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

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Background—The internal mammary artery (IMA) is the preferred conduit for bypassing the left anterior descending (LAD) artery in patients undergoing coronary artery bypass grafting. Systematic evaluation of the frequency and predictors of IMA failure and long-term outcomes is lacking.

Methods and Results—The Project of Ex-vivo Vein Graft Engineering via Transfection (PREVENT) IV trial participants who underwent IMA-LAD revascularization and had 12- to 18-month angiographic follow-up (n=1539) were included. Logistic regression with fast false selection rate methods was used to identify characteristics associated with IMA failure (≥75% stenosis). The relationship between IMA failure and long-term outcomes, including death, myocardial infarction, and repeat revascularization, was assessed with Cox regression. IMA failure occurred in 132 participants (8.6%). Predictors of IMA graft failure were LAD stenosis <75% (odds ratio, 1.76; 95% confidence interval, 1.19–2.59), additional bypass graft to diagonal branch (odds ratio, 1.92; 95% confidence interval, 1.33–2.76), and not having diabetes mellitus (odds ratio, 1.82; 95% confidence interval, 1.20–2.78). LAD stenosis and additional diagonal graft remained predictive of IMA failure in an alternative model that included angiographic failure or death before angiography as the outcome. IMA failure was associated with a significantly higher incidence of subsequent acute (<14 days of angiography) clinical events, mostly as a result of a higher rate of repeat revascularization.

Conclusions—IMA failure was common and associated with higher rates of repeat revascularization, and patients with intermediate LAD stenosis or with an additional bypass graft to the diagonal branch had increased risk for IMA failure. These findings raise concerns about competitive flow and the benefit of coronary artery bypass grafting in intermediate LAD stenosis without functional evidence of ischemia.

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The internal mammary artery (IMA) conduit is considered the gold standard for bypassing the left anterior descending (LAD) coronary artery in patients undergoing coronary artery bypass graft surgery (CABG).[1] The IMA-to-LAD graft has been shown to be more durable than other arterial and vein grafts and coronary stents for the treatment of LAD disease, with patency rates >90% at the 5-year follow-up.[2–6] Additionally, most of the survival benefit observed in patients who undergo CABG compared with percutaneous coronary intervention or medical management might be attributed to the patency of the IMA-to-LAD graft.[7,8] Despite the common use of the graft, high-quality studies

Editorial see p 111
Clinical Perspective on p 138

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of IMA graft failure are limited in number and small in sample size, lack systematic angiographic evaluation in all participants regardless of symptoms, or have limited clinical follow-up.[9,10] We therefore sought to identify and characterize factors associated with IMA graft failure and to investigate the relationship between IMA graft failure and clinical outcomes in patients undergoing isolated CABG using data collected in the Project of Ex-vivo Vein Graft Engineering via Transfection (PREVENT) IV trial.[11,12]

Methods

Study Population

The design, primary results, and long-term follow-up of PREVENT IV have been published previously.[11–13] In short, PREVENT IV was a double-blind, multicenter, randomized, clinical trial in which edifoligide (an E2F transcription factor decoy) was compared with placebo in the ex vivo treatment of vein grafts during CABG surgery. The trial enrolled 3014 participants at 107 US sites between 2002 and 2003. The PREVENT IV protocol was approved by the institutional review boards of participating medical centers, and all patients gave informed consent. Participants were required to have primary, isolated CABG with at least 2 planned vein grafts and without comorbid illness that would significantly limit life expectancy. The first 2400 participants enrolled in PREVENT IV were assigned to an angiographic cohort; of this group, 1829 patients returned for scheduled coronary angiography at 12 to 18 months after surgery. Per protocol, participants in the angiographic cohort who underwent angiography for clinical reasons and had graft failure before programmed angiographic follow-up were exempt from additional angiography. As shown in Figure 1, the starting population of the present analysis was the complete PREVENT IV trial population. From this cohort, we excluded 269 participants in whom an IMA graft was not used to revascularize the LAD, diagonal branches, or any graft combination that involved the LAD or diagonal branches. Participants (n=559) who were not enrolled in the angiographic cohort were also excluded. Of the remaining cohort of 2186 participants, 481 were excluded because of loss to follow-up and 79 because of death before angiographic follow-up. Of the remaining 1626 participants who underwent cardiac catheterization, 87 were excluded because of missing data on IMA patency. The remaining 1539 participants subsequently represented the study population for the main analysis.

