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EXPEDITED PUBLICATIONS

F-18-Fluorodeoxyglucose Positron Emission Tomography Imaging-Assisted Management of Patients With Severe Left Ventricular Dysfunction and Suspected Coronary Disease

A Randomized, Controlled Trial (PARR-2)

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Objectives We conducted a randomized trial to assess the effectiveness of F-18-fluorodeoxyglucose (FDG) positron emission tomography (PET)-assisted management in patients with severe ventricular dysfunction and suspected coronary disease.

Background Such patients may benefit from revascularization, but have significant perioperative morbidity and mortality. F-18-fluorodeoxyglucose PET can detect viable myocardium that might recover after revascularization.

Methods Included were patients with severe left ventricular (LV) dysfunction and suspected coronary disease being considered for revascularization, heart failure, or transplantation work-ups or in whom PET was considered potentially useful. Patients were stratified according to recent angiography or not, then randomized to management assisted by FDG PET (n = 218) or standard care (n = 212). The primary outcome was the composite of cardiac death, myocardial infarction, or recurrent hospital stay for cardiac cause, within 1 year.

Results At 1 year, the cumulative proportion of patients who had experienced the composite event was 30% (PET arm) versus 36% (standard arm) (relative risk 0.82, 95% confidence interval [CI] 0.59 to 1.14; p = 0.16). The hazard ratio (HR) for the composite outcome, PET versus standard care, was 0.78 (95% CI 0.58 to 1.1; p = 0.15); for patients that adhered to PET recommendations for revascularization, revascularization work-up, or neither, HR = 0.62 (95% CI 0.42 to 0.93; p = 0.019); in those without recent angiography, for cardiac death, HR = 0.4 (95% CI 0.17 to 0.96; p = 0.035).

Conclusions This study did not demonstrate a significant reduction in cardiac events in patients with LV dysfunction and suspected coronary disease for FDG PET-assisted management versus standard care. In those who adhered to PET recommendations and in patients without recent angiography, significant benefits were observed. The utility of FDG PET is best realized in this subpopulation and when adherence to recommendations can be achieved. (J Am Coll Cardiol 2007;50:2002–12) © 2007 by the American College of Cardiology Foundation

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Severe left ventricular (LV) dysfunction due to coronary artery disease (CAD) is associated with high morbidity and mortality despite advances in medical and device therapies (1–6). Heart failure, a frequent complication of this condition, is also associated with significant health care costs (4). Although revascularization might be beneficial, perioperative morbidity and mortality often temper the enthusiasm to operate on such patients (7–9). Undoubtedly, these patients have much to gain when revascularization is beneficial but also much to lose when it is not helpful. For this reason, methods have been developed to define viable recoverable myocardium.

Positron emission tomography (PET) imaging with F-18-fluorodeoxyglucose (FDG) is considered the most sensitive viability imaging method for predicting LV function recovery (10–13). Several observational studies have shown that FDG PET can identify patients with viable myocardium who are at high risk for cardiac events if they do not undergo timely revascularization (14–20). However, because of their design, these studies could not determine whether clinical decisions assisted by FDG PET imaging actually altered patient outcome.

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The primary objective of this study was to determine whether patients whose management strategy included FDG PET imaging to assist in decision-making, had improved clinical outcomes compared with standard care where FDG PET was not available. In our experience, many patients are referred for viability imaging without recent knowledge of their coronary anatomy. As such, a secondary aim was to determine whether patients with or without recent coronary angiography gained a clinical benefit from management assisted by FDG PET imaging.

Methods

Details of the enrollment criteria and protocol are summarized in the following text. Full comprehensive details of the methods and design have been published separately (21).

Patients from 9 centers were enrolled between June 2000 and September 2004. The study was approved by the institutional review board at each site, and all patients enrolled gave written informed consent.

Patients. Candidates for enrollment were patients being considered for: 1) revascularization or revascularization work-up; 2) transplantation work-up; or 3) heart failure work-up; or 4) any patient for whom FDG PET viability imaging might be considered useful by the attending physician for decision-making and who met other inclusion criteria. Patients were identified from heart failure clinics, cardiology inpatients, cardiac catheterization laboratories, surgical referral rounds, and nuclear cardiology viability imaging referrals. Eligible patients were included if they were over 18 years of age; had an ejection fraction (EF) ≤35% documented by radionuclide ventriculography (RVG), LV angiogram, or echocardiography; had a high suspicion of CAD on the basis of one or more of the following: coronary angiography; previous revascularization; previous myocardial infarction (MI) (≥4 weeks) verified by chart review; and/or positive stress perfusion imaging for scar +/− ischemia (reports were reviewed by a cardiovascular nuclear imaging specialist). Excluded were patients in whom a definite decision had already been made for revascularization or transplantation such that the attending physician would in no way alter management on the basis of any potential viability findings; and those who had already had FDG viability imaging. Also excluded were those: with comorbidities that would likely affect survival over the study duration; <4 weeks post-MI; already identified to be unsuitable for revascularization; requiring emergency revascularization; with severe valvular disease that required surgery; or who were geographically inaccessible.

Abbreviations and Acronyms

CABG = coronary artery bypass graft
CAD = coronary artery disease
CI = confidence interval
EF = ejection fraction
FDG = F-18-fluorodeoxyglucose
HR = hazard ratio
LV = left ventricle/ventricular
MI = myocardial infarction
MRI = magnetic resonance imaging
PET = positron emission tomography
RVG = radionuclide ventriculography

Imaging. Patients underwent RVG imaging at baseline. The RVGs were acquired with a standard electrocardiogram-gated equilibrium technetium-99m red blood cell blood pool imaging protocol. The EF was measured from the left anterior oblique 45° acquisition (22).

Those randomized to the PET arm underwent imaging at 1 of 4 sites (see Appendix). The PET perfusion imaging was acquired at rest with a standard protocol with rubidium-82 or N-13-ammonia as described previously (21–23). For FDG imaging, nondiabetic patients were studied after an oral glucose load (21–23), whereas an insulin-euglycemic clamp was used for those with diabetes (21–24).

