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

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Background In contemporary coronary artery bypass graft (CABG) surgery, the association between symptomatic graft failure (GF) and long-term clinical outcome remains unclear. We sought to identify the clinical characteristics and outcomes of GF in symptomatic patients requiring cardiac catheterization within 1 year of CABG surgery.

Methods Using the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease registry, 5,276 patients undergoing CABG surgery from September 2002 to August 2011 were identified. Clinical outcomes in patients with symptomatic GF were observed. Predictors of GF were analyzed at a graft level, whereas long-term survival was assessed at a patient level. A propensity score matching technique was used to adjust for baseline characteristics.

Results Of our CABG cohort, 5.3% (281 patients [285 arterial and 653 vein grafts]) required symptom based coronary angiography within 1 year of CABG surgery. Acute coronary syndrome was the most common presentation (64.4%). At angiography, 27.0% (77/285) of arterial and 34.5% (225/653) of vein grafts were occluded. Respectively, arterial and vein GFs were treated as follows: percutaneous coronary intervention 61.0% versus 41.8%, re-do CABG 9.1% versus 0%, and medically without intervention 29.9% versus 58.2%. A strong trend toward reduced patient survival was noted with "arterial graft failure" (arterial ± vein GF) compared to "vein graft failure only" (no arterial GF) (adjusted hazard ratio 2.2, 95% CI 0.98-5.0, $P = .056$).

Conclusion Although the rate of cardiac catheterization within 1 year of CABG is infrequent, these patients exhibit high GF rates and commonly present with an acute coronary syndrome. In addition, "arterial graft failure" compared to "vein graft failure only" confers a higher risk of adverse long-term survival. (Am Heart J 2015;169:833-40.)

Saphenous vein grafts (SVGs), in combination with the left internal mammary artery (LIMA), continue to be the most commonly used vascular conduits during coronary artery bypass graft (CABG) surgery. However, graft failure (GF) has posed challenges for successful surgical revascularization. Vein graft patency rates have remained fairly static over the last 2 decades with reports of 70% to 80% vein graft patency at 1 year.[1-3] More importantly, investigators have demonstrated an association between early vein GF and adverse clinical events.[4-6] As such, total arterial revascularization has been advocated.[7] However, in clinical practice, this technique is commonly underused.[8,9]

Moreover, contemporary strategies in percutaneous coronary intervention (PCI) have shifted the referral pattern of CABG toward patients with complex coronary anatomy and multiple comorbidities.[10] Consequently, patency of these vascular conduits may become compromised. Accordingly, we sought to identify the clinical characteristics and outcomes of symptomatic GF in a contemporary cohort of patients requiring cardiac catheterization within 1 year of CABG surgery.

Methods

The Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) database has been previously described.[11] In brief, APPROACH is a prospective clinical data collection initiative capturing all patients undergoing cardiac catheterization and

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revascularization in the province of Alberta, Canada, since 1995. The registry contains detailed clinical information including each patient's age; sex; ejection fraction; and presence or absence of previous myocardial infarction, congestive heart failure, cerebrovascular disease, peripheral vascular disease (PVD), chronic obstructive pulmonary disease, present/prior smoking, renal function, renal dialysis, hyperlipidemia, hypertension, diabetes mellitus, liver disease, gastrointestinal disease, and malignancy as well as indication for revascularization. The APPROACH tracks therapeutic interventions including revascularization by CABG surgery or PCI. Extent of coronary artery disease is documented and reported via standardized coronary anatomy diagrams. Mortality is tracked through quarterly linkage to data from the Alberta Bureau of Vital Statistics.

Patient population

We included 5,276 patients who underwent isolated CABG surgery in a single center in Edmonton, Canada, between September 1, 2002, and August 31, 2011. In these patients, 10,338 saphenous vein grafts and 4,789 arterial grafts (99.5% LIMA, 0.5% right internal mammary artery [RIMA], and free radial) were implanted. All patients undergoing concomitant surgery (eg, valve, vascular, or congenital) and patients undergoing re-do CABG were excluded. We subsequently identified those patients undergoing coronary and bypass graft angiography within 1 year after CABG surgery. In patients who had ≥2 angiograms after surgery within the first year, data from last angiogram were used as this tracked all revascularization procedures performed during the 1 year from CABG. All CABG procedures were performed on-pump with an open saphenous vein harvest technique by 9 cardiovascular surgeons over the time frame referenced.