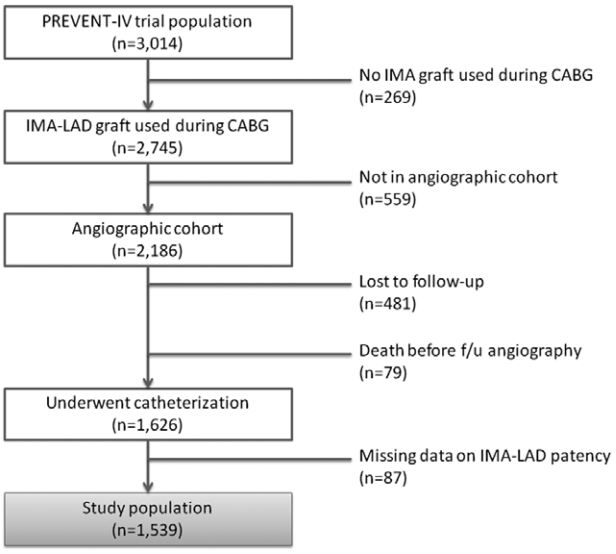

Figure 1. Flow diagram of study population. CABG indicates coronary artery bypass surgery; f/u, follow-up; IMA-LAD internal mammary artery–left anterior descending artery; and PREVENT IV, Project of Ex-vivo Vein Graft Engineering via Transfection IV.

Outcomes, Definitions, and Event Adjudication

The primary outcome of this study was IMA graft failure, defined as stenosis of at least 75% or occlusion of the diameter of the lumen of the IMA graft, which was assessed by quantitative coronary angiography 12 to 18 months after surgery or earlier when performed as part of medical care and IMA graft failure was found. Because 79 participants died before angiography, we performed a sensitivity analysis in which IMA graft failure was defined as a composite of angiographically determined graft failure or death before angiography. The secondary outcomes were clinical outcomes among participants who did or did not have IMA graft failure; these included death and composites of death or myocardial infarction (MI) or death, MI, or repeat revascularization through 5 years from the index CABG. All angiograms were analyzed at a core laboratory (PERFUSE Angiographic Core Laboratory, Boston, MA). Clinical events were assessed annually through mail and telephone contact with the participants. Five-year follow-up was complete in 95.1% of participants; consent for participation was withdrawn by 2.0% of participants, and an additional 2.9% were lost to follow-up. For reported events, medical records were collected and adjudicated by an independent clinical events committee using prespecified criteria.

Statistical Analysis

Baseline characteristics and medications among participants with and without IMA graft failure were summarized by medians and 25th and 75th percentiles for continuous variables and by percentages for categorical variables. Fast false selection rate in forward selection was used to select variables associated with graft failure in a logistic regression model. Fast false selection rate is a variable selection method that controls the rate that uninformative variables enter the model.[14] Candidate variables were identified on the basis of existing literature and investigator opinion, including age, sex, history of diabetes mellitus, renal failure, hypercholesterolemia, smoking, previous MI, ejection fraction, elective surgery, preoperative maximum stenosis of LAD, preoperative maximum stenosis of left main coronary artery, cardiopulmonary bypass, bypass graft quality, target artery quality, sequential versus single graft, and additional bypass graft to a diagonal branch of LAD. Graft quality and target artery quality were graded as good, fair, or poor on the basis of qualitative criteria by the surgeon at the time of surgery. Linearity assumptions were assessed for continuous variables, and transformations were applied when applicable. Odds ratios and 95% confidence intervals (CIs) were used to assess the relationship between the model variables and IMA graft failure.