PET IMAGING DATA ANALYSIS AND INTERPRETATION. All images were submitted to the PET imaging core laboratory for standardized processing. An automated method of image analysis was applied to the perfusion/FDG PET imaging data to yield quantified measures of the extent and severity of scar and mismatch (Fig. 1). These parameters were included with clinical parameters in a previously derived model that yielded a point estimate and 95% confidence interval (CI) for predicted LV function recovery after revascularization (21,22). Patients were classified as having low, moderate, or high likelihood of recovery if adequate revascularization could be achieved (low classification was considered when the upper confidence limit of the predicted EF change was 3% or less; high classification when the lower confidence limit for predicted change was above 3%; and moderate for those with confidence limits

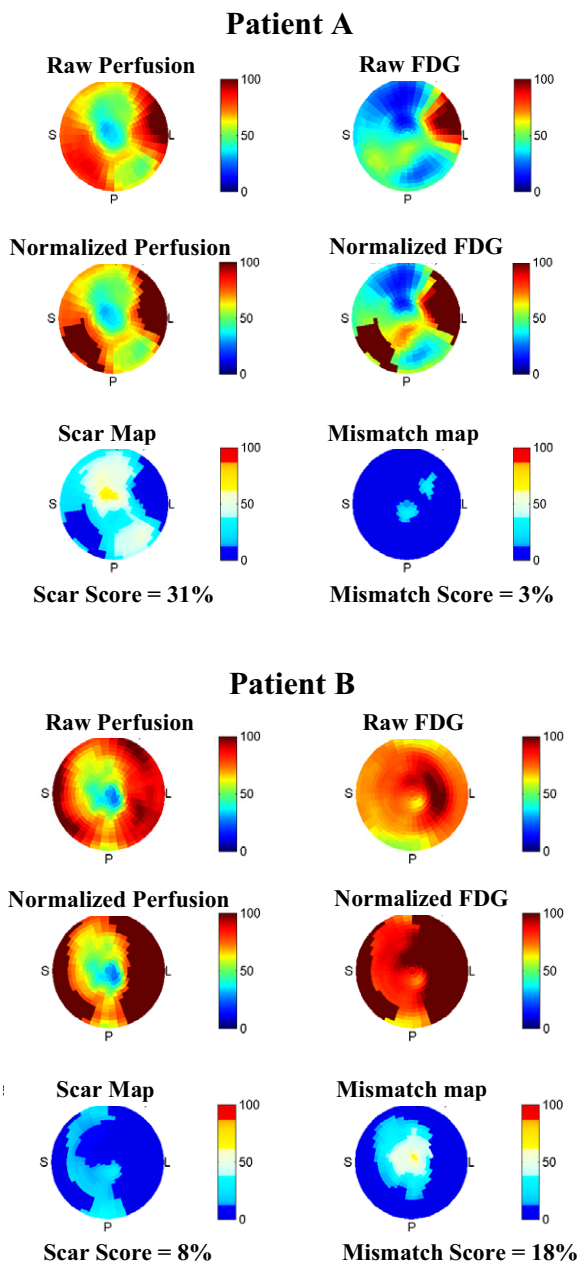

Figure 1 **Examples of Reconstructed Polar Maps for 2 Patients**

In each set, the **top panels** are the raw perfusion **(left)** and raw F-18-fluorodeoxyglucose (FDG) uptake **(right)** polar maps; the **middle panels** are the normalized perfusion **(left)** and FDG uptake **(right)**; the **lowest panels** are the scar score **(left)** and mismatch score **(right)**; color scale in the **lower panel** is shifted to allow visualization of defects (this does not affect the score determinations). **(Patient A)** Predominantly scar in the anteroseptal are inferolateral walls and apex. Of the total left ventricular (LV) myocardium; 31% was scar and 3% was mismatch. Interpretation was that there was a large scar and a small amount of hibernating viable myocardium and that the patient would not be expected to improve after revascularization. **(Patient B)** Partial mismatch (mixture of scar and hibernating myocardium) in the large defect involving the inferior wall and apex and extending to the anteroseptal wall. Of the total LV myocardium; 8% was scar and 18% was mismatch. The interpretation was that there was a large amount of hibernating viable myocardium and that the patient would be expected to improve after revascularization.

between high and low cut-points). Physicians experienced in reading PET data also reviewed the images to confirm the model's classification of the likelihood of recovery. Physicians considered the extent of scar and mismatch in their interpretation. Differences between the model and the interpreting physician were settled by consensus with another experienced imaging physician. In addition to a standard clinical report describing the imaging findings, a report detailing the extent of scar (defined as small [<16%], medium [16% to 27%], or large [>27%]) (21), the extent of total viable myocardium, the extent of mismatch (all as a percent of the LV), and the likelihood for recovery was faxed and delivered to the attending physician or surgeon (21). The physician or surgeon would then make a decision whether to proceed with revascularization (or revascularization work-up in those without recent angiography).

Randomization and interventions. Block randomization was performed. The randomization was pre-stratified by whether the patient had had angiography within the preceding 6 months and by the study center. Physicians and staff were unaware of allocation before randomization. Masking was employed where feasible, including masking of the allocation process, the outcomes using an adjudication process, and the interim analysis.

FDG-PET–ASSISTED MANAGEMENT ARM. When FDG PET identified significant viable myocardium, "revascularization" or "revascularization work-up" was recommended depending on whether or not the patient had recent angiography. When PET identified predominantly scar tissue, "no revascularization" was the recommendation. When the PET report was available, the physician or surgeon would then consider the imaging data in the context of the individual patient and make a decision to proceed or not proceed with revascularization (or revascularization work-up in those without recent angiography). In circumstances where the scar was large, aneurysm resection could be considered at the physician's and surgeon's discretion.

STANDARD CARE ARM. Standard care proceeded without FDG imaging available to the physician. An alternative test for viability definition could be considered.

We were aware that some patients could have "vessels which were unsuitable for revascularization." Such patients identified before recruitment were excluded from enrollment. Patients who were directed to undergo angiography but were subsequently considered to have "unsuitable anatomy" continued to be followed in their respective arms on an intention-to-treat basis.

