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Cardiac PET Perfusion: Prognosis, Risk Stratification, Clinical Management

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Abstract

Myocardial perfusion imaging (MPI) with positron emission tomography (PET) has expanded significantly over the past decade. With the wider availability of PET scanners and the routine use of quantitative blood flow imaging, the clinical use of PET MPI is expected to increase further. PET MPI is a powerful tool to identify risk, to quantify risk, and to guide therapy in patients with known or suspected coronary artery disease (CAD). A large body of evidence supports the prognostic value of PET MPI and ejection fraction in intermediate to high risk subjects, in women, in obese individuals and in post coronary artery bypass grafting (CABG) individuals. A normal perfusion study indicates low risk (< 1% annualized rate of cardiac events of cardiac death and non-fatal myocardial infarction), while an abnormal study indicates high risk. With accurate risk stratification, high quality images, and quantitation PET MPI may transform the management of patients with known or suspected CAD.

INTRODUCTION

The clinical use of myocardial perfusion imaging (MPI) with positron emitting radiotracers has experienced marked growth over the past decade with increasing scanner and radiotracer availability. Currently ~200 medical centers in the US as well as several North American and European centers are offering clinical PET MPI services. We have witnessed an exponential increase in the evidence base for the diagnostic and prognostic value of PET MPI. The purpose of this paper is to summarize the available literature on prognosis, risk

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stratification and clinical management of patients with known or suspected heart diseases using relative PET MPI.

PET MPI RISK MARKERS

Patients who undergo PET MPI are typically unable to exercise and have several comorbid conditions that make them higher risk compared to patients who are able to exercise maximally on a treadmill test.^{1–4} In addition, perfusion defect size and severity, LVEF, stress myocardial blood flow (MBF) and coronary flow reserve (CFR, ratio of MBF at stress to rest), calcium score (CAC), transient ischemic dilation (TID) of the left ventricle, right ventricular (RV) tracer uptake, lung uptake, and atherosclerosis on CT coronary angiography are risk markers on PET MPI and hybrid PET MPI studies (Table 1).

Defect size and severity

The prognostic value of extent and severity of perfusion defects is well established.^{5, 6} Most prognostic studies of SPECT and PET MPI use semiquantitative measures of perfusion defect size and severity using a 17 segment model and visual or software derived scores (0–4 score, 0= normal, 4= absent uptake).⁷ Summed stress (SSS, jeopardized myocardium), summed rest (SRS, scar burden) and summed difference scores (SDS, ischemic burden) are calculated as the sum of the scores in the 17 segments. More recently, for ease of interpretation, the summed scores have been reported as percent myocardium abnormal (SSS), scarred (SRS) and ischemic (SDS) using the formula summed score *100/maximal possible score (for a 17 segment model with 0–4 scoring: SSS*100/68, SRS*100/68 and SDS*100/68).⁵ Larger defects, severe defects and defects in multiple vascular distributions indicate high risk.⁵ Based on the extent and severity of reversible perfusion defects, the PET MPI results can be categorized as low risk (involving <5% of the myocardium), intermediate risk (5–10% of the myocardium), or high risk (>10% of the myocardium).⁸

Gated PET MPI: Rest LV ejection fraction (LVEF), stress LVEF, and LVEF reserve

Left ventricular ejection fraction measured routinely and accurately with N-13 ammonia⁹ and Rubidium-82 PET,^{10–12} is a well-established risk-marker in many clinical settings. Indeed, with short-acting radiotracers such as Rubidium-82, rest, peak hyperemic LVEF and LVEF reserve (stress LVEF minus rest LVEF) can be measured, as opposed to SPECT MPI wherein LVEF is measured on the post-stress images (~15–60 minutes post stress).^{1, 13} Dorbala et al¹ demonstrated that LVEF at rest increases during peak vasodilator stress in patients with normal MPI. In contrast, patients with severe ischemia (Figure 1A), and those with 3 vessel/left main disease (Figure 1B) demonstrate a significantly lower LVEF during peak vasodilator stress and a lower LVEF reserve. A LVEF reserve < + 5% is a highly sensitive marker of left main/3-vessel CAD (sensitivity of 94% and a negative predictive value NPV of 97%). In a similar study of 110 patients, Brown et al¹³ found that the magnitude of ischemia on Rubidium-82 PET MPI was inversely correlated with a change in LVEF from rest to stress. The combined results of these studies suggest that LVEF reserve during vasodilator Rubidium-82 PET is inversely related to the magnitude of myocardium at risk. An abnormal LVEF reserve may identify severe 3-vessel/left main CAD, while a high LVEF reserve excludes the possibility of underlying multi-vessel CAD. On the basis of

these publications, rest and peak stress LVEF is routinely incorporated into clinical practice of PET MPI.