Of those participants in the angiographic cohort who had an IMA graft, 481 were lost to follow-up, and 79 died before angiography. Two sensitivity analyses were performed to address the biases introduced by competing risk or inability to perform angiographic follow-up. First, we assessed the composite end point of death or IMA graft failure. Second, we used inverse probability weighting for missing data so that participants were weighted according to their estimated probability of having observed angiographic follow-up.[15]

Event rates for postangiography clinical outcomes in participants with and without IMA graft failure were calculated with Kaplan-Meier methods among participants free of events at angiographic follow-up. When the postangiography clinical outcomes were assessed, the day of the angiography was considered day 0. Hazard ratios and 95% CIs were used to assess the relationship of per-patient IMA graft failure and clinical outcomes and were calculated with the Cox regression model. Covariates adjusted for in the postangiography clinical outcome models included variables that were associated with IMA graft failure and death before angiography. There was a strong indication of nonproportional hazards in the relationship between IMA graft failure and the composite outcome of death, MI, or revascularization. Immediately after protocol-mandated angiography, the rate of revascularization was substantially higher than during longer follow-up. To account for this, we estimated different hazard ratios for the periods before and after 14 days for outcomes containing revascularization.

Table 1. Clinical, Angiographic, and Procedural Characteristics

	Total Cohort With IMA-LAD Graft (n=2745)	Angiographic Population With IMA-LAD Grafts (n=1539)	Angiographic Population With IMA-LAD Graft Failure (n=132)	Angiographic Population Without IMA-LAD Graft Failure (n=1406)
Preoperative characteristics				
Age,* y	63 (56, 70)	63 (55, 69)	63 (56, 68)	63 (55, 69)
Male, %	80.1	82.1	77.3	82.5
BMI,* kg/m^2	29 (26, 33)	29 (26, 42)	29 (26, 33)	28 (26, 31)
Weight,* kg	88 (77, 100)	88 (78, 100)	84 (73, 93)	89 (79, 100)
Race, %				
White	91.0	90.8	85.6	91.3
Black	4.4	4.6	12.1	3.8
Other	4.6	4.6	2.3	4.8
Current smoker, %	22.3	20.9	25.0	20.5
Diabetes mellitus, %	38.0	36.0	25.0	37.1
Hypercholesterolemia, %	76.9	77.9	73.5	78.3
Hypertension, %	74.7	72.8	66.7	73.4
Congestive heart failure, %	9.5	6.6	5.3	6.8
Renal failure, %	2.2	1.1	1.5	1.1
Cerebrovascular disease, %	12.3	8.6	5.3	8.9
Peripheral vascular disease, %	11.6	10.1	6.8	10.4
Chronic lung disease, %	15.0	12.9	14.4	12.8
Previous MI, %	41.9	42.1	47.7	41.5
Previous PCI, %	25.4	27.0	29.5	26.8
History of cancer, %	7.9	7.5	11.4	7.1
Ejection fraction,* %	50 (40, 60)	50 (40, 60)	50 (45, 60)	50 (40, 60)
Angiographic characteristics				
LAD stenosis, %				
<50%	5.3	5.1	8.4	4.9
50%–74%	18.6	17.6	24.4	16.9
75%–95%	48.6	47.7	40.5	48.4
95%–99%	17.5	18.5	21.4	18.2
100%	10.1	11.1	5.3	11.7
LM stenosis, %				
0%	40.0	43.5	45.8	43.2
<50%	33.3	29.3	30.5	29.2
50%–74%	17.3	17.6	15.3	17.8
75%–95%	7.9	8.3	8.4	8.3
95%–99%	1.3	1.2	0.0	1.4
100%	0.1	0.2	0.0	0.2
Diseased vessels, n*	2 (2, 3)	2 (2, 3)	2 (2, 3)	2 (1, 3)
Procedural characteristics				
Elective procedure, %	…	51.1	47.3	51.4
Cardiopulmonary bypass, %	78.3	78.5	75.8	78.7
Left IMA use, %	99.4	99.3	98.5	99.4
Free IMA graft, %	1.4	1.2	2.6	1.1
Sequential IMA graft, %	5.4	5.3	7.6	5.0
Graft quality, %				
Good	86.4	91.3	86.5	91.8
Fair	7.9	8.1	11.1	7.8
Poor	0.7	0.6	2.4	0.5

(*Continued*)