For both arms, once initial testing and evaluation were completed, the physician or surgeon would then consider the imaging data in the context of the individual patient and make a decision to proceed or not with revascularization (or revascularization work-up in those without recent angiography). Every effort was made to ensure that all procedures and subsequent revascularizations were booked within 8 weeks of randomization. The management plans were

reviewed at 8 weeks after randomization. Revascularizations directed by initial work-up (with or without PET) were considered protocol revascularizations. Their associated hospital stays were not counted as events.

Cardiac event variable definitions and measurement. The primary event of interest was the occurrence of any of the following within 1 year of randomization: cardiac death, MI, or hospital stay for cardiac cause such as unstable angina or heart failure. Secondary outcomes included time to occurrence of the composite event and time to cardiac death. Events were assessed by telephone interview every 3 months. All events were reviewed and verified by an adjudication committee blinded to the randomization allocation.

In our initial design, cardiac transplantation had been included in the composite end point (21). This was an important event to capture for the planned cost analysis. However, we are aware that cardiac transplant can be considered a positive rather than a negative outcome. Hence for outcome analysis, patients with cardiac transplant were censored at the time of cardiac transplantation.

The definitions of each variable and the timing of their measurements have been described previously and are summarized in the following text (21).

Cause of death was determined from the death certificate and included death presumed to be tachyarrhythmic (i.e., abrupt loss of cardiac output and pulse without prior circulatory collapse and with no evidence of shock or pulmonary edema at the time of loss of cardiac output) or death from other cardiac cause (i.e., 5 min or more of circulatory collapse before loss of cardiac output and pulse with evidence of shock or severe pulmonary edema before loss of cardiac output and subsequent death).

Myocardial infarction was defined as 2 or more of the following: ischemic chest pain lasting at least 20 min, accompanied by documentation in the medical record of new ST-segment elevation >1 mm in at least 2 contiguous leads, new left bundle branch block, evolution of creatine kinase (CK) rise >2× normal or CK-myocardial band above upper limit of normal, or new Q waves in 2 contiguous leads.

Procedure-related MI was defined as the following: 1) coronary artery bypass graft (CABG): an enzymatic MI reflects cases with increased CK-myocardial band ≥70 or troponin-T ≥1.5; clinical MI includes positive enzymes plus 1 or more of the following: new Q waves, new lack of R-wave progression, or new wall motion abnormalities; 2) percutaneous coronary intervention: post-percutaneous coronary intervention MI was based on the elevation of the CK-myocardial band >3× the upper limit of normal or by the occurrence of new Q waves.

Cardiac hospital stay was defined as hospital stay for a cardiac cause such as unstable angina, worsening heart failure, or non-protocol late revascularization.

Unstable angina was defined as anginal pain that occurred at rest and lasted at least 20 min or angina of at least Canadian Cardiovascular Society (CCS) class III with onset within 2 months or that was distinctly more frequent, longer in duration, or lower in threshold (i.e., increased at least 1 CCS class within 2 months and was at least CCS class III in severity).

Worsening heart failure was defined as: change of functional class (i.e., increased at least 1 New York Heart Association functional class in the last 2 months); change in clinical examination findings (new S_3, rales, elevated jugular vein pressure not previously noted); required adjustment of diuretic therapy; acute pulmonary edema; or cardiogenic shock.

Statistical analysis. The sample size of 206 patients/arm was chosen to provide the study with 80% power for distinguishing between an event rate of 50% and 35% in the 2 arms, allowing a 2-sided type I error rate of 5%, a crossover rate of 2.5%, and a further 10% lost to follow-up (21).

Primary analyses were conducted on an intention-to-treat basis. One interim analysis was performed once 50% of the patients had accrued, to determine whether the PET-directed approach was beneficial or hazardous. O'Brien-Fleming group (25) sequential stopping rules were used to maintain an overall significance level of 0.05. Significance boundaries were symmetrical, with alpha = 0.019 for the interim analysis and alpha = 0.043 for the final analysis.

Baseline characteristics of patients in the 2 arms were compared by using the *t* test for continuous variables and chi-square test for categorical variables. An uncorrected chi-square test was used to compare the proportion of events in each study arm. A logistic regression procedure was employed to adjust the comparison of these event rates with significant covariates that predicted outcome.

Categorical variables, including the components of the composite event, were analyzed by using an uncorrected chi-square test followed by multiple logistic regression analysis. Survival analyses were used to compare event-free survival. Kaplan-Meier survival curves were compared with the log-rank test. Proportional hazards methods were used as appropriate.

To address secondary objectives, intention-to-treat analysis was only undertaken for subgroups where there had been stratification before randomization or where the parameter significantly impacted the effect of FDG PET-assisted management or standard care on the outcome. This was the case for patients with and without recent angiography for which there was a priori stratification before randomization.

Because a patient's course might not adhere to the recommendations of the PET imaging, an additional post hoc analysis was conducted to determine the outcome in the ideal circumstances when decisions adhered to PET recommendations. Thus, an "adherence" group was defined among patients in the PET arm. This adherence group included patients: 1) who underwent PET; 2) who had moderate or high amounts of viability and adhered to the PET recommendations by undergoing protocol revascularization or revascularization work-up; and 3) who had low amounts of viability so did not undergo protocol revascularization or revascularization work-up or underwent aneu-

rysm resection because of a large scar. Patients who had events before PET imaging or before revascularization or revascularization work-up were excluded from this post hoc outcome analysis, as these events may have partly driven revascularization or revascularization work-up. Inclusion of these patients would not allow determination of the benefit of following the PET recommendations. The "adherence to PET" recommendations group was compared with patients in the standard care arm.

Finally, PET might add benefit after other stress and viability testing. Thus, in a post hoc analysis, patients with previous stress or viability imaging testing enrolled in the PET arm were compared with the standard arm with or without at least 1 test performed before or after randomization that could be used to assist with decision-making.

