

Comparison of Outcomes and Frequency of Graft Failure With Use of Free Versus In Situ Internal Mammary Artery Bypass Conduits (from the PREVENT IV Trial)



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Although in situ internal mammary artery (is-IMA) grafting remains the most frequent conduit in coronary artery bypass grafting (CABG), circumstances may necessitate free grafting of the IMA (f-IMA), though differences in outcomes have not been fully characterized. The purpose of this study was to compare clinical and angiographic outcomes of is-IMA versus f-IMA coronary bypass grafts in patients who underwent elective CABG surgery. In 1,829 patients in the angiographic cohort of PREVENT IV, 1,572 (85.9%) had at least 1 IMA graft; of these, 34 (2.2%) patients had at least 1 f-IMA graft and 1,538 (97.8%) had at least 1 is-IMA graft without additional f-IMA grafts. Characteristics of patients, procedure, and grafts/targets were compared between cohorts. Primary endpoints included death, myocardial infarction, and revascularization, as well as incidence of graft failure (stenosis >75%) on angiography at 12-18 months postoperatively. Patients receiving is-IMA grafts were more often of white race and higher weight. Aortic cross-clamp time was shorter in the f-IMA cohort (39.5 vs 57.0 min, $p = 0.04$), but duration of bypass was similar (93.5 vs 100.0 minutes, $p = 0.793$). Of the in situ grafts, 97.3% were via the left internal mammary artery (LIMA), 86.6% were of good quality, and the left anterior descending (LAD) was bypassed in 88.2%. This compares with free grafts, which were via the LIMA in 68.0%, of good quality in 96.1%, and bypassed the LAD in 58.8% and first obtuse marginal (OM1) in 23.5%. Rates of death, myocardial infarction, and revascularization were similar between groups. The rate of graft failure was higher in f-IMA grafts (23.3%) compared with is-IMA grafts (8.5%; $p < 0.01$). Although clinical outcomes were similar with use of free versus in situ IMA grafts, higher rates of graft failure were encountered with use of the f-IMA graft. In conclusion, in situ grafts should be the preferred conduit for patients who undergo CABG surgery. © 2018 Elsevier Inc. All rights reserved. (Am J Cardiol 2019;123:571–575)

The superior long-term patency of the internal mammary artery (IMA) in coronary artery bypass grafting (CABG) compared with autologous vein grafting has been well established, resulting in this being the preferred conduit in patients undergoing CABG.^{1–5} Historically, the preferred technique involved mobilization of the left IMA as a

vascular pedicle about its origin from the subclavian artery, as an in situ graft (is-IMA), with a single anastomosis to the distal coronary target.⁶ Although nuances to this technique have been previously studied, such as pedicled versus skeletonized graft techniques, and unilateral versus bilateral IMA grafting, use of the IMA as a free graft (f-IMA) has been insufficiently characterized in the literature, and few studies have directly compared clinical or angiographic outcomes of f-IMA and is-IMA grafts.^{7–9} With the longstanding preference toward arterial grafting in CABG and a revitalized interest in the use of alternative arterial conduits, further study is warranted to determine the outcomes and role of free IMA grafting. As such, the purpose of this study was to compare the patient populations, technical characteristics, and clinical and angiographic outcomes of patients who underwent free versus in situ IMA grafting in CABG.

Methods

This study was reviewed and approved by the Institutional Review Board of the Duke Clinical Research Institute, and the need for individual patient consent was

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waived. Study data were extracted for post hoc analysis from PREVENT IV, a randomized controlled trial that included clinical and catheter-based angiographic outcomes of patients who underwent CABG.¹⁰ Inclusion criteria for PREVENT IV consisted of adult patients aged 18-80 years who underwent a first isolated CABG for atherosclerotic coronary artery disease with at least 2 planned autogenous vein grafts. Patients were excluded on the basis of previous CABG or valve surgery, planned concomitant valve surgery, presence of vasculitis or hypercoagulable state, comorbidities predictive of survival <5 years, or enrollment in another trial. The present study utilized a limited dataset from PREVENT IV, which included and sorted patients into 2 comparison groups: (1) the free IMA (f-IMA) cohort, defined as patients who received at least 1 f-IMA graft with or without at least 1 concomitant in situ IMA (is-IMA) graft ($n = 34$), and (2) the is-IMA cohort, defined as patients who received at least 1 is-IMA graft and no concomitant f-IMA grafts ($n = 1,538$). Classification of “free” versus “in situ” IMA grafts at the time of PREVENT IV data entry was at the discretion of the investigator.