Hyperemic myocardial blood flow and coronary flow reserve

One of the exciting advances with PET MPI is the incorporation of absolute MBF and CFR into clinical practice. Accurate attenuation correction and simultaneous tomographic acquisition of counts in list mode (with newer PET scanners) and quick quantitation using commercial software have moved MBF and CFR assessment from a predominantly research arena to mainstream clinical practice. Measurement of MBF is validated (in comparison to microspheres and other radiotracers) for most PET perfusion tracers.¹⁴ Quantitative MBF may offer a potential solution for one of the challenges of relative PET MPI – balanced ischemia.¹⁴ Several investigators have shown, using the various positron radiotracers that non-invasively measured CFR and peak stress MBF are inversely related to underlying coronary artery stenosis severity.¹⁵ However, vasodilator CFR predominantly is a measure of endothelium independent coronary flow abnormalities, and to a lesser extent endothelium dependent flow abnormalities.¹⁴ Hence, even in patients without CAD, peak hyperemic blood flow and CFR values could be reduced suggesting concomitant microvascular dysfunction. Coronary angiography may be necessary to differentiate between epicardial coronary artery stenosis, microvascular dysfunction and a combination.¹⁶ Because CFR provides a view of the overall vascular health including epicardial and microvascular vessels, it offers important prognostic value. Coronary flow reserve is currently measured routinely in most practices.

Other high risk markers

Transient ischemic dilation (TID) of the left ventricle with exercise¹⁷ and vasodilator SPECT¹⁸ MPI is a risk marker for multi-vessel severe obstructive CAD. Transient ischemic dilation of the left ventricle can result from a true ischemic cavity dilation or global subendocardial ischemia resulting in apparent cavity dilation. Rischpler et al. studied 265 patients¹⁹ and demonstrated that compared to patients without TID (1.13), those with TID (> 1.13) on rest and vasodilator Rubidium-82 PET had a greater degree of jeopardized myocardium, scar and ischemia, a lower LVEF reserve ($5.0 \pm 6.4\%$ vs. 1.8 ± 7.9 , $P < 0.05$) and a lower CFR (2.1 ± 0.8 vs. 1.7 ± 0.6 , $P < 0.02$).¹⁹ However, this study was not adequately powered for determining the prognostic value of increased TID ratio. Increased RV perfusion tracer uptake at rest indicates high RV pressures²⁰ and is sometimes seen in patients with pulmonary artery hypertension and with congenital heart disease.²¹ A transient increase in RV tracer uptake is a marker for severe left main CAD on post-exercise SPECT MPI, but this marker had not been evaluated with PET MPI (as exercise stress is infrequently used).²² Finally, as with SPECT radiotracers, increased lung uptake of PET perfusion radiotracers (primarily N-13 ammonia and less commonly with Rubidium-82) may be noted with lung disease, systolic LV dysfunction and severe ischemia. Increased lung radiotracer uptake may also be seen, for unclear reasons, in smokers with N-13 ammonia and in inflammatory or malignant lung lesions.²³ The incremental prognostic value of these risk markers with PET MPI is not well-defined.

RISK STRATIFICATION WITH PET MPI

Extensive observational studies support the value of pharmacological Rubidium-82 PET MPI for risk stratification of patients with known or suspected CAD. However, prospective clinical trials using PET MPI data to drive patient management are limited. Also, prognostic studies of N-13 ammonia MPI,²⁴ and exercise stress PET MPI are limited.