Results

Nine sites randomized 430 patients. Coronary artery disease criteria listed previous angiography (remote or recent) and/or previous revascularization as 1 of the criteria in 349 patients. In 25 patients, a history of MI, verified by chart review, was the single criterion listed. In 29 patients, positive stress perfusion imaging was the single criterion listed. In 28 patients, both MI and positive imaging were listed. Patients were randomized to FDG PET-assisted management (218 patients) or standard care (212 patients). The baseline characteristics were similar (Table 1).

Eighteen patients (9 PET arm, 9 standard arm) with LV dysfunction who initially seemed to meet inclusion criteria were found to have an EF >0.35 on the RVG done at the time of enrollment. Although these patients were randomized inappropriately, they were followed and included in the intention-to-treat analysis. Additional patients were enrolled to ensure that a sufficient number of patients met all inclusion criteria. Hence, 430 patients were enrolled in the study.

In the PET arm, 207 patients underwent PET imaging. Eleven did not. In the standard arm, 5 underwent PET imaging (after another initial test) and 207 did not. The PET image quality was considered poor in 4 cases (1.9%), owing to poor FDG uptake, and fair in 16 cases (7.7%). When image quality was poor, the perfusion data were used in combination with the best interpretation possible from the FDG data. The attending physician was informed of the poor image quality.

In the PET arm, 58, 103, and 46 patients were considered to have high, moderate, and low amounts of viability, respectively; 104 (47.7% of group) underwent protocol revascularization. Of these, 71 (68%) underwent CABG. Five patients underwent late revascularization (109 total revascularizations).

In the standard arm, 74 (34.9% of group, p = 0.007 compared with PET) underwent protocol revascularization. Of these, 55 underwent CABG (74%; p = NS compared with PET). Nine patients underwent late revascularization (83 total revascularizations). The effect of PET-assisted management was not modified by having or not having revascularization (p = NS for interaction).

Coronary anatomy. Among the patients with available angiography data for review (recent pre-randomization angiography or post-randomization), 268 of 300 (89.3%) had 2-vessel, 3-vessel, or left main disease with >50% stenoses: 148 of 165 (89.7%) patients in the PET arm compared with 120 of 135 (88.9%) patients in the standard arm (p = NS). Distal disease of >50% in at least 2 distal segments was noted in 51 (30.9%) PET arm patients and 47 (34.8%) standard arm patients (p = NS). Distal disease in the left anterior descending coronary artery was noted in 28 (17%) PET arm patients with angiography and 23 (17%) standard arm patients with angiography (p = NS). A small number of patients (10, 3.3%) did not have a significant stenosis at the time of the post-randomization angiogram in spite of meeting 1 or more inclusion criteria (6 in the PET arm, and 4 in the standard arm). Because our goal was to determine the added value of FDG PET among patients being assessed for viability and these patients had been referred for such and because these patients met the inclusion criteria set and had been randomized, these patients were included in the primary intention-to-treat analysis.

Cardiovascular events. One-year follow-up data was completed for 209 patients (96% of randomized) in the PET

Table 1 Characteristics of Patients at Entry

	FDG PET-Assisted Management (n = 218)	Standard Care (n = 212)
Age, mean (SD)	63.0 (10.0)	62.0 (10.3)
Gender, male (%)	184 (84.4)	179 (84.4)
Baseline EF, mean (SD)	27.0 (7.4)	26.1 (8.0)
Diabetes, n (%)	90 (41.3)	77 (36.3)
Prior infarction, n (%)	176 (80.7)	170 (80.2)
Angiography in previous 6 months, n (%)	115 (52.8)	109 (51.4)
Prior CABG, n (%)	46 (21.1)	34 (16.0)
Angina (CCS class II–IV), n (%)	101 (46.3)	97 (45.8)
Dyspnea (NYHA functional class II–IV), n (%)	175 (80.3)	177 (83.5)
Creatinine (μmol/l), mean (SD)	110 (62)	106 (38)

CABG = coronary artery bypass graft; CCS = Canadian Cardiovascular Society; EF = ejection fraction; FDG = F-18-fluorodeoxyglucose; NYHA = New York Heart Association; PET = positron emission tomography.

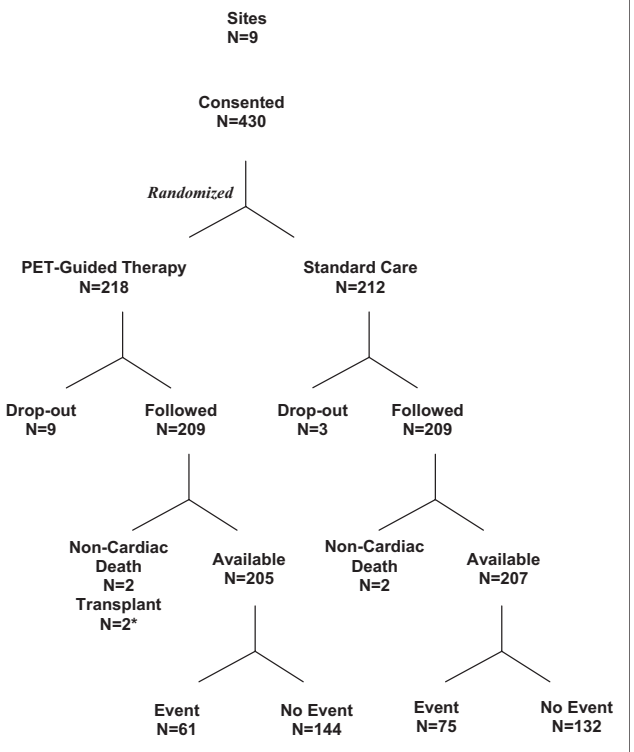

Figure 2 **Flow Diagram of Recruitment, Randomization, Dropouts, Noncardiac Death, and Events at 1 Year***

*Two patients had cardiac transplant before any other cardiac event and were censored at the time of transplantation. PET = positron emission tomography.

arm and 209 patients (99% of randomized) in the standard arm (Fig. 2). First events were cardiac death (n = 29), MI (n = 13), and cardiac hospital stay (n = 94). Two patients were censored at the time of cardiac transplant, which occurred before any cardiac event. Thus, 136 patients experienced an event of interest; 45 patients had cardiac deaths.