Angiographic data

Coronary and bypass graft angiography was performed in the standard fashion with selective engagement of all aortocoronary anastomosis. If a conduit could not be identified by selective engagement, an aortic root angiogram was performed. All angiographic data were obtained from a coronary artery reporting and archiving tool diagram contained in APPROACH. For the purposes of this study, *significant GF* was defined as angiographic arterial or vein graft stenosis of ≥70% (ratio of minimal lumen diameter to reference vessel diameter) as determined by the angiographer. In patients with arterial GF, review of the surgical record was performed in an attempt to identify the possible reasons for arterial conduit occlusion. Details of repeat revascularization (PCI or CABG) or medical management were also obtained from the APPROACH registry. A heart team approach was used to determine the need and mode of repeat revascularization.

Statistical analysis

Patient characteristics among those with and without subsequent cardiac catheterization post-CABG were compared using χ^2 or t test, where appropriate. $P < .05$ was regarded as significant. To identify significant predictors of graft occlusion in post-CABG patients requiring coronary angiography within 1 year, 2 logistic regression analyses were performed using arterial graft occlusion and vein graft occlusion as the outcome variables (graft level). All demographic and clinical variables significantly associated with graft occlusion ($P < .10$) were entered into these models. Because of the extremely small numbers of RIMA and free radial graft utilization, an arterial graft failure most commonly indicated LIMA failure. Patients with concomitant arterial and vein graft failure were analyzed collectively as having "arterial graft failure" (given the prognostic value of the LIMA), whereas patients with isolated vein graft failure (ie, without arterial graft failure) were labeled as having "vein graft failure only." A comparable distribution of clinical variables among patients who had arterial graft failure versus patients with vein graft failure only was obtained using the Rosenbaum and Rubin propensity score matching technique. The propensity match was performed using the patients with vein graft failure only conditional on the observed baseline (measured at recruitment) characteristics. The propensity score was calculated using logistic regression. The following variables were included in the model: age, sex, diabetes mellitus, pulmonary disease, cerebrovascular disease, dialysis, heart failure, diabetes, current smoker, hypertension, hyperlipidemia, PVD, prior myocardial infarction, body mass index, and cross-clamp time. Greedy matching techniques were applied to match patients who had vein graft failure only with patients having arterial graft failure by matching the participants with the nearest propensity score, that is, within 2 decimal places of the propensity score for each case. Overlap of propensity scores between patients with vein graft failure only and arterial graft failure was evaluated using histograms and χ^2 values and probability values. Differences in baseline factors between groups were calculated before and after propensity adjustment to assess balance. After the match, Kaplan-Meier curves and log-rank tests were used to determine statistically significant survival differences between patients with vein graft failure only compared to patients with arterial graft failure. Similarly, Cox regression analysis was used in the propensity-matched groups to test whether there were statistically significant differences in survival between patients in the vein graft failure only group and patients in the arterial graft failure group after adjustment for repeat revascularization in the arterial or vein GF territory. Time to event was measured from the date of coronary and bypass graft angiography after CABG surgery. Finally, to adjust for the reduced sample

Table I. Baseline characteristics according to need for cardiac catheterization

	Cardiac catheterization (n = 281)	No cardiac catheterization (n = 4995)	*P*
Age (y)	63.4	65.3	.003
Male (%)	80.4	83.2	.13
Ethnicity (%)			
European	96.0	95.4	
South Asian	2.8	3.3	.88
Chinese	1.2	1.3	
BMI (kg/m^2)	29.1	29.3	.55
Hypertension (%)	83.3	83.2	.52
Dyslipidemia (%)	96.1	96.7	.58
Diabetes (%)			
Type 1	2.1	2.4	.47
Type 2	32.7	33.5	.42
Smoking status (%)			.51
Current	29.2	25.3	
Former	45.6	49.2	
Never	22.8	23.0	
Unknown	2.4	2.5	
Heart failure (%)	6.0	8.1	.12
Prior stroke (%)	11.1	12.6	.23
PVD (%)	10.8	9.5	.26
Prior myocardial infarction (%)	63.7	61.6	.26
Prior PCI (%)	23.1	18.2	.03
Renal insufficiency (%)			
Dialysis independent	7.1	11.1	.06
Dialysis dependent	0.7	1.3	.30
CCS class (%)			
I	0.7	2.5	
II	23.1	25.0	.002
III	17.4	22.7	
IV	53.0	44.6	
Unknown	5.8	5.2	
NYHA class (%)			
1	34.4	26.4	
2	22.6	33.2	.25
3	34.4	30.7	
4	8.6	9.7	
Extent of CAD (%)			
Isolated left main	34.9	32.0	
3-vessel CAD	56.3	56.0	.72
2-vessel CAD	5.5	7.2	
Not available	3.3	4.8	
Preoperative LVEF (%)			
Normal	42.9	42.2	
Mild	21.0	21.6	
Moderate	5.0	4.7	.63
Severe	0	1.1	
Not available	31.0	30.4	
Surgery			
Cross-clamp time (min)	62.4	62.1	.92