Prognostic value of perfusion defects on PET MPI

One of the main strengths of radionuclide imaging is its ability to accurately stratify risk in patients with known or suspected CAD. The prognostic value of the size and extent of stress and rest PET perfusion defects has been described by several single center observational studies in a total of over 9000 patients.^{2-4, 25, 26} (Table 2) Marwick et al³ demonstrated that patients with normal Rubidium-82 PET MPI have a low annual cardiac mortality rate (0.9%) and patients with an abnormal MPI have a much higher rate of cardiac mortality 4.3 %. These results, in high risk patients (known CAD in 85%, normal MPI in 24%), were reproduced in more contemporary intermediate risk patient cohorts. The PET MPI prognostic studies (Table 2) vary widely in the included number of patients^{4,2, 25} number of events^{2, 4, 25} and type of events (composite events: all cause death (ACD), myocardial infarction (MI), hospitalization, and late revascularization,⁴ ACD alone,² or a combination of cardiac death (CD)/MI and ACD).²⁵ Despite these differences, each of these studies consistently demonstrated similar findings: a normal scan indicates low-risk (< 1% annual cardiac event rate) while an abnormal scan indicates worse prognosis.^{2, 4, 25} Furthermore, there is a graded increase in risk of cardiac events from normal to severely abnormal MPI. Also, stress MPI provides incremental prognostic value even after accounting for rest LVEF and several other important clinical parameters (N=1432; cardiac death or non-fatal MI = 83).^{2, 25} The cumulative evidence is now strong and indicates that a normal scan offers excellent prognosis and the magnitude of stress and rest perfusion defects on PET MPI provide valuable risk stratification of patients undergoing pharmacological stress testing.

Net reclassification improvement with PET MPI

Novel metrics of net reclassification improvement (NRI), and integrated discrimination improvement (IDI), are more sensitive for identifying the incremental prognostic value of novel risk markers when compared to the conventional metrics, and have gained popularity.²⁷ The NRI also provides a better clinical reclassification of risk (i.e., identify whether a marker is better for predicting events – reclassify into a higher risk, or for predicting no events – reclassify into a lower risk). The incremental value of PET MPI for NRI was demonstrated in 7061 patients from 4 medical centers in the PET Prognosis Multicenter Registry²⁸ (Table 2). As the myocardial perfusion worsened, the unadjusted and risk adjusted hazard of cardiac death rate increased gradually (Figure 2); patients with a severely abnormal scan compared to those with a normal scan experienced a 5-fold higher hazard of cardiac death. Even after accounting for differences in age, sex, other clinical factors and rest LVEF, patients²⁹ with larger percentage of ischemic and scarred myocardium experienced higher cardiac and all-cause mortality. The percentage of ischemic or scarred myocardium also provided meaningful risk reclassification for cardiac death in 1 in 9 patients (into annual risk categories of <1%, 1–2.9%, and >3%). This study confirmed

the powerful and incremental value of the extent and severity of PET perfusion defects over clinical factors and rest ejection fraction in patients with known or suspected CAD.

Incremental prognostic value of rest LVEF, stress LVEF and LVEF reserve

Reduced LVEF and increased LV volumes are powerful risk markers for cardiac mortality.^{30–32} Mortality risk increases exponentially in patients with a low rest LVEF (Figure 3).^{25,332} In patients with low LVEF, stress perfusion abnormality further stratifies risk, such that for the same rest LVEF, a patient with severe ischemia has a much higher risk compared to a patient without ischemia.²⁵ Also, comparing two patients with a similar degree of Rubidium-82 MPI abnormality, risk is higher in the patient with a lower stress LVEF (Figure 4). Furthermore, even after accounting for differences in clinical factors and perfusion findings, patients with LVEF reserve < 0 (stress LVEF minus rest LVEF) have a higher risk of annualized cardiac events compared to patients with an LVEF reserve > 0 (Figure 5). Together, multiple studies^{2, 25, 28} confirm the independent prognostic value of rest LVEF, stress LVEF and LVEF reserve. Importantly, rest LVEF is a significant determinant of outcomes even after accounting for clinical factors, degree of perfusion abnormality and CFR.³⁴