Primary clinical endpoints included the rates of death, myocardial infarction (MI), and revascularization. The second primary clinical endpoint was graft failure, as defined by graft stenosis >75% on angiographic follow-up at 12-18 months postoperatively. Graft failure was specific to the IMA used in the index procedure, whereas revascularization was inclusive of any vessel during follow-up. Angiographic data were sent to a core laboratory for centralized analysis. Functional imaging studies were not utilized in lieu of cardiac catheterization to determine incidence and degree of stenosis.

Standard univariable analysis was used to compare the f-IMA and is-IMA cohorts on the basis of patient and technical characteristics. Continuous variables were presented as medians with interquartile ranges and compared using the Wilcoxon rank-sum test. Categorical variables were presented as counts with percentages and compared using either the chi-square or Fisher's exact test, where appropriate. Rates of death, MI, and revascularization were assessed using an unadjusted Cox proportional hazards model. Results were expressed in the form of Kaplan-Meier event rates, hazard ratios (with 95% confidence intervals), and the associated p values. Rates of graft failure were expressed as raw frequencies with odds ratios and corresponding p values.

Results

Patient demographics are depicted in Table 1. Those who underwent f-IMA grafting tended to have races listed as “other” and lower body weight but were otherwise similar. New York Heart Association class, left ventricular ejection fraction, and preoperative vasoactive and anticoagulant medication administration was statistically similar between cohorts.

In regard to operative details, the distribution of elective versus urgent/emergent cases was similar between groups (Table 1). Although the overall duration of surgery and cardiopulmonary bypass times were similar between cohorts, patients who underwent f-IMA grafting had lower

aortic cross-clamp times (39.5 vs 57.0 minutes, $p = 0.04$) and were less likely to undergo surgery utilizing cardiopulmonary bypass (52.9% vs 80.3%, $p < 0.001$). Target distributions, graft quality, and target quality are represented in Table 1.

The rate of death per 100 patient-years of follow-up was 3.32 and 2.27 for f-IMA and is-IMA grafts, respectively (HR 1.46, 95% CI 0.60 to 3.54, $p = 0.41$; Table 2). The incidence of graft failure at 12 to 18 months was 23.3% in f-IMA grafts compared with 8.5% in is-IMA grafts (OR 3.27, 95% CI 1.38 to 7.79, $p < 0.01$). In grafts targeting the LAD, graft failure occurred in 14.8% (4/27) of f-IMA grafts compared with 7.9% (99/1255) of is-IMA grafts. At 5 years, 32 (2%) patients were lost to follow-up, 15 (1%) withdrew consent, and 1,525 (97%) completed the study out of a total of 1,572 in the original cohort.

Discussion

While clinical and anatomic considerations often dictate the selection of and technique for anastomosis of vascular conduits in CABG, use of the IMA either as a free or in situ graft has yielded superior outcomes since its earliest use several decades ago. In this series, f-IMA grafts were more often harvested from the right IMA in contrast to is-IMA grafts, which were predominantly of left IMA origin. Patients with f-IMA grafts underwent a lower proportion of procedures utilizing cardiopulmonary bypass; of the cases that did, the aortic cross-clamp time was shorter than cases utilizing is-IMA grafts, albeit with similar overall operative times. Although rates of death, MI, and revascularization were similar between f-IMA and is-IMA graft patients, the incidence of graft failure was higher in those who underwent f-IMA grafting.

Previous studies reporting the patency rates of various arterial conduits have demonstrated conflicting results. Dion et al reported a 15-month patency rate of 86.4% in 59 patients with f-IMA grafts compared with 100% patency in those who underwent is-IMA grafting.^{9,11} In situ IMA grafting had thus remained the preferred technique whenever possible. This finding is concurrent with the present study, which reports a higher graft failure rate of 23.3% for f-IMA grafts compared with 8.5% for is-IMA grafts. Interestingly, these results are similar to much older reports, such as that of Loop et al in 1986, reporting a 77% patency rate within 18 months in f-IMA grafts, with 86% patency in the subgroup with f-IMA grafts to the LAD.¹ Despite the seemingly inferior patency rates of f-IMA grafts in these studies, other series have reported contradictory results. Tatoulis et al analyzed outcomes in f-IMA grafts, reporting a patency rate of 94.5% in those receiving interval angiography for recurrent symptoms, far better than previous results.¹² In fact, Assi et al reported improved patency rates in free right IMA grafts (98%) compared with in situ right IMA grafts (91%) approximately 3 years after surgery, though follow-up angiography was only performed in 15% to 22% of patients, again for the indication of recurrent symptoms, which may underestimate overall patency rates in the original cohort.¹³ Also in this study, the results were comparable to traditional pedicled left IMA patency rates of 91% at a median follow-up of 7.1 ± 4.8 years. Outcomes