Abbreviations: *BMI*, body mass index; *CCS*, Canadian Cardiovascular Society; *NYHA*, New York Heart Association; *CAD*, coronary artery disease, *LVEF*, left ventricular ejection fraction.

size created by the propensity matching technique, 1,000 bootstrap samples were created to derive robust estimates of SEs and CIs for the hazard ratios (HRs) of the Cox regression analyses. Patients without events were censored on April 31, 2013. IBM SPSS Statistics (version 21) software (Armonk, NY) was used for all analyses.

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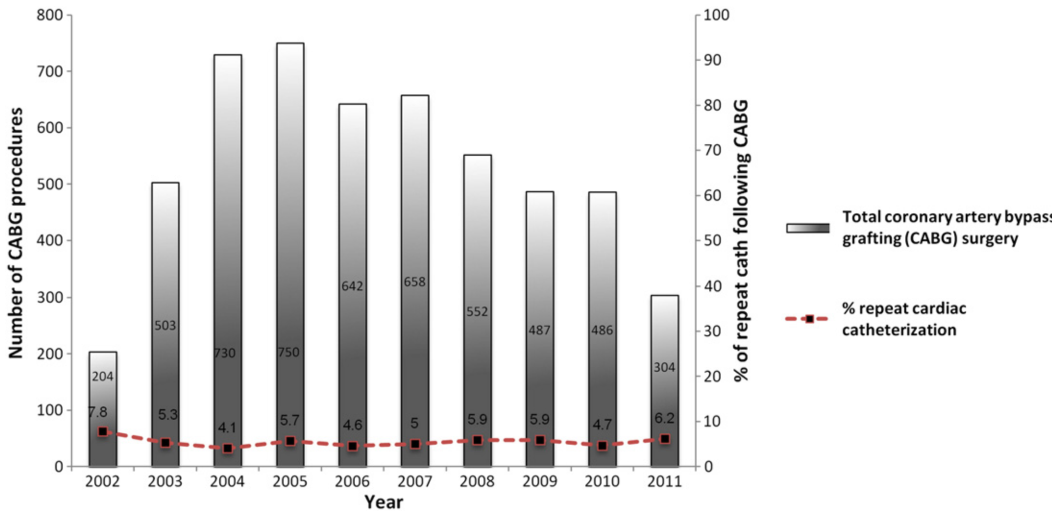
Results

Baseline characteristics

Of our study population, 5.3% (n = 281) underwent coronary and bypass graft angiography within 1 year of surgery with 18.5% (n = 52) of these performed within 1

Figure 1



Frequency of cardiac catheterization within 1 year of CABG surgery (2002-2011).

month. Table I outlines the baseline characteristics of patients undergoing symptom based cardiac catheterization within 1 year of CABG compared to those who did not undergo cardiac catheterization. Patients receiving cardiac catheterization were younger, more likely to have a prior PCI, and had worse angina at baseline before CABG.

Frequency and indication for cardiac catheterization post-CABG

The temporal distribution of cardiac catheterization within 1 year of CABG is represented in Figure 1. The annual rate appears constant ranging from 4% to 6%. The indications for cardiac catheterization within 1 year after CABG were acute coronary syndrome (ACS) (64.4% [181/281]), stable angina (25.6% [72/281]), heart failure/cardiogenic shock (5.0% [14/281]), cardiac arrest/significant arrhythmia (2.8% [8/281]), and other (2.1% [6/281]).

Graft failure

In the 281 patients who underwent coronary and bypass graft angiography at 1 year, 285 arterial grafts and 653 vein grafts were implanted at the time of the index CABG surgery. Of these, 27.0% (77/285) of arterial and 34.5% (225/653) of saphenous vein grafts were occluded. Of the failed arterial grafts, 44.2% (34/77) had concomitant vein GF.