Incremental prognostic value of CFR over perfusion defects

Several studies^{34, 35} have documented the incremental prognostic value of PET derived CFR over clinical factors and perfusion defect size and severity in patients with known or suspected CAD. In one study,³⁴ the risk of cardiac mortality was 5.6 fold higher in patients with the lowest tertile of CFR (<1.5) compared to the highest tertile of CFR. Patients with reduced CFR experienced higher cardiac mortality even after accounting for differences in clinical factors, extent and severity of perfusion defects and EF with a reclassification of risk in 10% of patients.³⁴ Another notable finding in this study was a lower risk of events in patients with high CFR (compared to low CFR), even among patients with severely abnormal scan, severely ischemic scans or reduced rest LVEF ($<40\%$) (Figure 6).³⁴ It is becoming clear from the early experience from several studies^{34–36} that a normal CFR may be an excellent marker of cardiac event free survival. More details of quantitative blood flow and its prognostic value will be covered in another review in this series.

Prognostic value of PET MPI and calcium score

Coronary artery calcification is pathognomonic of atherosclerosis and a high calcium score is associated with greater burden of coronary atherosclerosis³⁷ and ischemia.³⁸ In general, absence of coronary calcification (CCS=0), is associated with an excellent prognosis (0.4% annual rate of non-fatal myocardial infarction or cardiac death).³⁹ Also, patients with a low burden of calcified atherosclerosis and a normal MPI are low risk. Conversely, patients with high coronary calcification (CAC ≥ 400) have higher event rates $\sim 2\%$,³⁹ and higher frequency of ischemic burden on MPI (ischemic scan frequency: CAC = 0, 1.6%, 1–399, 7.6%, and CAC ≥ 400 , 28.8%, respectively).³⁸ A high calcium score does not always imply hemodynamically significant stenosis, and many patients with high burden of calcified coronary atherosclerosis may have a normal MPI.³⁸ In patients with high calcium score and a normal MPI, while the short term risk may be low (especially in asymptomatic patients),⁴⁰ their long-term risk of cardiac events is increased.^{40–42} Likewise, symptomatic patients with

a high burden of calcified coronary atherosclerosis (CAC score of ≥ 1000 vs. CAC < 1000)⁴³ appear to be at a higher risk despite normal PET MPI. A calcium score of > 100 is prevalent in patients undergoing PET MPI. In one study, 30% of patients with normal MPI had a CAC > 100 and patients with CAC were more likely to be started on therapy or optimized on therapy for CAD. Because of its prognostic value and ability to potentially alter management, CAC is routinely being incorporated into perfusion protocols or estimated from an attenuation correction CT scan,⁴⁴ at most centers.

Prognostic significance of impaired vasodilator heart rate reserve

Impaired chronotropic response to exercise stress⁴⁵ and to adenosine stress⁴⁶ likely reflect perturbations of autonomic tone and relate to high mortality. Similar findings were observed in patients undergoing vasodilator PET MPI; cardiac mortality rate is high (12.8% vs. 0.4%, respectively, $P < 0.0001$) in patients with a low vasodilator heart rate reserve (stress minus rest heart rate, ≤ 4 bpm vs. ≥ 15 bpm). The results of this study also suggest that a low vasodilator heart reserve portends a high cardiac mortality risk independent of age, particularly in the patients with high risk PET scans and in patients with systolic dysfunction (LVEF $\leq 45\%$).

Prognostic value of PET MPI in specific subsets of patients: Women

PET MPI offers significant advantages for the evaluation of women with suspected CAD due to increased accuracy, accurate attenuation correction and lower radiation dose. Sex differences in the prognostic accuracy of stress Rubidium-82 PET MPI were compared in 6,037 patients from the multicenter PET registry (2904 women and 3133 men).³³ As expected, women differed from men in several baseline scan characteristics, and were generally older, with higher mean rest LVEF and a higher frequency of normal scans, while, men had a higher frequency of prior coronary revascularization or prior MI. Women experienced lower cardiac mortality (3.7% vs. 6.0%, $P < 0.0001$). In both men and women, worsening stress MPI was associated with higher risk of cardiac mortality (Figure 7A) and provided incremental risk reclassification over clinical variables. Despite significant sex differences in clinical characteristics, the results of this study affirm that the prognostic value of PET MPI is similar in women and men independent of age (Figure 7B).

