Utility of nuclear stress imaging in predicting long-term outcomes one-year post CABG Surgery

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Background. **Early MPI after CABG is currently considered rarely appropriate in asymptomatic patients. This study aimed to identify prognostic value of nuclear stress-imaging post-CABG.**

Methods. **This was a single center prospective study looking at long-term outcomes post-CABG. Per protocol participants underwent SPECT-MPI stress testing and coronary angiogram on the same day, 1-year following CABG. Defect size was semi-quantified. The primary outcomes were the composite of death and congestive heart failure.**

Results. **Eighty-four participants underwent nuclear stress-imaging and angiography, with a median follow-up of 11.1 years. Three separate stress findings predicted the primary outcome: inability to reach stage 3 of a Bruce protocol (OR 7.3, CI 2.4-22.1, $P < 0.001$), LVEF < 45% (OR 4.0, CI 1.1-15.3, $P = 0.041$) and a moderate-large stress defect size (HR 2.31, CI 1.1-1.5, $P = 0.04$). These findings appear to be additive and strongest among patients who underwent exercise stress testing (HR 10.6, CI 3.6-30.6, $P < 0.001$). Graft disease was identified in 39 (46%) patients and compared to those individuals with no graft disease, did not predict long-term adverse outcomes ($P = 0.29$).**

Conclusion. **In clinically stable patients early after revascularization with CABG, SPECT-MPI can identify patients at higher risk of heart failure and death. (J Nucl Cardiol 2020;27:1970–8.)**

Key Words: CAD • SPECT • MPI • Heart failure • Outcomes research • Exercise testing

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The authors of this article have provided a PowerPoint file, available for download at SpringerLink, which summarizes the contents of the paper and is free for re-use at meetings and presentations. Search for the article DOI on SpringerLink.com.

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Abbreviations	
ACC	American College of Cardiologist
ACEi	Angiotensin Converting Enzyme Inhibitor
AHA	American Heart Association
CAD	Coronary artery disease
CABG	Coronary artery bypass graft
CHF	Congestive heart failure
CTO	Chronic total occlusion
HR	Hazard ratio
LIMA	Left internal mammary artery
LVEF	Left-ventricular ejection fraction
MI	Myocardial infarction
OR	Odds ratio
SPECT-MPI	Single Photon Emission Computer Tomography Myocardial Perfusion Imaging
SD	Standard deviation
VA	Veterans affair

See related editorial, pp. 1979–1981

INTRODUCTION

Coronary artery disease (CAD) is one of the leading causes of morbidity and mortality in the United States, affecting nearly 20% of individuals above the age of 65[1] and accounting for 370,000 deaths each year.[2] Coronary artery bypass grafting (CABG) surgery can achieve complete revascularization among suitable patients with multi-vessel disease and is performed in over 400,000 patients annually.[3] Although the 5-year survival following CABG is 75-80%,[4,5] nearly 20% of patients develop congestive heart failure (CHF) within 2 years following the operation.[6] As such, strategies that can identify those individuals at risk of death and heart failure following successful CABG may be important for prevention.

The long-term outcomes of surgical revascularization are dependent upon patency rates of the bypass grafts. Historically, patency rates of saphenous vein grafts range from 41% to 50% at 10 years post-CABG,[7–9] including 12-20% of the grafts which become occluded or jeopardized within the first post-operative year.[9] The multicenter Veterans Affairs cooperative trial (NCT0005847) compared radial artery vs saphenous vein grafts and demonstrated that 11% of study grafts were occluded and nearly 20% had a significant stenosis at one year.[10] Despite evidence showing graft disease in nearly 1 of 5 patients early post-CABG, Current guidelines do not recommend cardiac testing to assess graft patency in asymptomatic patients within 5 years of CABG.[11,12]

Considering that stress-induced defect size at 1-year post-CABG might be an important identifier of future cardiac events, we tested the added value of stress nuclear imaging, in a cohort of patients who were scheduled to return for invasive angiography at one year following CABG. We hypothesized that stress nuclear imaging, provided incremental value to the identification of graft disease by coronary angiography, by identifying those patients at 1-year post-CABG who were at risk for major cardiovascular events including heart failure.