Table 1. Continued

	Total Cohort With IMA-LAD Graft (n=2745)	Angiographic Population With IMA-LAD Grafts (n=1539)	Angiographic Population With IMA-LAD Graft Failure (n=132)	Angiographic Population Without IMA-LAD Graft Failure (n=1406)
Target artery quality, %				
Good	67.7	70.0	74.4	69.6
Fair	22.5	22.0	18.6	22.3
Poor	8.0	8.0	7.0	8.1
Surgery duration,* min	232 (194, 272)	227 (191, 270)	227 (191, 270)	231 (192, 274)
CPB duration,* min	100 (80, 123)	99 (80, 122)	99 (80, 121)	102 (81, 123)
Time on ventilator, * h	7 (5, 13)	7 (5, 12)	7 (4, 12)	8 (5, 14)
ICU length of stay,* h	26 (22, 47)	25 (21, 44)	25 (21, 44)	27 (22, 48)
Hospital length of stay,* d	6 (5, 8)	6 (5, 7)	6 (5, 7)	6 (5, 8)

BMI indicates body mass index; CPB, cardiopulmonary bypass; ICU, intensive care unit; IMA-LAD, internal mammary artery–left anterior descending artery; LM, left main coronary artery; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

*Median (interquartile range).

Results

Baseline and Perioperative Characteristics

The baseline clinical, angiographic, and perioperative characteristics of the PREVENT IV total and angiographic populations using an IMA-LAD graft are displayed in Table 1. Of the IMA grafts included in this analysis, 99.4% were left IMA grafts. Baseline and surgical characteristics tended to be similar in the angiographic cohort with IMA use compared with the overall PREVENT IV trial population who received an IMA graft (n=2745). Among the angiographic population with IMA use (n=1539), a total of 132 (8.6%) had IMA graft failure at follow-up (angiogram, 350–563 days after randomization). Among those with IMA graft failure, 68 had an IMA graft stenosis of 75% to 95%, 3 had a subtotal stenosis (95%–99%), and 61 had an occluded IMA graft. In general, participants who had IMA graft failure less frequently had diabetes mellitus, had less severe stenosis of the LAD, and had similar target artery quality but worse graft quality as assessed by the operator during surgery. Other clinical and procedural characteristics were similar. Participants with IMA graft failure had similar surgery duration and in-hospital recovery, as measured by intensive care and hospital lengths of stay.

Medications at 1 Year

At 1 year, similar proportions of patients with and without IMA graft failure were taking aspirin (95.3% and 94.4%, respectively; P=0.68), β-blockers (76.6% and 73.2%, respectively; P=0.41), nitrates (8.6% and 5.6%, respectively; P=0.16), and statins (82.8% and 80.9%, respectively; P=0.59). More patients with than without IMA failure were taking clopidogrel or ticlopidine (33.6% and 20.8%, respectively; P=0.0008), and fewer patients with than without IMA failure were taking an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker (44.5% and 57.2%, respectively; P=0.006).

Predictors for IMA Graft Failure

As shown in Table 2, the absence of diabetes mellitus, less severe preoperative LAD stenosis, and an additional bypass graft to the diagonal were associated with IMA graft failure at follow-up. When an alternative approach was used in which the outcome included IMA graft failure or death before angiography, preoperative LAD stenosis and having an additional bypass graft to the diagonal remained associated with IMA graft failure, but not having diabetes mellitus did not. A sensitivity analysis using inverse-probability-weighted methods yielded similar results (Table I in the online-only Data Supplement).

Events Between CABG Surgery and Angiographic Follow-Up

Of the 132 participants with IMA graft failure, 4 had an MI between the CABG surgery and angiographic follow-up, and 9 had a repeat revascularization procedure; of these procedures, 5 were attributable to IMA graft failure. Of the 1407 participants without IMA graft failure, MI occurred in 14 and repeat revascularization in 45 between the CABG surgery and angiographic follow-up.