Patients with prior CABG

Patients with prior CABG are a high risk cohort with multiple comorbidities.⁴⁷ In these patients MPI is not only important to diagnose ischemia as a cause of symptoms, but, also understand the risk of abnormal scans, so as to plan appropriate management including high risk revascularization as needed. As with all patients, patients with prior CABG and a larger magnitude of stress MPI abnormality are at a higher risk of cardiac and all cause death. Also, magnitude of stress MPI abnormality provided improved risk reclassification for all-cause mortality [category free NRI 0.422 (0.240–0.602, $P < 0.001$)] and for cardiac death [category free NRI 0.552 (0.268–0.836, $P < 0.001$)]. The results of this study confirm the value of PET MPI in risk stratification of patients with prior CABG.

Obese patients

Obesity is a growing epidemic contributing to the increased burden of CAD. Although, noninvasive evaluation of CAD in obese individuals is challenging, due to accurate attenuation correction and high quality imaging, PET MPI is an excellent imaging choice in the obese. The prognostic value in obese patients has been recently reported from the PET prognosis multicenter registry (mean BMI 30.5 ± 7.4 Kg/m²). A normal PET MPI was associated with a very low cardiac mortality in patients with BMI in the normal, overweight, obese, moderately obese and severely obese patients (annualized cardiac mortality 0.38%, 0.43%, 0.15%, 0.2%, and 0.1%, respectively). A worsening scan abnormality (mild, moderate, severely abnormal) was associated with a greater hazard ratio for cardiac death, in each of the BMI categories, thereby establishing the prognostic utility of PET MPI in overweight and obese individuals.

PET MPI TO GUIDE CLINICAL MANAGEMENT DECISIONS

Radionuclide MPI is the most extensively validated non-invasive method to guide patient management, and to assess response to therapy. We will briefly discuss the literature on the role of PET MPI to guide coronary angiography and revascularization, to assess response to aggressive medical and life- style interventions, and to assess improvement in left ventricular function following coronary revascularization.

PET MPI to guide decisions for coronary angiography and revascularization

Large prospective clinical trial data using PET MPI to guide coronary angiography and revascularization decisions are lacking. Based on expert opinion and data from large observational studies, <5%, 5–10% and >10% ischemic myocardium on PET MPI are used to define low (< 1%), intermediate (1–3%) and high risk (> 3%)²⁹ and incorporated in the current ACC/AHA appropriate use documents on coronary angiography⁴⁸ and coronary revascularization⁸ (Figures 8A and 8B).^{5, 49} Invasive coronary angiography is deemed appropriate for patients with: high risk MPI (>10% ischemic myocardium), high risk markers such as T1D, significant stress induced LV dysfunction, discordant and ongoing symptoms or significant ECG changes during stress coronary angiography, or intermediate risk findings and specific symptoms.⁴⁸ Invasive coronary angiography is however, not considered appropriate in patients with low risk PET findings (% ischemic myocardium < 5%).⁴⁸

Appropriate use of coronary revascularization⁸ is determined by symptom status (Canadian Cardiovascular Society Class I–IV angina), imaging findings (low/intermediate/or high risk), current medical therapy (no therapy to maximal therapy), and coronary anatomy. Coronary revascularization is considered appropriate in patients with high risk findings on PET MPI, significant symptoms (CCS class III or IV angina), and less appropriate in patients with low risk PET findings and in asymptomatic patients (Figure 9). The results of the ongoing ISCHEMIA study (<https://ischemiatrial.org/>) will inform us more definitively if patients with stable angina, CAD suitable for revascularization, and moderate to severe ischemia on imaging would benefit from coronary revascularization.

PET MPI to assess changes in myocardial perfusion in response to aggressive life style changes and lipid lowering therapy