Arterial graft failure

Arterial GF rate (27.0%) (77/285) was characterized as follows: 68 were LIMAs (68/260), 6 were radial artery conduits (6/19), and 3 were right internal mammary arteries (3/6). Of the arterial GF, 33.7% (26/77) were due to failed anastomosis technique, 29.9% (23/77) were due to an atretic arterial conduit with competitive flow from moderate native artery stenosis, and 23.3% (18/77) were due to poor distal anastomosis run-off in the native coronary artery. In the remaining failed arterial grafts, the underlying etiology could not be established. Arterial GF territory was treated as follows: PCI in 61.0% (47/77 [native artery intervention in 28/47 and conduit intervention in 19/47]) and re-do CABG in 9.1% (7/77). The remaining GFs were treated medically without intervention in 29.9% (23/77). Multivariate predictors of arterial GF are listed in Table II. Female gender appeared as a significant predictor of arterial GF. Overall, increasing age tended to protect against arterial GF.

Vein graft failure

A 34.5% (225/653) vein GF rate was observed in symptomatic patients requiring cardiac catheterization within 1 year of CABG. Of the SVGs that failed, 33.7% were anastomosed to the posterior descending artery; 38.7%, to an obtuse marginal artery; 19.2%, to a diagonal artery; 4.9%, to a ramus intermedius branch; 2.2%, to the left circumflex; and 1.3%, to the left anterior descending (LAD) artery. We collected data on native artery size in relation to vein GF available for 270 native arteries. We observed a 43% (69/160) vein GF rate in recipient arteries ≤1.5 mm versus a 27% (30/110) vein GF rate in recipient arteries >1.5 mm in caliber (P = .001). Vein GF territory was treated as follows: PCI in 41.8% (94/225 [SVG conduit intervention in 16/94 and the native coronary artery intervention in 78/94]), re-do CABG in 0% (0/225), and medically without intervention in 58.2% (131/225). Multivariate predictors of vein GF are listed in Table II. Native artery caliber ≤1.5 mm was a strong predictor of vein GF.

Table II. Predictors of graft failure

	Arterial graft failure (n = 76)		Vein graft failure (n = 225)	
Variable	Odds	*P*	Odds	*P*
Age (y)				
<60	1.0		1.0	
60-65	0.47 (0.21, 1.07)	.07	1.04 (0.48, 2.22)	.93
66-71	0.79 (0.37, 1.69)	.55	0.94 (0.45, 1.97)	.87
72-78	0.30 (0.11, 0.77)	.01	0.82 (0.38, 1.75)	.60
>79	0.54 (0.22, 1.29)	.16	0.82 (0.38, 1.79)	.62
Female	2.25 (1.20, 4.25)	.01	0.74 (0.42, 1.34)	.33
BMI	0.95 (0.89, 1.01)	.07	1.00 (0.98, 1.02)	.93
Smoking (current vs former)	1.38 (0.75, 2.52)	.30	1.53 (0.87, 2.68)	.14
Diabetes	0.74 (0.41, 1.33)	.31	0.71 (0.44, 1.15)	.17
PVD	1.00 (0.42, 2.44)	.99	1.18 (0.55, 2.54)	.68
Cross-clamp time	1.00 (0.99, 1.01)	.48	1.01 (1.00, 1.02)	.30
Native artery ≤1.5 mm	–	–	2.41 (1.40, 4.14)	.001
No. of SVG grafts (every 1 vein graft increase)	–	–	0.98 (0.77, 1.25)	.86

Long-term mortality

Median duration of follow-up was 5.8 years (interquartile range 4.2) in the large cohort and 5.4 years (interquartile range 4.0) in those patients undergoing cardiac catheterization within 1 year of CABG. Table III shows the adjusted baseline characteristics of patients with "arterial graft failure" compared to "vein graft failure only". Propensity adjustment yielded excellent balance between the arterial graft failure and vein graft failure only patient groups, as the standardized difference was well below the recommended maximum value of 10% for every risk factor. The long-term propensity–matched survival rate according to the type of graft failure is outlined in Figure 2. Patients with "arterial graft failure" had a strong trend toward worse long-term survival compared to patients with "vein graft failure only" (adjusted HR 2.2, 95% CI 0.98-5.0, *P* = .056). As an exploratory analysis, we also controlled for subsequent repeat revascularization of failed graft territory (both arterial and vein). Similarly, we found "arterial graft failure" was associated with adverse long-term survival (adjusted HR 2.3, 95% CI 1.05-4.96, *P* = .037).