METHODS

The Human Studies Subcommittee of the Research and Development committee at the Minneapolis VA Medical Center and the Executive Committee of the VA Cooperative Study (CSP#474) approved this study. All patients gave informed consent. The design was a prospective analysis of consecutive patients enrolled from the Minneapolis VA Medical Center to participate in the multicenter VA Cooperative trial on radial artery vs saphenous vein graft patency rates (NCT0005847).[10] All subjects within the sub-study agreed to undergo either exercise or pharmacologic stress single photon emission computer tomography- myocardial perfusion imaging (SPECT-MPI) and coronary angiogram one year post-CABG.

Stress Test

Methods regarding stress procedure and image acquisition have been previously described.[13] In brief, patients deemed suitable for a treadmill exercise test underwent a standard Bruce protocol. Patients were allowed to exercise until an end-point was reached (moderate to severe angina, shortness of breath, fatigue, or leg weakness, ≥ 2 mm ST-segment depression, hypotension, or severe arrhythmias). Technetium-99m tetrofosmin (Myoview) was injected at near-peak exercise, and the patients were asked to continue exercising for an additional minute. For the purpose of our analysis reaching stage 3 of Bruce protocol was defined as completing at least 6 minutes of exercise. In those patients who were not deemed candidates for exercise based on review of their clinical history, a pharmacologic stress test was performed with adenosine. The Adenosine infusion was given at a rate of 140 mcg/kg/min over 3 minutes.

All images were acquired and processed according to the American Society of Nuclear Cardiology (ASNC) guidelines using one-day rest/stress protocol.[14] All raw data of gated SPECT images were reconstructed using standard back-projection and identical filtering.

Quantitative SPECT was performed using a previously validated automated program that determines the extent and severity of left ventricle perfusion defect size and the extent of reversible (ischemia) or fixed (scar) perfusion defects.[15] In addition to perfusion data, the left-ventricular ejection fraction (LVEF), end-diastolic volume, and end-systolic volume were measured from the gated SPECT as previously described.[15] The SPECT images were interpreted by 2 experienced readers according to a standard segment scoring system that provides semi-quantitative information regarding total number of defects and the degree of ischemia vs infarction. The agreement between the 2 readers was 82% with a Kappa value of 0.62.[14] The interpretation of the SPECT was made without knowledge of the results of the coronary angiogram.

Coronary Angiogram

Coronary angiography was performed 1-year post-CABG and within 24 hours of the SPECT-MPI. All cine-angiograms were performed using standard techniques, including nitroglycerin administration, in at least 2 orthogonal angiographic views (45° left anterior oblique and 45° right anterior oblique). All angiograms were interpreted at a core laboratory, blinded to the results of the SPECT-MPI, using quantitative coronary angiography per the VA Cooperative study protocol.[10] Graft disease was defined as stenosis severity $\geq$ 70% including complete occlusions.

Outcome Measures

The primary end-point was the composite of death and new-onset heart failure. New heart failure was defined as a new outpatient clinic diagnosis or hospital admission for heart failure occurring after one year post-CABG. Patients with previous history of heart failure were counted as not reaching the heart failure end-point. Secondary end-points included myocardial infarction, revascularization and new stroke. Myocardial infarction and new stroke were identified by reviewing all discharge summaries of participants using local electronic medical records and the VA VistaAWeb which gives access to all medical records within the VA system. New revascularization was identified using CART Cath system (centralized reporting system for coronary angiograms and interventions) and discharge summary review.

Pre-operative left-ventricular function was assessed by either left ventriculogram during pre-operative angiogram, echocardiography, or quantitative SPECT. Left-ventricular function at one year post-CABG was determined by quantitative SPECT imaging at the time of stress test.