Due to the high sensitivity of PET and quantitative assessments of relative and absolute myocardial perfusion by PET, it has been used in several studies for assessing response to therapy; we discuss below 3 of the studies that used relative PET MPI.^{50, 51} In a 409 patient study, myocardial perfusion improved in parallel with intensity of medical therapy and predicted clinical outcomes.⁵¹ Patients with bigger and more severe perfusion abnormalities (OR 4.87, $P < 0.001$) and patients with worsening of perfusion between the baseline and follow-up scans (2.6 years later, OR 1.36, $P 0.01$) had higher cardiac events (coronary revascularization, non-fatal myocardial infarction and cardiac death). Also, in another study, a visual improvement in myocardial perfusion was detected after 6 months of aggressive lipid lowering [high dose atorvastatin (80 mg, $N=72$) compared to placebo ($N=73$)], with greater improvement in patients with larger perfusion defects ($> 64\%$ of the heart).⁵² Finally, in a detailed prospective study, Gould et al.,⁵⁰ randomized patients with documented angiographic CAD (LVEF $> 25\%$ and not taking lipid lowering drugs) to aggressive risk factor modification (low fat vegetarian diet, mild to moderate exercise, stress management, and group support, $N=20$) versus usual care by their physicians (primarily anti-anginal medications, $N=15$). After 5 years of intervention, the severity, size and combined size and severity of the perfusion defects on stress PET (Rubidium-82 or N-13 ammonia) improved in the experimental patients and worsened in the control patients, while changes on quantitative coronary angiography were much less apparent (Figure 10). This study demonstrated that progression or regression of CAD in response to therapy can be followed by non-invasively by rest and dipyridamole PET MPI. Indeed, PET MPI appears to be more sensitive than quantitative coronary angiography in detecting short-term and long-term changes in coronary atherosclerosis in response to therapeutic interventions.⁵⁰

PET MPI to predict recovery of function after revascularization

Accurate non-invasive quantification of myocardial viability and ischemia are of paramount significance for identification of patients who may benefit from coronary revascularization. In patients with ischemic cardiomyopathy, percent peak activity of radiotracer at rest, stress,^{11, 12, 53} late retention of N-13 ammonia¹² or Rubidium-82,^{54–56, 39, 42, 43} and mismatch between perfusion and F-18 FDG imaging have been used to identify viable myocardium. Percent peak activity ($< 50\%$) on N-13 ammonia PET^{11, 53} has a high negative predictive value (NPV $> 86\%$) and a modest positive predictive (PPV 48%) to predict significant improvement in regional wall motion after revascularization. Also, stress perfusion and FDG imaging have higher predictive values for recovery of function compared to rest perfusion (stress perfusion PPV 63% , NPV 87% and FDG PET imaging PPV 76% , NPV 92%). Data on late tissue retention of N-13 ammonia and late Rubidium-82 tissue kinetics as markers of viability are limited.^{54, 57, 58} In current clinical practice percent peak perfusion tracer activity is 50% is considered to represent viable myocardium. When percent peak perfusion tracer activity is $< 50\%$, metabolic imaging with FDG may be considered. Late retention of perfusion tracers is not commonly used.^{11, 12, 53–56}

CONCLUSIONS

A large critical mass of literature supports the value of PET MPI, rest LVEF, stress LVEF, LVEF reserve by Rubidium-82 MPI for risk assessment. The use of CFR and calcium score can further refine risk stratification by PET MPI. PET MPI is more sensitive than anatomic measures of coronary atherosclerosis to determine response of coronary atherosclerosis to aggressive risk factor modification. Rest and stress PET MPI are important components of the viability evaluation in patients with systolic dysfunction to predict functional response to revascularization. The prognostic value of PET MPI is confirmed in several single center studies and a large recent multicenter registry study of PET MPI. Also, the prognostic value of PET MPI is validated across multiple centers and in several unique subsets of patients. PET MPI provides a meaningful reclassification of risk after accounting for clinical factors and LVEF. The percent of ischemic myocardium on PET MPI and LVEF are used to guide the appropriate use of coronary angiography and coronary revascularization in patients with stable angina. Overall, the current literature suggests that the prognostic value of PET MPI is equivalent to that of SPECT MPI. Due to superior image quality, lower radiation dose and ability to quantify perfusion, PET MPI may be the test of choice when available particularly in patients requiring pharmacological stress testing.