Discussion

In the contemporary surgical era, we found that the need for symptom-based cardiac catheterization after CABG at 1 year remains infrequent. The most common clinical indication for cardiac catheterization was an ACS. In these patients, high rates of arterial and vein GF were noted and were often treated with repeat revascularization. Still, "arterial graft failure" compared to "vein graft failure only" 1 year post-CABG portends a worse long-term prognosis.

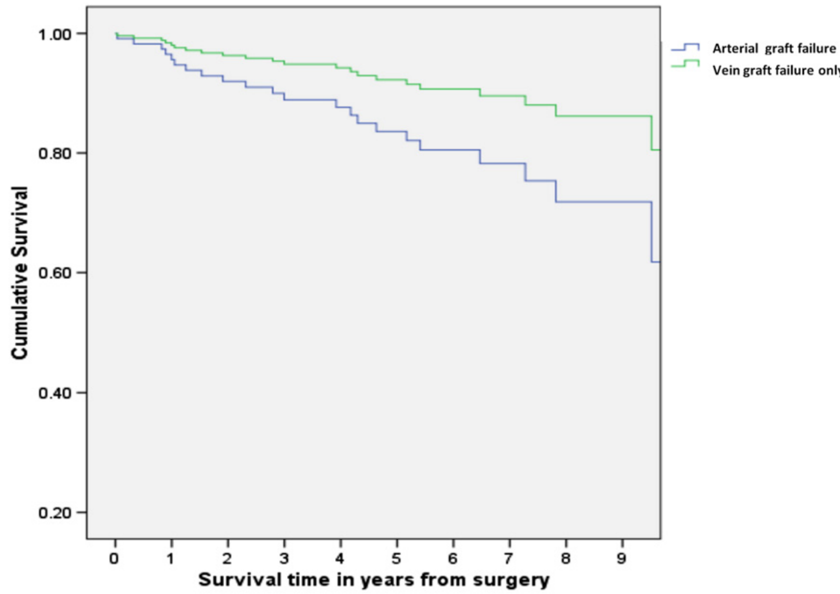
Table III. Propensity-matched patients with graft failure

	Arterial graft failure (n = 58)	Vein graft failure only (n = 123)	*P*
Age (y)	66.8	68.3	.39
Male (%)	76.0	82.9	.26
BMI (kg/m^2)	27.4	31.2	.22
Hypertension (%)	27.6	25.2	.39
Dyslipidemia (%)	93.1	98.4	.07
Diabetes (%)			
Type 1	1.7	1.6	.96
Type 2	25.9	33.3	.31
Smoking status (%)			
Current	39.7	35.0	
Former	31.0	41.5	.57
Never	27.6	22.8	
Unknown	1.7	0.8	
Heart failure (%)	0	3.3	.17
Prior stroke (%)	5.2	15.4	.05
PVD (%)	10.3	11.4	.84
Prior myocardial infarction (%)	56.9	63.4	.40
Prior PCI (%)	17.2	21.1	.54
Renal insufficiency (%)			
Dialysis independent	5.4	5.9	.92
Dialysis dependent	0	0	
CCS class (%)			
I	1.7	0	
II	19.0	24.4	
III	19.0	15.4	.55
IV	55.2	53.6	
Unknown/none	5.1	6.6	
NYHA class (%)			
1	8.6	10.6	
2	5.2	9.8	
3	10.3	11.4	.82
4	3.4	1.6	
Not available	72.4	66.7	
Extent of CAD (%)			
Isolated left main	15.5	13.0	
3-vessel CAD	37.9	48.8	
2-vessel CAD	25.9	25.2	.60
1-vessel CAD	6.9	4.1	
Not available	13.8	8.9	
Surgery			
Cross-clamp time (min)	61.4	64.3	.44

The survival benefit seen with the LIMA to LAD artery anastomosis[12,13] grants it a class I indication[14] due to its extended patency in the long term.[15] As such, the LIMA to LAD artery anastomosis has been considered a measure of surgical quality control.[16] The present study confirms the high utilization rate of LIMA to LAD artery anastomosis (99.5%) in a contemporary CABG population. However, in patients returning within 1 year for a clinically indicated cardiac catheterization, high rates of arterial GF were noted, which compromises the survival advantage of this conduit.