Statistical Analysis

Categorical variables are reported as frequencies and percentages; continuous variables are reported as mean with standard deviation (SD). Missing variables were censored from the analysis, unless specified. For continuous variables, between-group comparisons were performed with Student's t-test or ANOVA. Categorical variables were compared with chi-square test. Backward stepwise logistic regression was performed in order to identify multivariable predictors of outcomes. Cox proportional hazards models were used to calculate hazard ratios in event free survival analysis. Statistical analysis was performed using STATA version 15 (StataCorp. 2017. College Station, TX: StataCorp LLC). A two-tailed P value of < 0.05 was considered statistically significant.

RESULTS

Between February 2003 and February 2008, 87 patients were enrolled in the study. The median follow-up was 11.1 (mean 9.9 ± 3.4) years. As shown in Table 1, the cohort was all male, with a median age at enrollment of 59 years (mean 59.7± 7.5). A total of 273 grafts were placed, 86/87 patients had a left internal mammary artery graft (LIMA) placed, in addition to one or more grafts, with the majority of patients (71/87) having more than 3 vessels bypassed. Table 2 details the findings of the follow-up coronary angiogram.

Nuclear Stress-Imaging

Stress testing with SPECT-MPI was performed in 84/87 (97%) patients at one year after CABG. Exercise was the designated stress protocol for 86% (72/84) of patients, while the remaining 14% (12/84) underwent pharmacological testing with adenosine infusion. Of the patients who underwent exercise testing, 70% (49/72) achieved stage 3 of a standard Bruce protocol, but only 46% (33/72) reached 80% of their maximum predicted heart rate. Although the majority of patients 68% (57/84) had normal perfusion images, a moderate or large stress-induced defect was seen in 21% (18/84) of patients. Individuals with a moderate or large stress-induced defect tended to have lower LVEF (46% vs 56%) compared to those with no or a small defect ($P < 0.001$). The presence of a stress-induced defect was not associated with graft disease (Table 3). The sensitivity, specificity, and accuracy of stress SPECT-MPI to predict graft disease in this cohort has been previously described.[13]

Table 1. Baseline characteristics of cohort (n = 87)

Clinical variable	*N* (%)
Age, mean (SD)	59.7 (± 7.5)
Sex (male)	87 (100%)
BMI, mean (SD)	31 (± 5.5)
Smoking	
Active	25 (29%)
Former	38 (44%)
Prior	
MI	19 (22%)
Stroke	4 (4.6%)
CHF	4 (4.6%)
Hypertension	75 (86%)
Hyperlipidemia	68 (78%)
Diabetes Mellitus	29 (33%)
Vascular disease	14 (16%)
COPD	13 (15%)
Cancer	4 (4.6%)
Chronic renal failure	2 (2.3%)
Atrial fibrillation	3 (3.5%)
Dementia	1 (1.2%)
Cirrhosis	0 (0%)
No. of grafts, mean (SD)	3.1 (± 0.7)
2	16 (18%)
3	43 (49%)
4	28 (32%)
LVEF, mean % (SD)	
Pre-operative	51 (± 12)
1 year post-operative	54 (± 11)
Pre-operative medications	
Beta-blockers	66 (76%)
ACEi	56 (64%)
Statin	59 (69%)
Aspirin	59 (69%)
Anti-coagulation	2 (2%)
Medications at 1 year	
Beta-blockers	78 (90%)
ACEi	61 (70%)
Statin	75 (86%)
Aspirin	63 (72%)
Anti-coagulation	7 (8%)

Long-Term Adverse Cardiovascular Outcomes

The primary outcome of new CHF or death was observed in 30 individuals, with 18 deaths, and 15 new diagnoses of CHF. Of the 18 patients who died, 3 were diagnosed with new-onset heart failure prior to dying (Table 4). Patients meeting the primary outcome tended to be older (62.4 vs 58.4, $P = 0.02$), and had a lower pre-operative (46% vs 53%, $P = 0.02$), otherwise there were no differences in clinical characteristics between the two groups (Table 5).