The cumulative proportion of patients who experienced the composite event was 30% in the PET arm and 36% in the standard arm (relative risk 0.82, 95% CI 0.59 to 1.14, p = 0.16). Two events in the PET arm occurred before PET imaging.

For all patients, the hazard ratio (HR) for the composite event, in the PET arm compared with the standard care arm, was 0.78 (95% CI 0.58 to 1.1, p = 0.15) (Fig. 3). For patients with EF ≤0.35 on RVG at the time of enrollment and after excluding those identified as not having significant coronary stenosis, the HR was 0.77 (95% CI 0.55 to 1.09, p = 0.14).

Cardiac death. There were 19 cardiac deaths in the PET arm and 26 in the standard arm. By intention-to-treat analysis, the HR for cardiac death was 0.72 (95% CI 0.40 to 1.3, p = 0.25) (Fig. 4). Further analysis was undertaken for the subgroups with and without prior angiography, because this was defined a priori and there was stratification before

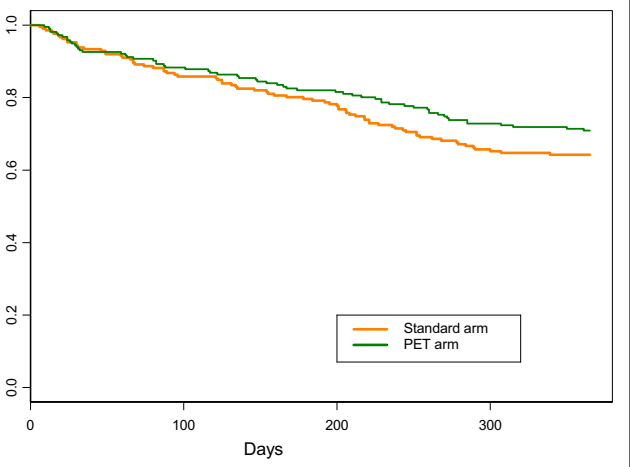

Figure 3 **"Survival Curves" (on the Basis of Time to First Occurring Outcome of the Composite Event)**

Mantel-Haenszel (log-rank) test for differences between 2 survival curves; chi-square = 2.1, hazard ratio = 0.78, 95% CI 0.58 to 1.1, p = 0.15. PET = positron emission tomography.

randomization. There were no differences between PET and standard arms for those who had recent angiography (relative risk = 1.29; 95% CI 0.57 to 2.95; p = 0.69).

Among 206 patients without recent angiography, 1 had a noncardiac death and 4 dropped out, leaving 201 patients. There was a significant reduction in cardiac deaths in the PET arm compared with standard care: 7 of 99 (7.1%) versus 17 of 102 (16.7%) (relative risk = 0.42, 95% CI 0.18 to 0.98; p = 0.036). The HR for the PET arm was 0.4 (95% CI 0.17 to 0.96; p = 0.035) (Fig. 5). There were no

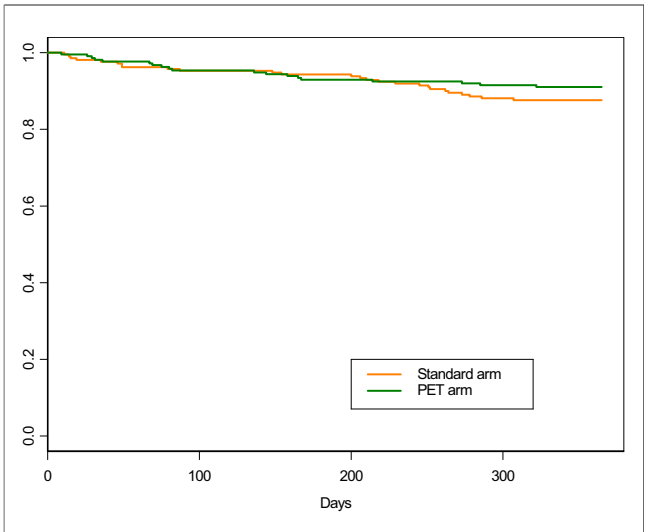

Figure 4 **"Survival" Curves (on the Basis of Time to Cardiac Death) for All Subjects**

Mantel-Haenszel (log-rank) test for differences between 2 survival curves; chi-square = 1.3, hazard ratio = 0.72, 95% CI 0.4 to 1.3, p = 0.25. PET = positron emission tomography.

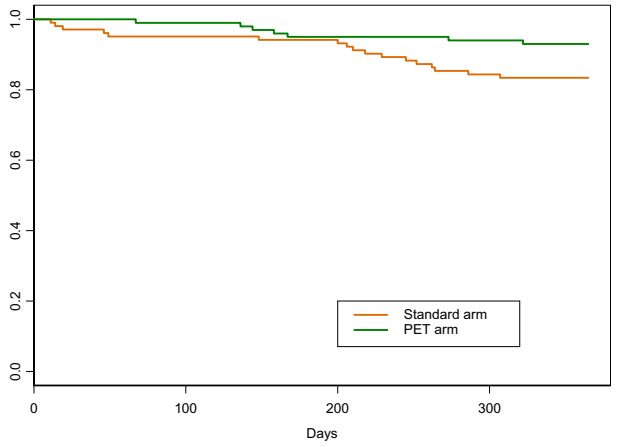

Figure 5 "Survival Curves" (on the Basis of Time to Cardiac Death) for Patients Without Recent Angiography

Mantel-Haenszel (log-rank) test for differences between 2 survival curves; chi-square = 4.5, hazard ratio = 0.4, 95% CI 0.17 to 0.96, p = 0.035. PET = positron emission tomography.

differences in demographic parameters between PET and standard care arms.

Compared with patients with recent angiography, those without had lower EF (p = 0.007), had worse renal function (p = 0.002), had more previous CABG (p < 0.0001), were older (p = 0.053), and tended to have more previous MIs (p = 0.06). Thus, patients without recent angiography represented a sicker population (Table 2).

