Insights into the pathogenesis of vein graft disease: lessons from intravascular ultrasound. *Cardiovasc Ultrasound* 2004;**2**:8.
16. 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.
17. Harskamp RE, Williams JB, Hill RC, de Winter RJ, Alexander JH, Lopes RD. Saphenous vein graft failure and clinical outcomes: toward a surrogate end point in patients following coronary artery bypass surgery? *Am Heart J* 2013;**165**:639–643.
18. Buxton BF, Durairaj M, Hare DL, Gordon I, Moten S, Orford V, Seevanayagam S. Do angiographic results from symptom-directed studies reflect true graft patency? *Ann Thorac Surg* 2005;**80**:896–900; discussion 900–901.
19. 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.
20. Deb S, Singh SK, de Souza D, Chu MWA, Whitlock R, Meyer SR, Verma S, Jeppsson A, Al-Saleh A, Brady K, Rao-Melacini P, Belley-Cote EP, Tam DY,

Devereaux PJ, Novick RJ, Fremes SE, SUPERIOR SVG Study Investigators. SUPERIOR SVG: no touch saphenous harvesting to improve patency following coronary bypass grafting (a multi-Centre randomized control trial, NCT01047449). *J Cardiothorac Surg* 2019;**14**:85.
21. Farooq V, Serruys PW, Garcia-Garcia HM, Zhang Y, Bourantas CV, Holmes DR, Mack M, Feldman T, Morice MC, Ståhle E, James S, Colombo A, Diletti R, Papafaklis MI, de Vries T, Morel MA, van Es GA, Mohr FW, Dawkins KD, Kappetein AP, Sianos G, Boersma E. The negative impact of incomplete angiographic revascularization on clinical outcomes and its association with total occlusions: the SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial. *J Am Coll Cardiol* 2013;**61**:282–294.
22. Tonino PAL, Fearon WF, De Bruyne B, Oldroyd KG, Leesar MA, Ver Lee PN, MacCarthy PA, van't Veer M, Pijls NHJ. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. *J Am Coll Cardiol* 2010;**55**:2816–2821.
23. Ferguson TB, Chen C, Babb JD, Efird JT, Daggubati R, Cahill JM. Fractional flow reserve-guided coronary artery bypass grafting: can intraoperative physiologic imaging guide decision making? *J Thorac Cardiovasc Surg* 2013;**146**:824–835.e1.
24. Glineur D, Grau JB, Etienne P-Y, Benedetto U, Fortier JH, Papadatos S, Laruelle C, Pieters D, El Khoury E, Blouard P, Timmermans P, Ruel M, Chong A-Y, So D, Chan V, Rubens F, Gaudino MF. Impact of preoperative fractional flow reserve on arterial bypass graft anastomotic function: the IMPAG trial. *Eur Heart J* 2019;**40**:2421–2428.
25. Spadaccio C, Glineur D, Barbato E, Di Franco A, Oldroyd KG, Biondi-Zoccai G, Crea F, Fremes SE, Angiolillo DJ, Gaudino M. Fractional flow reserve-based coronary artery bypass surgery: current evidence and future directions. *JACC Cardiovasc Interv* 2020;**13**:1086–1096.
26. Morice M-C, Feldman TEE, Mack MJ, Ståhle E, Holmes DR, Colombo A, Morel M-A, van den Brand M, Serruys PW, Mohr F, Carrié D, Fournial G, James S, Leadley K, Dawkins KD, Kappetein AP. Angiographic outcomes following stenting or coronary artery bypass surgery of the left main coronary artery: fifteen-month outcomes from the synergy between PCI with TAXUS express and cardiac surgery left main angiographic substudy (SYNTAX-LE MANS). *EuroIntervention* 2011;**7**:670–679.
27. Robert EW, Guthaner DF, Wexler L, Alderman EL. Six-year clinical and angiographic follow-up of patients with previously documented complete revascularization. *Circulation* 1978;**58**:I194–I199.