Predictors of the Primary Outcome (Death and CHF)

Nuclear stress testing. The presence of a moderate to large stress-induced defect on MPI was predictive of the primary outcome with a HR 2.3 (CI 1.1-1.5 $P = 0.04$) Figure 1A. In addition, patients who reached stage 3 of Bruce protocol had an 86% relative risk reduction (RRR) in the incidence of heart failure ($P < 0.001$) and a 69% RRR in the composite end-point ($P < 0.001$). Regression models showed inability to reach stage 3 was associated with an 11 times increase (OR 11.8; CI 2.8-49.2, $P = 0.001$) in the odds of new heart failure and a 7 times increase (OR 7.3; CI 2.4-22.1, $P < 0.001$) in the odds of the composite end-point. None of the parameters studied were able to predict the secondary end-points.

Left-ventricular ejection fraction. LVEF, both pre-operatively and at 1-year post-CABG, predicted adverse outcome, though the best predictor was LVEF at 1-year. The odds of adverse events considerably increased when the LVEF was below 45%, (OR 4.0 CI 1.1-15.3, $P = 0.04$), but not when using a cut-off of 50% ($P = 0.17$).

Integration of SPECT findings. Prediction models drastically improved when summing the 3 independent predictors (moderate-large defect size, inability to reach stage 3, and LVEF < 45%) observed on nuclear stress-imaging (Table 6, Figures 1B, 2). This association appeared to be strongest in patients who underwent exercise stress testing rather than adenosine. When excluding patients, who underwent pharmacological stress testing, logistic regression models showed a 19-fold increase in the rate of the primary outcome ($P = 0.002$). Similarly, Cox hazard models revealed a hazard ratio of 10.6 (CI 3.6-30.6, $P < 0.001$) for the primary outcome.

Invasive coronary angiography. As seen in Figure 3, graft disease on coronary angiogram was not a predictor of long-term outcomes. There was no difference in 1-year LVEF (55% vs 54%, $P = 0.67$) in patients with or without graft disease.

DISCUSSION

The principal finding of this study was that stress nuclear MPI at 1-year following CABG, predicted adverse outcomes related to heart failure and death, among asymptomatic patients. Duration of exercise,

Table 2. Angiogram results 1-year post-CABG

Angiographic findings	Number of patients $n = 85$
Presence of a graft CTO	
1 vessel	15
2 vessels	10
More than 2 vessels	0
Disease to the LIMA graft	7
Distal stenosis	10
Graft disease	
0—Vessel	46 (54%)
1—Vessel	23 (27%)
2—Vessels	14 (16%)
3—Vessels	2 (2%)

LVEF and stress-induced defect size on MPI all independently predicted outcomes, while the presence of graft disease on coronary angiogram did not. Intuitively, graft failure has been thought as the primary driver for adverse events post-CABG, but prior studies have shown mixed results.[16–18] The reasons for an abnormal stress-induced defect are multiple and are not necessarily dependent upon the presence or absence of graft disease. Incomplete revascularization of some segments of the coronary arteries, because of either technically difficult vessels or peri-infarct tissue at the time of surgery might account for the abnormal segments. The use of stress-induced defect size as a means of identifying long-term risk is rational, because it addresses both graft disease and native coronary arteries that might not have been viewed as suitable for grafting. This conclusion corroborates the work of others in which identifying unprotected coronary territory or MPI defects, was more informative and prognostic than angiography alone in post revascularized patients.[19–21]

The utility of stress-imaging within 5 years of CABG is uncertain in asymptomatic patients, if the test is used as a means of identifying ischemic territories in need of revascularization. The combined societal guidelines (American Heart Association, American College of Cardiology and American Society of Nuclear Cardiologist) labeled the use SPECT-MPI in asymptomatic patients 3-5 years post-CABG as rarely appropriate.[12] The guidelines reference three studies exploring the role of nuclear imaging in asymptomatic patients post-CABG.