Adherence to PET recommendations. Among the 218 patients randomized to the PET arm, 207 had PET imaging. For those who underwent PET imaging, 156 of 207 (75.4%) adhered to the PET recommendation. Table 3 describes why patients with high or moderate amounts of viability on PET did not undergo revascularization workup or revascularization. Table 4 tabulates the reasons why patients with low amounts of viable myocardium underwent revascularization or work-up. Among the patients with low viability: 1) 3 had aneurysm resection; these patients were considered to have adhered to PET recommendations, because scar had been identified and appropriate treatment ensued; 2) 8 patients did not adhere to PET recommendations: 5 had revascularization, 1 had attempted revascularization that was not successful, and 2 had revascularization work-up without revascularization (Table 4).

Table 3 Reasons for "No Revascularization" or "No Revascularization Work-Up" in Patients With High or Medium Viability

Patient refusal/withdrawal	4 (1.9%)
Renal failure	9 (4.3%)
Multiple other comorbidities (age, COPD, vasculopathy)	5 (2.4%)
Cardiac event (death)	2 (0.5%)
Cardiac event (hospitalized, CHF, arrest)	1 (1.0%)
Symptoms stabilized	13 (6.2%)
Scar on other prior test	2 (1.0%)
Unknown (could not be determined)	7 (3.4%)
Total patients among 207 patients with PET*	43 (25.7%)

*Does not include 11 patients who did not have positron emission tomography (PET) imaging in the PET arm.
CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease.

Thirty patients with high or moderate amounts of viability underwent revascularization work-up without getting revascularized. Reasons for these patients not undergoing revascularization are listed in Table 5.

Figure 6A shows the distribution of patients who adhered to recommendations on the basis of the amount of viable myocardium. Adherence rates were 86.2%, 66.0%, and 82.6%, respectively, for high, moderate, and low amounts of viability (p < 0.05 moderate vs. others). Figure 6B shows the distribution of patients who underwent protocol revascularization or revascularization work-up in each group: 86.2%, 66.0%, and 23.9% for high, moderate, and low viability, respectively (p ≤ 0.01).

In the post hoc analysis, which compared the "adherence to PET" subgroup with standard care, previous CABG had a significant association with the outcome (HR = 2.1; p = 0.0003). Adjusting for this, the HR for the "adherence to PET" subgroup was 0.62 (95% CI 0.42 to 0.93, p = 0.019) (Fig. 7).

Other testing. In the PET arm, 86 patients had a stress or viability imaging test in the 3 months before randomization.

Table 2 Characteristics of Patients With and Without Recent Angiography

	Patients With Recent Angiography (n = 224)	Patients Without Recent Angiography (n = 206)
Mean age, yrs (SD)	61.6 (10.2)	63.5 (10.1)*
Gender, male (%)	191 (85.3)	172 (83.5)
Baseline EF, mean (SD)	27.5 (7.7)	25.5 (7.6)†
Diabetes, n (%)	93 (41.5)	74 (35.9)
Prior infarction, n (%)	173 (77.2)	173 (84.0)*
Prior CABG, n (%)	11 (4.9)	69 (33.5)‡
Angina (CCS class II–IV), n (%)	108 (48.2)	90 (43.7)
Dyspnea (NYHA functional class II–IV), n (%)	182 (81.3)	169 (82.0)
Creatinine (μmol/l), mean (SD)	104 (59)	112 (42)†

*p > 0.05; ≤ 0.08. †p < 0.01. ‡p < 0.0001.
Abbreviations as in Table 1.

Table 4 Reasons for "Revascularization" or "Revascularization Work-Up" in Patients With Low Amounts of Viability

Recurrent or persistent symptoms	5 (2.4%)
LMCA disease	1 (0.5%)
TVR for region of viability	1 (0.5%)
Unknown	1 (0.5%)
Total patients among 207 patients with PET*	8 (3.9%)

Does not include 3 patients with aneurysm procedures. *Does not include 11 patients who did not have positron emission tomography (PET) imaging in the PET arm.
LMCA = left main coronary artery; TVR = target vessel revascularization.

In the standard arm, 93 patients had stress or viability testing in the 3 months before randomization and 77 had testing after randomization. A total of 138 patients had at least 1 stress or viability imaging test in the standard arm. For patients in the PET arm with prior stress or viability testing, there was a significant benefit compared with: 1) those in the standard arm with testing: unadjusted HR = 0.5 (95% CI 0.28 to 0.88; p = 0.017) and adjusted HR = 0.46 (95% CI 0.25 to 0.81; p = 0.007) (after adjustment for prior CABG [HR = 1.9; p = 0.04], which was a confounder); 2) patients in the standard arm without recent testing: HR = 0.44 (95% CI 0.24 to 0.82; p = 0.009; no confounders); and 3) patients in the PET arm without prior testing: HR = 0.48 (95% CI 0.27 to 0.86; p = 0.013; no confounders).

Discussion

To our knowledge, the PARR (PET and Recovery Following Revascularization)-2 study is the largest randomized study to evaluate whether FDG PET-assisted management has a beneficial effect on clinical outcomes and is the first randomized trial to evaluate viability imaging in patients with severe LV dysfunction.

Although patients in the FDG PET-assisted management arm tended to have fewer cardiovascular events within 1 year, this difference was not significant. Thus the findings for the primary outcome must be considered inconclusive. Regarding secondary outcomes, by intention-to-treat, patients without recent angiography in the FDG PET-assisted management arm had a statistically significant reduction in cardiac death.

From post hoc analyses, under the ideal circumstances when there is adherence to PET recommendations, a significant reduction in adverse outcomes was observed. In addition, patients in the PET arm with recent stress or viability testing had better outcome than those with testing in the standard arm and those without testing in either arm.

Table 5 Reasons for Not Undergoing Revascularization in 30 Patients With High or Moderate Viability Who Underwent "Revascularization Work-Up"

Diffuse disease, anatomy not amenable to revascularization	12 (5.8%)
Patent grafts	6 (2.9%)
No major flow limiting stenosis	6 (2.9%)
Symptoms stabilized	2 (1.0%)
Unknown	4 (1.9%)
Total patients among 207 patients with PET*	30 (13.4%)

*Does not include 11 patients who did not have positron emission tomography (PET) imaging in the PET arm.