Table 2. Predictors for IMA-LAD Graft Failure

	OR	95% CI	P
IMA graft failure*			
Preoperative LAD stenosis (<75%)	1.86	1.26–2.75	0.002
Not having diabetes mellitus	1.86	1.22–2.81	0.004
Additional bypass graft to diagonal	1.92	1.33–2.76	0.001
IMA graft failure or death before catheterization†			
Age, per year	1.03	1.01–1.05	0.001
Female sex	1.55	1.09–2.20	0.015
Hypercholesterolemia	0.67	0.48–0.94	0.019
Renal failure	3.57	1.45–8.84	0.006
Preoperative LAD stenosis (<75%)	1.49	1.07–2.08	0.017
Current smoker	1.48	1.02–2.13	0.038
Additional bypass graft to diagonal	1.49	1.11–2.01	0.009

CI indicates confidence interval; IMA, internal mammary artery; LAD, left anterior descending artery; and OR, odds ratio.

*IMA graft failure model was built on data from 1396 participants with complete data on all candidate variables and was fit on 1538 participants with complete data on the chosen variables.

†The predictive model for the composite of IMA graft failure or death before catheterization was built on 1467 participants with complete data on all candidate variables and was fit on 1616 participants with complete data on the chosen variables.

IMA Graft Failure and Clinical Outcomes

Duration of follow-up was 1815±245 days in participants with IMA failure and 1813±239 days in those without IMA failure. The occurrence of clinical events from follow-up angiography among participants with and without IMA graft failure is illustrated in Figure 2. As shown, a markedly higher rate of the composite of death, MI, or repeat revascularization was found within the first 14 days after angiography among participants with IMA graft failure compared with those without IMA graft failure (14.4% versus 4.9%; adjusted hazard ratio, 3.92; 95% CI, 2.30–6.68; $P<0.0001$). After the first 14 days, a trend toward more events was observed after IMA graft failure over 4 years of follow-up (adjusted hazard ratio, 1.45; 95% CI, 0.85–2.48; $P=0.17$). This association was driven predominantly by an association between IMA graft failure and repeat revascularization, with less of a relationship between IMA graft failure and either death or the composite of death or MI (Table 3). When assessing outcomes by IMA graft stenosis severity (Table 4), we found that participants with total IMA graft occlusion were more likely to have a subsequent cardiovascular event (45.9% versus 36.8%), including death (8.2% versus 2.9%), compared with participants with nonoccluded, failed IMA grafts.

Discussion

In the present study, we sought to identify characteristics associated with IMA graft failure and to determine its relationship with subsequent clinical outcomes. We found that patients with less severe preoperative LAD stenosis and those who had an additional bypass graft placed to the diagonal branch were at higher risk for IMA graft failure. When the analysis was restricted to those who completed angiographic follow-up, the absence of diabetes mellitus was also associated with IMA graft failure. IMA graft failure led to increased risk for early adverse clinical events, mostly repeat revascularization, whereas the association with long-term clinical outcomes was less clear.