In support of our study results, having a SPECT-MPI with a defect greater than 7 segments was associated with a two-fold increase in mortality at median 5.8 years follow-up.[22] Unlike our study however, many of those patients were symptomatic and were different than the present cohort. In a larger prospective study of only asymptomatic patients, an abnormal stress-induced nuclear imaging test at 6 years post-CABG was a significant identifier of increased risk of either death or MI during the next 3 years of follow-up.[23] In the largest cohort involving nearly two thousand patients, Zellweger et al.,[24] demonstrated a low event rate (1.9%) at one year follow-up when SPECT was obtained within 5 years post-CABG. The value of the present study is that data from both the diagnostic coronary angiogram with graft patency as the primary objective along with the stress-imaging tests were available at one year, with long-term outcome measures captured for nearly 10 years. Including new-onset heart failure to the outcome measures, in addition to mortality, strengthens the potential benefit of targeting at risk patients. Although, enrollment for our study started more than a decade ago, we believe our findings are still relevant today, as the optimal management of chronic ischemic heart disease with statins, aspirin, beta-blockers and ACEi/ARB has not significantly changed.

To our knowledge this is the first description of long-term outcomes in an unselected cohort undergoing both coronary angiography and functional testing one year post-CABG. Of interest, the angiographic presence or absence of graft disease was not as predictive of future cardiovascular events, compared with the stress-induced defect size. Our interpretation is that graft disease is one component of the vasculature that may signal increased risk, but equally important, include native vessels that were not deemed suitable for grafting, either because they

Table 3. Graft disease and stress test results

Stress findings	(−) Graft disease (45)	(+) Graft disease (38)	*P* value
Normal or small defect	36 (80%)	29 (76%)	0.7
Moderate or large defect	9 (20%)	9 (24%)	

P value calculated using Pearson χ^2 for categorical variables and standard *t* test for continuous variables

Table 4. Cardiovascular End-points

Adverse events	*N* (%)
Composite (death and new heart failure)	30 (34%)[a]
Death	18 (21%)
New heart failure	15 (17%)
Myocardial infarction	1 (1%)
Stroke	5 (6%)
Revascularization	6 (7%)

[a]Three patients were diagnosed with congestive heart failure prior to death, composite end-point only counts patient as reaching one event

were small caliber vessels or perfused partially infarcted myocardial regions. Alternatively given our cohort's size it is likely that our study was underpowered to detect differences in outcomes between patients with and without graft disease. This was also the likely reason we did not see a difference in traditional MACE end-points (death, MI, revascularization and stroke).

Several variables obtained during the one year post-CABG nuclear stress-imaging test independently predicted adverse outcomes (duration of exercise, LVEF and MPI stress-induced defect size). These variables' predictive value appears to be additive. By assigning a point for each of the following findings: LVEF $\leq 45\%$, moderate or large defect size, or inability to reach stage 3 in a standard Bruce protocol, we were able to more precisely identify patients reaching the primary outcomes, predicting up to 62% of deaths and new heart failure. A LVEF cut-off of 45% was used, as events appeared to significantly increase below this cut-off point. Having ≥ 2 of the aforementioned findings was associated with a mark decrease in the probability of event free survival (HR 10.6, $P < 0.001$), when excluding patients who underwent adenosine stress testing. When including all patients, who underwent stress testing at one year, OR and HR still remained clinically and statistically significant at 8.6 ($P = 0.002$) and 5.2 ($P < 0.001$), respectively. It is interesting that predictive models improved when excluding patients who underwent pharmacological stress test as the event rates do not differ between patients who were able to exercise vs not (33.3% vs 34.7%, $P = 1.0$). Though it is difficult to make any conclusions of the contribution of patients who underwent pharmacological testing given the low number of participants ($n = 12$), but we speculate cardiac testing is less predictive of outcomes in this group which may be