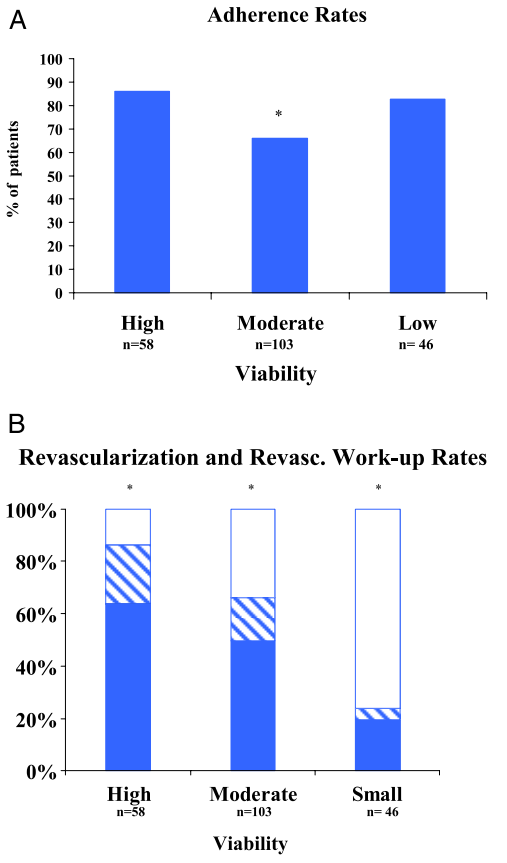

Figure 6 Rates of Adherence, Revascularization, and Revascularization Work-Up

(A) Rates of adherence to positron emission tomography recommendations for revascularization or revascularization work-up (*p < 0.05 for moderate vs. others). **(B)** Rates of revascularization **(solid bars)**; revascularization work-up without revascularization **(hatched bars)**, and no revascularization **(open bars)**. Rates of revascularization + revascularization were different between groups (*p < 0.01 vs. other amounts of viability).

Existing published reports and ongoing trials. Observational studies have consistently demonstrated that patients with viable myocardium on FDG PET are at high risk for cardiac death or events if they do not undergo timely revascularization (14–20,26–28). However, many of these studies are small and have inherent biases in patient selection that might influence outcome. The current trial also has some potential bias in patient selection and referral, because the management course was not absolutely mandated by the test. However, this was also true for the standard care arm. Although it is not possible to prove that such clinical bias is balanced between groups, randomization is expected to balance this as much as possible.

One previous study randomized patients to PET versus technetium-99m sestamibi single-photon emission com-

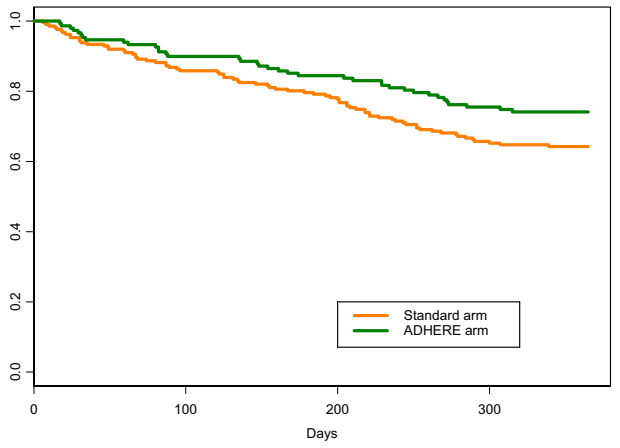

Figure 7 **"Survival Curves" (on the Basis of Time to First Occurring Outcome Out of the Composite Event)**

The positron emission tomography adherence group versus standard care arm. Mantel-Haenszel (log-rank) Test for differences between 2 survival curves; adjusted hazard ratio = 0.62, 95% CI 0.42 to 0.93, p = 0.019.

puted tomography-guided management (29). This study did not show a significant difference in outcome. However, only 36 of 103 patients had severe LV dysfunction. Considering the lower risk of such patients and the small sample size, the study was likely underpowered.

The ongoing STICH (Surgical Treatment for Ischemic Heart Failure) trial (30) compares revascularization to medical therapy to surgical reconstruction of the LV (9). Magnetic resonance imaging (MRI) is being used for viability imaging but is not used to direct therapy. Viability testing is permitted to select patients suitable for randomization, but is not used to direct therapy after randomization. Although the trial will yield vital data regarding surgical therapies in patients with severe LV dysfunction (EF <35%), data on viability imaging will be observational and, hence, might be unable to provide an unbiased estimate of the effects of imaging on decision-making or outcome. In the ongoing HEART (Heart Failure Revascularisation Trial) study (31), patients with EF <35% and large amounts of jeopardized myocardium on perfusion imaging or dobutamine echocardiography will be randomized to revascularization or medical therapy. Patients might also undergo PET or MRI. As with the STICH trial, useful data on the role of revascularization will arise. However, data on the role of viability imaging and decision-making might be incomplete, because patients with moderate or lesser amounts of hibernation and ischemia are not included and the use of PET or MRI is ad hoc rather than randomized.

Current findings and clinical relevance. Although the lower event rate in the PET-assisted management arm would seem supportive of findings from previous observational studies, the results did not reach statistical significance, so a definitive conclusion cannot be drawn regarding the composite end point.

The observed event rates of 36% in the standard arm and 30% in the PET arm were lower than projected. This reduced our ability to detect a significant difference. Longer-term follow-up is underway and would be expected to provide additional power. The demographic data were similar to many previous viability studies that enrolled patients with severe LV dysfunction (14–20). Thus, the lower-than-expected event rates might reflect improvements in medical, device, and revascularization therapy (1–6,8,9).

The randomization was pre-stratified by whether the patient had angiography within the preceding 6 months. In the patients without angiography in the preceding 6 months, a lower mortality was demonstrated for FDG PET-assisted management. At first glance this might seem difficult to understand. However, this group was sicker than those with recent angiography (older with more previous CABG and MIs, lower EF, and worse renal function). Patients with previous bypass are already known to have significant disease that is likely to be more diffuse and less amenable to repeat revascularization. Such patients are also at increased risk for redo surgery or intervention (32). It is such patients where decisions for revascularization become even more critical. Thus, it is not surprising that a technique that can optimize patient selection of those more or less likely to benefit might have a mortality benefit in this population.