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Figure 1. LVEF Reserve in Relation to Magnitude of Ischemia (A) and Angiographic Extent of CAD (B)

The bar graphs show Rubidium-82 vasodilator LVEF reserve stratified by magnitude of ischemia and magnitude of angiographic CAD. LVEF reserve was lowest in patients with severe reversible defects and in patients with left -main/3-vessel CAD. Reproduced with permission from reference.¹

Figure 2. Unadjusted (A) and Risk Adjusted (B) Hazard of Cardiac Events Stratified by % Myocardium Abnormal

Unadjusted (top) and risk adjusted (bottom) hazard curves showing significantly higher hazard of cardiac events in patients with mild, moderate, severe, or very severely abnormal PET MPI, when compared to the reference group (normal PET MPI). Reproduced with permission from reference.²⁵

Figure 3. Predicted Cardiac Mortality in Women and Men as a Function of Rest LVEF on PET MPI

The predicted CAD mortality rate increases exponentially with decline in rest LVEF in both women (left) and men (right). Reproduced with permission from reference.³³

Figure 4. Predicted All Cause Death Rate as a Function of Stress LVEF and Abnormality on PET MPI

The bar graphs demonstrate a graded increase in all-cause mortality across stress LVEF categories of >50%, 40–50% and <40% in patients with normal (SSS = 0–3), mildly abnormal (SSS 4–8) or moderate to severely abnormal (SSS >8) PET MPI. Reproduced with permission from reference.²

Figure 5. Predicted Cardiac Events and All Cause Death Rates in Patients with LVEF Reserve 0 Compared to Patients with LVEF Reserve < 0

The bar graphs show that annualized cardiac events (cardiac death or MI) and all cause death are higher in patients with LVEF reserve < 0 compared to patients with LVEF reserve > 0 . † $P < 0.001$. Reproduced with permission from reference.²⁵

Figure 6.

Annualized mortality stratified by CFR tertiles and total scan abnormality (A), ischemia (B) and LVEF (C). Patients in the upper tertile of CFR (high CFR) had the lowest events, even in high risk scans -total scan abnormality ≥10%, ischemia ≥10% and LVEF < 40%.

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Figure 7. A and B. Risk Stratification of Men and Women with PET MPI
A. Cumulative cardiac mortality increases gradually across categories of scan abnormality from normal to severely abnormal in women (left) and in men (right).
B. The bar graphs demonstrate a proportional increase in cardiac mortality with older age and with scan abnormality in both women (left) and men (right).
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8A.

8B.

Figure 8. PET MPI Findings to Guide Appropriate Use of Coronary Angiography in Suspected CAD (A) and in Known Obstructive CAD (B)

An algorithmic approach to appropriate use of coronary angiography and coronary revascularization in patients with stable symptoms based on PET MPI results. Adapted with permission from reference.⁴⁸

A= appropriate; I = inappropriate; U = uncertain. PCI = percutaneous coronary intervention. CABG = coronary artery bypass graft.

High Risk Findings on Noninvasive Study						CCS Class III or IV Angina					
Symptoms Med Rx						Stress Test Med Rx					
Class II or IV Med Rx	A	A	A	A	A	High Risk Med Rx	A	A	A	A	A
Class II or IV Med Rx	A	A	A	A	A	High Risk Med Rx	A	A	A	A	A
Asymptomatic Med Rx	U	A	A	A	A	Int. Risk Med Rx	A	A	A	A	A
Class II or IV Med Rx	A	A	A	A	A	Int. Risk Med Rx	U	U	A	A	A
Class I or II Med Rx	U	A	A	A	A	Low Risk Med Rx	U	A	A	A	A
Asymptomatic Med Rx	U	U	A	A	A	Low Risk Med Rx	U	A	A	A	A
Coronary Anatomy	CTD of 1-v: no other disease	1-2-v: disease no prox LAD	1-v: disease of prox LAD	2-v: disease with prox LAD	3-v: disease no left main	Coronary Anatomy	CTD of 1-v: no other disease	1-2-v: disease no prox LAD	1-v: disease of prox LAD	2-v: disease with prox LAD	3-v: disease no left main