Table 5. Baseline characteristics for patients' meeting/not primary end-point

Baseline characteristics	(−) Primary outcome	(+) Primary outcomes	*P* value*
Age, mean (SD)	58.5 (± 6.2)	62.4 (± 8.9)	0.02
BMI, mean (SD)	30.5 (± 4.6)	30.8 (± 7.1)	0.77
Smoking			
Active	18 (32%)	7 (24%)	0.60
Former	23 (40%)	15 (52%)	0.58
Prior			
MI	12 (21%)	7 (23%)	0.75
Stroke	2 (4%)	2 (7%)	0.50
CHF	1 (2%)	3 (10%)	0.08
Hypertension	50 (88%)	25 (83%)	0.57
Hyperlipidemia	48 (84%)	20 (67%)	0.06
Diabetes	17 (30%)	12 (40%)	0.34
PVD	9 (16%)	5 (17%)	0.92
COPD	6 (11%)	7 (23%)	0.11
Atrial fibrillation	1 (2%)	2 (7%)	0.23
Radial graft	28 (50%)	16 (55%)	0.2
No. of grafts, mean (SD)	3.1 (± 0.71)	3.2 (± 0.68)	0.42
LVEF, mean % (SD)			
Pre-operative	53 (± 11)	46 (± 13)	0.02
1-year post-operative	57 (± 9)	50 (± 13)	< 0.001

*P value calculated using Pearson χ^2 for categorical variables and standard t test for continuous variables

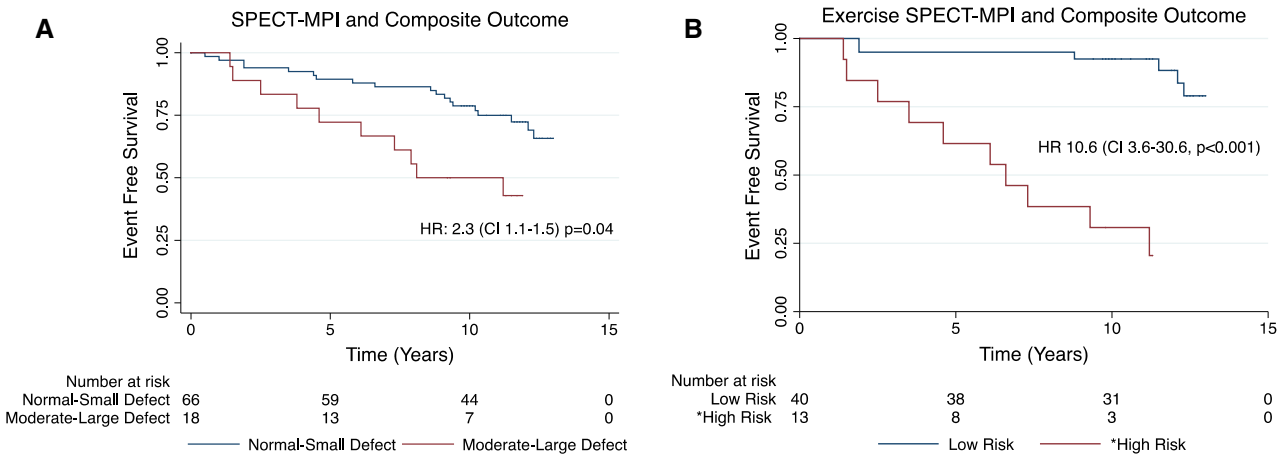

Figure 1. (**A**) Survival Curve showing a significant increase in the probability of survival in patients with normal or mild (vs moderate or large) defect size on SPECT-MPI Stress. (**B**) The probability of survival is markedly decreased in the high risk patients compared to normal. * High Risk: Patients who underwent exercise and were found to have two or three of the following findings: inability to reach stage 3 of a Bruce protocol, a moderate or large stress-induced defect or a LVEF $\leq$ 45%.