28. Bourassa MG, Campeau L, Lespérance J, Grondin CM. Changes in grafts and coronary arteries after saphenous vein aortocoronary bypass surgery: results at repeat angiography. *Circulation* 1982;**65**:90–97.
29. Laird-Meeter K, ten Katen HJ, Brower RW, van den Brand MJ, Serruys PW, Haalebos MM, Bos E, Hugenholtz PG. Angina pectoris, one to 10 years after aortocoronary bypass surgery. *Eur Heart J* 1983;**4**:678–686.
30. Brindis RG, Brundage BH, Ullyot DJ, McKay CW, Lipton MJ, Turley K. Graft patency in patients with coronary artery bypass operation complicated by perioperative myocardial infarction. *J Am Coll Cardiol* 1984;**3**:55–62.
31. Lytle BW, Loop FD, Taylor PC, Simpfendorfer C, Kramer JR, Ratliff NB, Goormastic M, Cosgrove DM, Schnauffer MJ. Vein graft disease: the clinical impact of stenoses in saphenous vein bypass grafts to coronary arteries. *J Thorac Cardiovasc Surg* 1992;**103**:831–840.
32. Huikuri HV, Yli-Mäyry S, Airaksinen KE, Ikäheimo MJ, Linnaluoto MK, Takkunen JT. Clinical and angiographic prediction of cardiac death after coronary artery bypass graft surgery. *Br Heart J* 1992;**67**:216–220.
33. Knatterud GL, White C, Geller NL, Campeau L, Forman SA, Domanski M, Forrester JS, Gobel FL, Herd JA, Hickey A, Hoogwerf BJ, Hunninghake DB, Terrin ML, Rosenberg Y. Angiographic changes in saphenous vein grafts are predictors of clinical outcomes. *Am Heart J* 2003;**145**:262–269.
34. 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.
35. 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.
36. 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.
37. 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.
38. 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.
39. Winer HE, Glassman E, Spencer FC. Mechanism of relief of angina after coronary bypass surgery: an angiographic study. *Am J Cardiol* 1979;**44**:202–208.
40. Loop FD, Lytle BW, Cosgrove DM, Stewart RW, Goormastic M, Williams GW, Golding LAR, Gill CC, Taylor PC, Sheldon WC, Proudfit WL. Influence of the internal-mammary-artery graft on 10-year survival and other cardiac events. *N Engl J Med* 1986;**314**:1–6.
41. Zeff RH, Kongtahworn C, Iannone LA, Gordon DF, Brown TM, Phillips SJ, Skinner JR, Spector M. Internal mammary artery versus saphenous vein graft to the left anterior descending coronary artery: prospective randomized study with 10-year follow-up. *Ann Thorac Surg* 1988;**45**:533–536.
42. Gaudino M, Benedetto U, Fremes S, Biondi-Zoccai G, Sedrakyan A, Puskas JD, Angelini GD, Buxton B, Frati G, Hare DL, Hayward P, Nasso G, Moat N, Peric M, Yoo KJ, Speziale G, Girardi LN, Taggart DP, RADIAL Investigators. Radial-artery or saphenous-vein grafts in coronary-artery bypass surgery. *N Engl J Med* 2018;**378**:2069–2077.
43. Korpilahti K, Engblom E, Hämäläinen H, Syvänne M, Hietanen E, Arstila M, Puukka P, Rönnemaa T. Significance of graft occlusion and coronary atherosclerosis 5 years after coronary artery bypass grafting. A quantitative angiographic study with serial exercise testing. *J Intern Med* 1999;**245**:545–552.
44. Blankenhorn DH, Nessim SA, Johnson RL, Sanmarco ME, Azen SP, Cashin-Hemphill L. Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. *JAMA* 1987;**257**:3233–3240.
45. Solo K, Lavi S, Kabali C, Levine GN, Kulik A, John-Baptiste AA, Fremes SE, Martin J, Eikelboom JW, Ruel M, Huitema AA, Choudhury T, Bhatt DL, Tzemos N, Mamas MA, Bagur R. Antithrombotic treatment after coronary artery bypass graft surgery: systematic review and network meta-analysis. *BMJ* 2019;**367**:l5476.