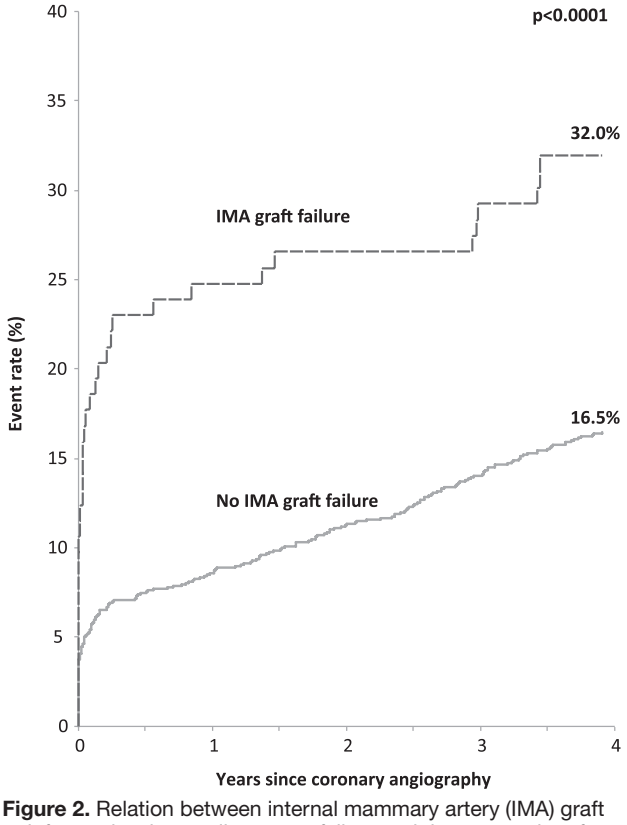

Figure 2. Relation between internal mammary artery (IMA) graft to left anterior descending artery failure and the composite of death, myocardial infarction, or repeat revascularization over 4 years after angiographic follow-up.

To the best of our knowledge, this analysis represents the first robust assessment of IMA graft failure and long-term clinical outcomes in a large cohort of patients undergoing CABG surgery with systematic angiographic follow-up. Evidence from previous studies on predictors of IMA graft failure is conflicting with respect to the relation between IMA graft failure and the severity of the stenosis in native vessels. Angiographic predictors for IMA graft failure were assessed by Manninen et al[16] and by Gaudino et al[17] over several years of follow-up, and the severity of stenosis of the native vessel was not found to influence the patency rate of the IMA bypass graft. In contrast, 2 other small studies have suggested that arterial graft failure was associated with low-grade recipient artery stenosis and competitive flow.[18,19] The study with the most clinical impact was performed by Berger et al.[9] In that study, the authors assessed the long-term patency of IMA bypass grafts in 273 grafts in 230 patients. IMA graft failure was defined as diffuse and >95% conduit narrowing (“string sign”), and angiographic follow-up was performed for clinical reasons. Using stepwise multivariable logistic regression, the authors found that lower-diameter stenosis of the native artery was the only significant predictor for IMA graft failure (odds ratio, 21.5; 95% CI, 5.18–64.38). This observation was also found when the analysis was restricted to IMA-LAD grafts. Despite the differences in the definitions of IMA graft failure, the findings of this study are strikingly similar to the results of our study and imply that the decision to use an IMA should be carefully considered in light of the severity of the stenosis of the target vessel. In addition, our study shows that one should also take into account the risk of introducing “competitive flow” when placing an additional bypass graft to the diagonal branch of the LAD. Our study clearly delineates the negative impact on the patency of the IMA-LAD graft, as illustrated by an almost 2 times higher occurrence of graft failure.

Adaptation of the IMA Graft to the Coronary Circulation

The benefit of IMA grafts over vein grafts has been observed consistently regardless of age, sex, stenosis severity, or left ventricular function, with widening survival differences over time.[7,20,21] A number of risk factors, including hypercholesterolemia, lipoproteins, diabetes mellitus, smoking, age, and prior chest radiation (which may negatively influence the quality of the arterial graft), have been identified to result in IMA graft failure. There are a number of reasons why IMA graft failure may be less common than for other grafts. During harvesting and suturing, the IMA graft is more resilient after surgical trauma because of its muscular wall and abundant collateral blood supply; therefore, endothelial function and vascular wall function are better preserved compared with vein grafts.[22] In addition, the diameter of the IMA graft is generally closely matched with the diameter of the LAD, which

Table 3. Relationship of IMA Graft Failure to Clinical Outcomes

Outcome	No IMA Graft Failure, n (%)	IMA Graft Failure, n (%)	HR	95% CI	*P*
Death, MI, or revascularization					
≤14 d	84 (5.5)	19 (14.4)	3.92	2.30–6.68	<0.0001
>14 d	172 (11.8)	17 (15.0)	1.45	0.85–2.48	0.17
Death or MI	118 (7.7)	14 (10.6)	1.29	0.66–2.50	0.46
Death	83 (5.4)	7 (5.3)	1.10	0.50–2.39	0.82

Outcomes were adjusted for age, sex, hypercholesterolemia, renal failure, preoperative left anterior descending artery stenosis, current smoker, and diabetes mellitus. These models were fit on 1355, 1400, and 1480 participants, respectively, who had complete data on the variables for which the model was adjusted. CI indicates confidence interval; HR, hazard ratio; IMA, internal mammary artery; and MI, myocardial infarction.