Table 1
Baseline characteristics

Variable	Free IMA (n = 34)	In situ IMA (n = 1538)	p value
Age (years)	62 (53-69)	63 (56-70)	0.245
Women	5 (15%)	284 (19%)	0.576
White	29 (85%)	1388 (90%)	0.023
Black	0 (0.0%)	80 (5%)	
Other	5 (15%)	70 (5%)	
Weight (kg)	83 (77-89)	88 (78-100)	0.014
Hypertension	19 (56%)	1115 (73%)	0.033
Hypercholesterolemia*	28 (82%)	1170 (76%)	0.395
Diabetes mellitus	8 (24%)	573 (37%)	0.101
Current smoker	11 (32%)	318 (21%)	0.098
Chronic lung disease	2 (6%)	212 (14%)	0.307
Atrial fibrillation/flutter	3 (9%)	103 (7%)	0.496
Renal failure	0 (0%)	23 (2%)	1.000
Myocardial infarction	13 (38%)	665 (43%)	0.560
Within 30 days	8 (24%)	307 (20%)	0.607
Prior percutaneous coronary intervention	5 (15%)	415 (27%)	0.110
Congestive heart failure	0 (0%)	126 (8%)	0.106
Peripheral vascular disease	2 (6%)	169 (11%)	0.574
Cerebrovascular disease	5 (15%)	156 (10%)	0.385
New York Heart Association class	16 (47%)	588 (39%)	0.687
Ejection fraction (%)	50 (45-60)	50 (40-60)	0.533
Number of narrowed coronary arteries			0.526
0	1 (3%)	64 (4%)	
1	8 (24%)	280 (18%)	
2	16 (47%)	610 (40%)	
3	9 (27%)	582 (40%)	
Medications (24 hours prior to surgery)			
Angiotensin-converting enzyme inhibitor	8 (24%)	553 (36%)	0.135
Angiotensin receptor blocker	1 (3%)	115 (8%)	0.509
Aspirin	13 (38%)	819 (53%)	0.083
Beta-blocker	27 (79%)	1031 (67%)	0.128
Diuretics	4 (12%)	291 (19%)	0.290
Digoxin	1 (3%)	67 (4%)	1.000
Heparin	11 (32%)	492 (32%)	0.964
Nonsteroidal anti-inflammatory drug	0 (0%)	100 (7%)	0.165
Warfarin	1 (3%)	8 (1%)	0.179
Statin	22 (65%)	888 (58%)	0.416
Type of surgery			0.106
Emergent/salvage	0 (0%)	1 (0.1%)	
Emergent	3 (9%)	37 (2%)	
Urgent	14 (41%)	728 (47%)	
Elective	17 (50%)	771 (50%)	
Duration of surgery (minutes)	232 (196-281)	229 (191-272)	0.355
Duration of aortic cross-clamp (minutes)	39.5 (0.0-65.5)	57.0 (33.0-75.0)	0.040
Cardiopulmonary bypass pump station	18 (53%)	1235 (80%)	<.001
Duration of bypass pump (minutes)	93.5 (79.0-120.0)	100.0 (80.0-123.0)	0.793
Number of hours ventilated post-operatively	8 (5-17)	7 (5-12)	0.289
Need for reintubation	0	44 (3%)	0.623
Additional number of hours ventilated			
N	0	40	
Median (interquartile range) (hours)	-	29 (12-120)	
Internal mammary artery			
Left	34 (68%)	1531 (97%)	
Right	16 (32%)	43 (3%)	
Graft quality			
Good	49 (96%)	1359 (87%)	
Fair	1 (2%)	120 (8%)	
Poor	1 (2%)	7 (0.4%)	
Unknown	0 (0%)	83 (5%)	

(continued)

Table 1 (Continued)

Variable	Free IMA (n = 34)	In situ IMA (n = 1538)	p value
Graft target			
Left anterior descending	30 (59%)	1392 (88%)	
First diagonal	1 (2%)	36 (2%)	
Second diagonal	0 (0%)	5 (0.3%)	
Left circumflex	1 (2%)	3 (0.2%)	
Ramus intermedius	3 (6%)	11 (0.7%)	
First obtuse marginal	12 (24%)	15 (1%)	
Second obtuse marginal	0 (0%)	5 (0.3%)	
Right coronary artery	0 (0%)	15 (1%)	
Posterior descending artery	1 (2%)	6 (0.4%)	
Other	3 (6%)	90 (6%)	
Target artery quality			
Good	39 (77%)	1077 (69%)	
Fair	10 (20%)	342 (22%)	
Poor	2 (4%)	119 (8%)	
Unknown	0 (0%)	27 (2%)	

* Hypercholesterolemia was defined as physician-diagnosed or treated hyperlipidemia, which may include total cholesterol >200 mg/dl, LDL \geq 130 mg/dl, and HDL <30 mg/dl.