46. Achuff SC, Griffith LS, Conti CR, Humphries JO, Brawley RK, Gott VL, Ross RS. The "angina-producing" myocardial segment: an approach to the interpretation of results of coronary bypass surgery. *Am J Cardiol* 1975;**36**:723–733.
47. Benchimol A, dos Santos A, Desser KB. Relief of angina pectoris in patients with occluded coronary bypass grafts. *Am J Med* 1976;**60**:339–343.
48. Hoel B, Eie H, Semb G, Sivertssen E. Aortocoronary vein bypass in patients with angina pectoris. *Acta Med Scand* 2009;**197**:383–390.
49. Hattler B, Carr BM, Messenger J, Spertus J, Ebrahimi R, Bishawi M, Quin JA, Almassi GH, Collins JF, Kozora E, Grover FL, Shroyer ALW. Clinical and angiographic predictors of patient-reported angina 1 year after coronary artery bypass graft surgery. *Circ Cardiovasc Qual Outcomes* 2019;**12**:e005119.
50. Aintablian A, Hamby RI, Hoffman I, Weisz D, Voleti C, Wisoff BG. Significance of new Q waves after bypass grafting: correlations between graft patency, ventriculogram, and surgical venting technique. *Am Heart J* 1978;**95**:429–440.
51. Biancari F, Anttila V, Dell'Aquila AM, Airaksinen JKE, Brascia D. Control angiography for perioperative myocardial Ischemia after coronary surgery: meta-analysis. *J Cardiothorac Surg* 2018;**13**:24.
52. Yoon SH, Kim YH, Yang DH, Roh JH, Lee EY, Lee PH, Sugiyama D, Chang M, Ahn JM, Choi WJ, Kang JW, Lim TH, Kim JB, Jung SH, Chung CH, Choo SJ, Lee JW, Kang SJ, Park DW, Lee SW, Lee CW, Park SW, Park SJ. Risk of new native-vessel occlusion after coronary artery bypass grafting. *Am J Cardiol* 2017;**119**:7–13.
53. Kroncke GM, Kosolcharoen P, Clayman JA, Peduzzi PN, Detre K, Takaro T. Five-year changes in coronary arteries of medical and surgical patients of the Veterans Administration Randomized Study of Bypass Surgery. *Circulation* 1988;**78**:I144–I150.
54. Cashin WL, Sanmarco ME, Nessim SA, Blankenhorn DH. Accelerated progression of atherosclerosis in coronary vessels with minimal lesions that are bypassed. *N Engl J Med* 1984;**311**:824–828.
55. Dimitrova KR, Hoffman DM, Geller CM, Dincheva G, Ko W, Tranbaugh RF. Arterial grafts protect the native coronary vessels from atherosclerotic disease progression. *Ann Thorac Surg* 2012;**94**:475–481.
56. Zhang M, Guddeti RR, Matsuzawa Y, Sara JDS, Kwon TG, Liu Z, Sun T, Lee SJ, Lennon RJ, Bell MR, Schaff HV, Daly RC, Lerman LO, Lerman A, Locker C. Left internal mammary artery versus coronary stents: impact on downstream coronary stenoses and conduit patency. *J Am Heart Assoc* 2016;**5**:e003568.
57. Alderman EL, Corley SD, Fisher LD, Chaitman BR, Faxon DP, Foster ED, Killip T, Sosa JA, Bourassa MG. Five-year angiographic follow-up of factors associated with progression of coronary artery disease in the Coronary Artery Surgery Study (CASS). CASS Participating Investigators and Staff. *J Am Coll Cardiol* 1993;**22**:1141–1154.
58. Zhu YY, Hayward PAR, Hare DL, Reid C, Stewart AG, Buxton BF. Effect of lipid exposure on graft patency and clinical outcomes: arteries and veins are different. *Eur J Cardiothorac Surg* 2014;**45**:323–328.