Table 6. Prediction models of long-term outcomes in patients with multiple SPECT abnormalities

	OR	*P* value	HR	*P* value
Model 1	8.6 (2.3–33.0)	0.002	5.2 (2.1–12.7)	< 0.001
Model 2	18.9 (4.0–89.0)	< 0.001	10.6 (3.6–30.6)	< 0.001

This table reflects the additive value of the multiple predictive factors found on SPECT-MPI. Predictive models incorporate patients with $\geq$ 2 abnormalities (moderate to large defect, LVEF $\leq$ 45% or inability to reach stage 3 of a standard Bruce Protocol) in comparison to patients with normal SPECT-MPI. Model 1 consists of all patients who underwent Stress SPECT-MPI. Model 2 excludes patients who underwent pharmacological stress testing

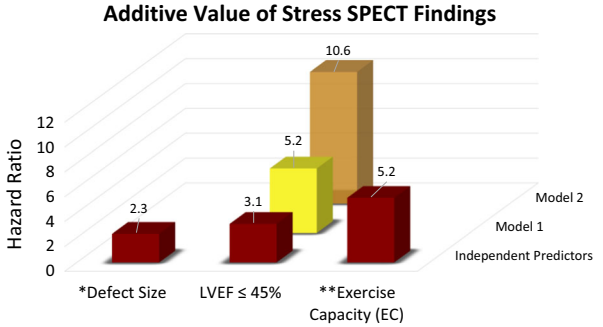

Figure 2. Models 1 and 2 incorporate patients with $\geq$ 2 abnormalities (Moderate to large defect, LVEF $\leq$ 45% or inability to reach stage 3 of a standard Bruce Protocol) in comparison to patients with normal SPECT-MPI. Model 1 consists of all patients who underwent Stress SPECT-MPI. Model 2 excludes patients who underwent pharmacological stress testing. *Moderate to large stress induce defect. **Inability to reach stage 3 of standard Bruce protocol.

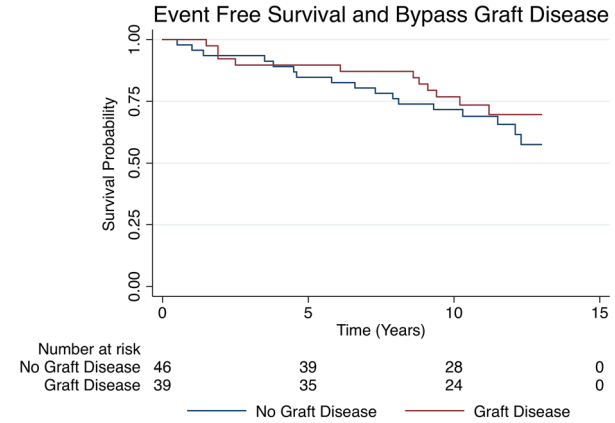

Figure 3. Kaplan-Meier curve showing no difference in the probability of survival in patients with or without bypass graft disease on coronary angiogram at one year post surgery.

limited by other co-morbidities (i.e., reason unable to exercise).

We believe that the low number of vascular events, including strokes, myocardial infarction and revascularization make traditional end-points such as MACE less relevant. While new congestive heart failure in patients who have undergone prior CABG is a very common finding with significant implications in both quality of life and health care cost.[25,26]

NEW KNOWLEDGE GAINED

The utility of stress-imaging in asymptomatic patients within 5 years of surgical revascularization is uncertain. We have shown that stress-induced defect size, exercise capacity and LVEF, obtained during stress SPECT-MPI 1 year following CABG surgery, were important predictors of death and heart failure over the proceeding 10 years, in an unselected cohort. Nuclear stress-imaging provides a more comprehensive profile of overall myocardial health and function by incorporating several data points, including qualitative defect size which could reflect non-bypassed territories, peri-infarct regions, hibernating myocardium, or scar. Though it is important to note, our findings and prediction models need to be validated prospectively in a larger cohort of patients.

Disclosure

The authors of this manuscript have no conflict of interest.

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