Table 2

Relation between internal mammary artery type and outcomes

Outcome	Free IMA rate* (count)	In situ IMA rate (count)	HR (95% CI)	p value
Death	3.32 (5)	2.27 (166)	1.46 (0.60 - 3.54)	0.41
Myocardial infarction	1.35 (2)	0.49 (35)	2.71 (0.65 - 11.25)	0.17
Revascularization	5.74 (7)	3.43 (224)	1.61 (0.76 - 3.41)	0.22
Outcome	Rate[†] (Count/Total)	Rate (Count/Total)	OR (95% CI)	p value
Stenosis >75%	23.33 (7/30)	8.51 (118/1387)	3.27 (1.38 - 7.79)	<0.01

* Rate per 100 patient-years of follow-up.

[†] Rate computed as raw frequency at the end of follow-up (1.5 years) of those who had an angiography. CI = confidence interval; HR = hazard ratio; IMA = internal mammary artery; OR = odds ratio.

including perioperative MI, reoperation for hemorrhage, sternal infection or nonunion, and 30-day mortality were statistically similar between free and in situ right IMA grafts in this study. It is thus evident that a combination of patient and graft characteristics determines the outcomes of these conduits.

Several hypotheses in the literature have been suggested to explain the higher rate of graft failure in f-IMA grafts. From a physiologic standpoint, complete transection of the IMA results in severing of the vasa vasorum, the native blood supply to the conduit, thus forcing the conduit to rely on intravascular nourishment, which may or may not be adequate in certain settings. Similarly, free grafts are denerated in the process of harvesting, which may contribute negatively to its long-term function and ability to autoregulate.¹⁴ These concepts have been previously identified as potential sources of inferior radial artery free graft patency, especially in regard to vasospasm, thus it is not an unreasonable explanation.¹⁵

Although the present study demonstrates a lower rate of graft failure with is-IMA grafting, there are several factors that dictate the choice of free versus in situ IMA that must be accounted for as potential confounders. For example, the length of conduit available for pedicled grafts may be inadequate to reach vessel targets without tension. This may

prompt the surgeon to harvest the conduit as a free graft instead. Furthermore, in the process of harvesting what is intended to be a pedicled graft, injury to the IMA may prompt conversion to a free graft depending on the site of injury, in an effort to reduce the opportunity for long-term graft failure.⁹ Additionally, patients with unsuitable venous conduits may require alternative arterial conduits including a free IMA. It is also likely that these technical considerations also explain the increased frequency of free grafts on the right side as well as tendency toward non-LAD targets reported in our study.

The present study has several limitations. First, while data quality and methods were held to a uniform standard, post hoc analysis of clinical trial data did not allow randomization devoted to the independent variables of interest. Second, clinical decision-making preceding choice of left versus right and free versus in situ IMA grafting was not captured in the PREVENT IV dataset, and could not be used in an adjusted analysis. Furthermore, classification of grafts as "free" versus "in situ" were at the discretion of the investigator in PREVENT IV; however, despite the absence of a formal definition in PREVENT IV, these are presumed to be standard definitions which experienced site investigators should have no difficulty properly describing. Third, variables such as graft length, implications of bilateral IMA

harvesting, and use of prophylactic or therapeutic vasodilator administration intraoperatively and postoperatively were not captured in the dataset. Last, despite the large dataset afforded by PREVENT IV, only a limited number of patients underwent free IMA grafting, let alone angiographic follow-up; thus, our sample size is somewhat limited, as in other relevant studies.

Conclusion

In conclusion, the rates of death, MI, and revascularization were similar between use of free versus in situ IMA grafts; however, the rate of graft failure was significantly higher in those who underwent CABG with at least 1 f-IMA graft. Although clinical and technical circumstances often dictate the selection of vascular conduit and technique of implantation, our findings suggest that in situ IMA grafts should remain the preferred technique over free IMA grafts unless the clinical situation mandates otherwise.

Disclosures

Disclosures for Drs. Alexander and Lopes are available at <https://dcricri.org/about-us/conflict-of-interest>. Morgan Cox is supported by a National Institutes of Health T32 Training Grant with grant number T32HL069749. Dr. Gibson reports receiving research grant support from the sponsor of the trial. The remaining investigators have nothing to disclose.

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