limits flow turbulences that create frictional force and shear stress–induced endothelial injury. However, these differences do not fully explain the superior patency and resistance to atherosclerosis of the IMA graft compared with vein grafts and coronary arteries. A number of structural and physical properties of the IMA graft are additionally thought to play a role.[23] The endothelium of the IMA may play a key role because it is markedly different from other bypass grafts. Specifically, it has fewer fenestrations and lower intracellular junction permeability, which may prevent lipoproteins from entering the subendothelial space.[24] In addition, the endothelial cells of the IMA are rich in heparin sulfate and endothelial nitric oxide synthase. When endothelial nitric oxide synthase is expressed, it produces low concentrations of nitric oxide, which preserves good endothelial function and integrity, allows arterial remodeling in response to flow (enlargement of arterial lumen or intimal thickening for reduction in vessel lumen), and contributes to the antithrombotic properties and endothelial homeostasis, which in turn confer protection from atherosclerosis.[24,25]

Mechanisms of IMA Failure

When IMA graft failure occurs, technical error is the most common cause in the early postoperative period. In the subsequent weeks to months, localized neointimal hyperplasia may occur at the cleft between the native artery and the IMA graft at the anastomotic suture site, on the hood and on the floor of the native LAD, which can result in a localized stenosis.[24] Performing an IMA bypass on a low-grade LAD stenosis or supplying an infarcted LAD territory leads to competitive flow and low flow, respectively, and adversely affects IMA graft patency ("disuse atrophy"). Causes for late (and rare) IMA failure include progressive fibrointimal proliferation and atherosclerosis either in the IMA graft or in the native LAD vessel.[23] In this study, we assessed IMA graft patency at 12 to 18 months. Unfortunately, we know little about when the graft actually failed.

Need for Physiological Assessment in Angiographic Intermediate Lesions

Our study raises concerns about the performance of CABG with the use of IMA in the treatment of native vessels with only mild or moderate stenosis. Although competitive flow between native and grafted coronary vessels is likely at play here, the use of angiography as a surrogate for physiological impact of these intermediate severe lesions is imprecise.[26] The measurement of hyperemic translesional pressure ratio, or fractional flow reserve, has been applied to study coronary bypass graft failure and has shown that lower graft occlusion rates are found in participants with fractional flow reserve–assessed functionally significant lesions compared with functionally nonsignificant lesions (n=164; 9% versus 21% at 1 year).[27] The angiographic percentage diameter stenosis in this study displayed a similar but less precise correlation with graft failure. Although unnecessary grafting of functionally nonsignificant lesions is believed to be of little clinical consequence, it may affect the decision to perform CABG instead of percutaneous coronary intervention when it involves the LAD in the setting of multivessel disease.

Limitations

The present study has a number of limitations. First, we measured IMA graft failure at 12 to 18 months after CABG, which excluded cases in which failure would have led to a fatal outcome before angiography (ie, those with diabetes mellitus). We tried to account for this bias by including early deaths in the end point for IMA graft failure. Second, the timing of IMA graft failure before angiography was unknown, and whether this coincided with nonfatal events that occurred between

Table 4. Number of Clinical Events Among Participants With IMA Graft Failure (≥75% Stenosis) by LAD Stenosis Severity

	IMA Graft Stenosis at Follow-Up, n (%)			
	<75% (n=1407)	75%–95% (n=68)	95%–99% (n=3)	100% (n=61)
Death, MI, or repeat revascularization	271 (19.3)	25 (36.8)	1 (33.3)	28 (45.9)
Death or MI	104 (7.4)	6 (8.8)	0	8 (13.1)
Death	76 (5.4)	2 (2.9)	0	5 (8.2)
MI	30 (2.1)	4 (5.9)	0	3 (4.9)
Repeat revascularization	195 (13.9)	21 (30.9)	1 (33.3)	23 (37.7)

IMA indicates internal mammary artery; LAD, left anterior descending; and MI, myocardial infarction.