The high GF rates in symptomatic patients requiring coronary and bypass graft angiography 1 year after CABG likely reflect the challenges with contemporary CABG surgery as surgeons are called upon to operate on increasingly complex vessels with a high burden of

Figure 2



Year	0	1	2	3	4	5	6	7	8
Arterial	58	55	51	43	36	30	22	17	11
Vein	123	119	103	88	71	58	46	34	16

Propensity-matched long-term survival stratified by graft failure.

coronary disease. In the current study, we have demonstrated that a large number of arterial GF cases were due to technical anastomotic challenges and/or poor distal flow of the native coronary vessel. This is also reflected in the predictors of arterial GF, as females are known to have smaller sized native coronary arteries and smaller graft conduits leading to lower graft patency.[17,18] Overall, we found older age tended to be protective against arterial GF. One plausible reason is that the severity of native coronary artery disease in the older patient prevents competitive flow in the graft conduit allowing retention of patency. The association between GF in moderately stenosed coronary vessels was initially described by Barner et al[19] who described vascular flow competition as the culprit for GF in these patients. This has been subsequently confirmed in larger studies.[12,20] For this reason, a functional assessment (ie, fractional flow reserve) of the LAD artery could be considered before considering a LIMA conduit (and CABG surgery) in native lesions that are borderline significant.[21]

Symptomatic vein GF was similarly high within 1 year of CABG surgery. Vein GF within a year is more often due to thrombus formation, triggered either by mechanical/technical errors or graft quality, resulting in complete occlusion.[2,22] There have been a limited number of investigations detailing the association between vein GF and clinical outcome. Lopes et al[23] report no difference in death but greater repeat revascularization in patients with vein GF. Our results are consistent; however, we note a higher incidence of vein GF in non-LAD artery anastomosis. This may relate to the anatomical distance from the aorta in conduits to the posterior descending artery or obtuse marginal arteries, where a long course from the aortic anastomosis to the distal anastomosis may be seen. There are also technical challenges with performing an anastomosis to the posterior descending artery or obtuse marginals given their recalcitrant location. The majority of vein GF was treated with PCI to the native vessel territory, as adverse events and durability for PCI in saphenous vein grafts are significantly worse than in native coronary vessels.[24] Smaller native artery caliber ($\leq$1.5 mm) appeared to be a strong predictor of vein GF. This finding is consistent with prior studies.[18,25-27] Likely, this is due to impaired distal run-off in smaller coronary arteries, predisposing to flow stasis and graft thrombosis. Perhaps in patients with a higher risk of vein GF, dual antiplatelet therapy could be considered,[28] although this remains speculative and requires further investigation.

In comparison to "vein graft failure only", we have demonstrated worse long-term survival with "arterial graft failure". Even when accounting for repeat revascularization of the corresponding territory, similar results were noted. Thus, our data support the need for long-term patency of arterial conduits, which, in our cohort, was most commonly the LIMA graft. Given the survival advantage with this particular conduit, particular focus on the LIMA to LAD artery anastomosis needs to be emphasized to ensure long-term patency. Given the increasing prevalence of "hybrid" operation rooms, consideration to immediate angiography of the conduit before sternal closure may ensure technical and angiographic success.[29,30]

Limitations

This study has several limitations. We only assessed patients with a clinical indication for coronary angiography after CABG surgery. In these patients, higher rates of arterial and vein GF were seen compared to documented GF rates in patients undergoing routine coronary angiography within a similar time frame post-CABG surgery.[1,20,31] This is probably due to the inherent sampling bias introduced by only examining clinically indicated cardiac catheterizations. Accepting this shortcoming, our study reflects contemporary real-world clinical practice where patients do not undergo routine coronary and bypass graft angiography. Reduced patient survival was noted with "arterial graft failure" recognizing a large proportion of these patients had both arterial and vein GF. The proportional utilization of RIMA and free radial arterial conduits in this study was low precluding any meaningful analysis of arterial type GF and outcomes. As occurs in clinical practice, it may be difficult to definitively establish the "culprit" (graft failure vs progression of native disease) for ACS presentation and decisions on repeat revascularization are individualized based on a heart team discussion. The utilization of fractional flow reserve to identify flow-limiting graft stenosis was not performed. As such, the significance of stenoses was determined by the physician performing angiography. We also did not have data on intraoperative graft flow rates, which has previously been associated with vein GF. Information on discharge medication and compliance to therapies was not readily available. Finally, information on differences in surgical techniques, surgical training, and simulation was not collected.

In summary, ACSs appear to be the predominant reason for clinically driven coronary and bypass graft angiography at 1 year after CABG surgery. Of these patients, GF is common with arterial conduit failure (LIMA failure) portending worse long-term survival. Particular focus in the perioperative period should be undertaken to protect arterial conduits, as the long-term survival advantage becomes compromised once occluded.

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