Post hoc analysis suggests that the group of patients in the PET arm who had already had some form of stress or viability testing had a significant benefit. This suggests that a diagnostic algorithm that includes PET after initial testing might provide a clinical benefit in this patient population. Interpretation here must be made with caution, because the study was not designed to compare specific types of alternate testing and because this was a post hoc analysis. Further verification of this finding in other clinical trials is required.

Study limitations and other considerations. Clinical decision-making is often complex for patients with severe LV dysfunction. In previous observational studies, between 30% and 50% (mean 42%) of patients who were classified as having viable myocardium did not undergo revascularization (14–20). In the current study, 24.6% of patients did not adhere to the recommendations that were based on the PET imaging data. This likely reduced our ability to detect a difference in the primary outcome analysis. The extent of viability is 1 of several factors that might influence a physician's decision for a given management course and thus impact subsequent outcome (33). Physicians must balance the best available information on the likelihood of recovery versus patient risk often due to other comorbidities. That FDG PET data do impact decision-making is supported by the data in Figure 6, showing that the likelihood of revascularization or revascularization work-up depended on the amount of viable myocardium. The current data also support that there are often other factors that complicate decisions and influence outcomes (33).

The interpretation of PET imaging can be complex and must consider extent of scar, mismatch, total viability, and combinations thereof. It is possible that our simplified approach of dividing patients into high-, moderate-, and low-likelihood for recovery also contributed to the lack of adherence. This effect was likely small, more likely affecting those patients at or near cut points. This again reflects the complexity of decision-making in patients with severe LV dysfunction.

To address the impact of adherence, we did a post hoc analysis comparing outcomes among patients who adhered to the PET recommendations versus standard care. These results showed a significant reduction in events under the ideal circumstances of when there is adherence to PET recommendations. Because the control group was not subject to this screening, potential bias in this post hoc analysis might exist. Adjustment was made for the lone confounder affecting outcome, namely previous CABG. Thus the groups were relatively balanced. Although this post hoc analysis must be interpreted with caution, it does indicate the importance of following PET imaging recommendations and the potential benefits that might ensue.

This study did not include follow-up perfusion or angiographic data to confirm the adequacy of revascularization. Although there seems to be no reason to suspect that the success rate of revascularization was different among those in each group who were revascularized, this cannot be confirmed or refuted. It seems unlikely to us that this impacted the outcome findings observed.

The current study demonstrates the difficulties in designing randomized trials to evaluate clinical outcomes for diagnostic tests and diagnostic strategies, as opposed to specific therapies. Not only do randomized clinical trials for diagnostic strategies depend on the test accuracy but also on the willingness of physicians and patients to follow the recommended treatment and the effectiveness of the treatment itself. Future trials of diagnostic strategies should consider these issues in their design.

OTHER MODALITIES. The study does not compare PET with specific alternative imaging modalities that often vary depending on site expertise and technique availability. Such a comparison was not the aim of the PARR-2 trial. Rather the primary aim was to determine whether a FDG PET-assisted management approach improves clinical outcomes compared with standard care.

ADVANCES IN IMAGING. The lessons learned from the PARR-2 trial might provide a framework to evaluate new hybrid PET/computed tomography devices (34) and other advanced viability imaging modalities, such as MRI. Magnetic resonance imaging, with its excellent anatomical resolution, is emerging as a useful tool for evaluating viability and predicting wall motion recovery. Whether this resolution advantage would translate into outcome benefit is not known. Few outcome studies have evaluated MRI in patient populations with severe LV dysfunction (20). Contrast-enhanced MRI might carry a potential risk for nephrogenic systemic fibrosis that might be as high as 1.5% in patients with reduced creatinine clearance (35). Impaired renal function is very common in the patient population with severe LV dysfunction, including the current study where 34% of patients had reduced creatinine clearance rates. This, along with the paucity of outcome data, suggests that FDG PET remains an important advanced viability imaging modality in severe LV dysfunction.

Conclusions

The urgent need for randomized controlled studies applying imaging technology that evaluate outcomes has recently been highlighted (36). The PARR-2 study represents such a trial. It is, to our knowledge, the first large randomized trial to evaluate whether a strategy that includes FDG PET to assist in directing management is effective in patients with severe LV dysfunction.

Although the event rate in the FDG PET arm was less than the standard arm, the overall study must be considered inconclusive, because there was no statistically significant difference for the primary outcome measure. However, there are a number of important findings from the PARR-2 study.

First, FDG PET did have important impact on management decisions in many patients, as evidenced by the different rates of revascularization and work-up relative to the extent of viability. Second, as with previous observational studies, there was a large proportion (approximately 25%) of patients who did not adhere to the PET recommendations in spite of moderate and even high amounts of viable myocardium. This implies that, for clinicians making decisions, the evidence for revascularization benefit is not convincing enough to warrant the potential or perceived added risk in some patients. Ongoing randomized trials will address this question further (30,31). Third, when patients who adhered to the PET recommendations were considered, there was a significant benefit for FDG PET, indicating the positive impact that FDG PET imaging might have under the ideal circumstances when viability data are considered and recommendations are followed. Fourth, an outcome benefit for PET-assisted management was observed when it was used in addition to a preceding test. This warrants further study. Finally, in a pre-defined intention-to-treat analysis, there was a patient population, without recent angiography, who represent the sickest group of patients, where FDG PET-assisted management yields a significant mortality benefit.

In conclusion, the data suggest that many patients with severe LV dysfunction and suspected CAD might not always benefit from FDG PET imaging. However, there is potential value for FDG PET, particularly in a high-risk patient population where decisions for therapy are most difficult. When patients adhere to FDG PET recommendations, a reduction in events might be realized.

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APPENDIX

For a list of the PARR Investigators and the participating centers, please see the online version of this article.