CABG surgery and angiographic follow-up is unknown. Third, physiological assessment was not performed in angiographic intermediate lesions, which would have provided the ability to determine whether a lesion was flow limiting and whether competitive flow was a cause for IMA graft failure. Fourth, protocol-driven angiography may have influenced revascularization after angiography and subsequent clinical events. Fifth, missing data resulting from loss of follow-up might also have affected our results. Lastly, the study may have been underpowered to detect a modest but clinically important relationship between IMA graft failure and subsequent long-term clinical outcomes.

Conclusions

We found that IMA graft failure was common and that bypassing intermediate-grade LAD stenosis or introducing competitive flow by placing an additional bypass graft to the diagonal branch significantly increased the risk of subsequent IMA graft failure. IMA graft failure at 12 to 18 months was associated with higher rates of early repeat revascularization but not long-term subsequent clinical outcomes. The decision to perform CABG with the use of an IMA graft should be made carefully when coronary angiography indicates an intermediate LAD lesion, and the use of functional assessment of ischemia may be warranted.

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Disclosures

Disclosures for Drs Alexander, Peterson, and Lopes are available at https://dcri.org/about-us/conflict-of-interest. Dr Harrington has received research grants and consultant/advisory fees from Merck & Co. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

In this study, the frequency, predictors, and impact of internal mammary artery (IMA) graft failure were evaluated in patients undergoing coronary artery bypass grafting. Using data from the Project of Ex-vivo Vein Graft Engineering via Transfection (PREVENT) IV trial, we identified 1539 participants with IMA–left anterior descending (LAD) graft and protocol angiography at 12 to 18 months after the index procedure. Our main findings included that IMA graft failure (defined as ≥75% stenosis) occurred in 132 participants (8.6%) at angiographic follow-up. Independent predictors of IMA graft failure were low-grade LAD stenosis, additional bypass graft to the diagonal branch, and not having diabetes mellitus. LAD stenosis and additional diagonal graft, but not diabetes mellitus, remained predictive of IMA graft failure in an alternative model that included IMA failure or death before angiography as the outcome. IMA failure was associated with a significantly higher incidence of subsequent acute (within 14 days of angiography) clinical events, mostly as a result of a higher rate of repeat revascularization. This study represents the first robust assessment of IMA graft failure and long-term clinical outcomes in a large cohort of patients undergoing coronary artery bypass grafting surgery with systematic angiographic follow-up, regardless of symptom status. Our study raises concerns about the performance of coronary artery bypass grafting with the use of IMA in the treatment of native vessels with only mild or moderate stenosis, as well as the use of an additional bypass graft to the diagonal branch. Thus, it confirms findings from smaller studies that have suggested that the severity of LAD stenosis and competitive flow are of key importance for patency of the IMA-LAD graft, which is thought to be responsible for the survival benefit observed in clinical studies that compared coronary artery bypass grafting with multivessel percutaneous coronary intervention or medical therapy.

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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

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SUPPLEMENTAL MATERIAL

Supplemental Table. Predictors for IMA-LAD Graft Failure, With Inverse Probability Weighting for Missingness

	OR	95% CI	P
IMA graft failure*			
Preoperative LAD stenosis (<75%)	1.99	1.40-2.85	<0.001
Not having diabetes	1.98	1.35-2.89	0.001
Additional bypass graft to diagonal	2.15	1.52-3.03	<0.001
Sequential IMA graft	2.09	1.11-3.93	0.022
IMA graft failure or death prior to cath†			
Age, per year	1.03	1.01-1.04	0.002
Hypercholesterolemia	0.71	0.53-0.97	0.029
Renal failure	3.14	1.50-6.57	0.002
Preoperative LAD stenosis (<75%)	1.63	1.20-2.20	0.002
Current smoker	1.55	1.11-2.16	0.011
Additional bypass graft to diagonal	1.47	1.11-1.94	0.007

IMA-LAD indicates internal mammary artery-left anterior descending artery.

*IMA graft failure model was built on data from 1396 participants with complete data on all candidate variables and was fit on 1538 participants with complete data on the chosen variables.

†The predictive model for the composite of IMA graft failure or death prior to cath was built on 1467 participants with complete data on all candidate variables and was fit on 1616 participants with complete data on the chosen variables.