Intermediate Risk Findings on Noninvasive Study						CCS Class I or II Angina					
Symptoms Med Rx						Stress Test Med Rx					
Class II or IV Med Rx	A	A	A	A	A	High Risk Med Rx	A	A	A	A	A
Class II or IV Med Rx	U	A	A	A	A	High Risk Med Rx	U	A	A	A	A
Asymptomatic Med Rx	U	U	U	U	A	Int. Risk Med Rx	U	A	A	A	A
Class II or IV Med Rx	U	U	A	A	A	Int. Risk Med Rx	U	U	U	A	A
Class I or II Med Rx	U	U	U	A	A	Low Risk Med Rx	U	U	A	A	A
Asymptomatic Med Rx	U	U	U	U	A	Low Risk Med Rx	U	U	U	U	U
Coronary Anatomy	CTD of 1-v: no other disease	1-2-v: disease no prox LAD	1-v: disease of prox LAD	2-v: disease with prox LAD	3-v: disease no left main	Coronary Anatomy	CTD of 1-v: no other disease	1-2-v: disease no prox LAD	1-v: disease of prox LAD	2-v: disease with prox LAD	3-v: disease no left main

Low Risk Findings on Noninvasive Study						Asymptomatic					
Symptoms Med Rx						Stress Test Med Rx					
Class II or IV Med Rx	U	A	A	A	A	High Risk Med Rx	U	A	A	A	A
Class I or II Med Rx	U	U	A	A	A	High Risk Med Rx	U	U	A	A	A
Asymptomatic Med Rx	U	U	U	U	U	Int. Risk Med Rx	U	U	U	U	A
Class II or IV Med Rx	U	U	A	A	A	Int. Risk Med Rx	U	U	U	U	A
Class I or II Med Rx	U	U	U	U	U	Low Risk Med Rx	U	U	U	U	U
Asymptomatic Med Rx	U	U	U	U	U	Low Risk Med Rx	U	U	U	U	U
Coronary Anatomy	CTD of 1-v: no other disease	1-2-v: disease no prox LAD	1-v: disease of prox LAD	2-v: disease with prox LAD	3-v: disease no left main	Coronary Anatomy	CTD of 1-v: no other disease	1-2-v: disease no prox LAD	1-v: disease of prox LAD	2-v: disease with prox LAD	3-v: disease no left main

Figure 9. PET MPI Findings (High risk, Intermediate risk, Low risk) to Guide Appropriate use of Coronary Revascularization

A matrix based on PET MPI results (High risk –Top; Intermediate risk-middle; low risk-bottom) and symptoms combined with coronary angiography findings to determine the appropriate use of coronary revascularization. Reproduced with permission from reference.⁸

Figure 10. Comparison of Changes in QCA and PET MPI Following Aggressive Risk Factor Modification

Comparison of mean changes in coronary artery disease by QCA (quantitative coronary angiography) and by PET (positron emission tomography) after aggressive risk factor modification. Following aggressive life style changes, myocardial perfusion improved much more than improvement in coronary stenosis by quantitative coronary angiography. Small changes in coronary luminal dimensions by aggressive risk factor modification can translate into much larger changes in myocardial perfusion, as myocardial perfusion is related to the lumen radius raised to the power of four. Min Dia = minimal absolute lumen diameter; % DS = percent diameter stenosis; SFR = stenosis flow reserve; Low quad = myocardial quadrant with the lowest average activity; % LV > 2.5 SD's = percentage of the left ventricle outside 2 standard deviations of normal; % LV < 60% of maximum = percentage of the left ventricle with less than 60% of maximal activity. Reproduced with permission from reference.⁵⁰

Table 1

High Risk Scan Features on PET MPI

Variables	High Risk Features
Stress variables	
ECG	>1 mm ST elevation >2 mm ST depression
Heart rate reserve ⁵⁹	< 4 beats
Imaging variables	
Stress defect size and severity ^{5, 25}	10%
Rest defect size and severity ^{5, 25}	10%
Reversibility size and severity ^{8, 48}	10%
Transient cavity dilation ¹⁹	>1.13
Increased lung uptake	Visual estimate
Rest LVEF ^{25, 33}	<40%
Stress LVEF ^{2, 25}	<40%
LVEF reserve ¹	<+5%
Increased RV tracer uptake	Visual estimate
Transient increase in RV tracer uptake ⁶⁰	10% increase in RV/LV uptake ratio with stress or 10% increase in the RV/LV ratio at stress compared to rest
Calcium score ⁴³	> 400
CT coronary angiography	Severe CAD
Quantitative blood flow assessment (CFR) ³⁴	< 1.5

ECG = electrocardiogram; LV = left ventricular; EF = ejection fraction; CAD = coronary artery disease; RV = right ventricular; LVEF reserve = stress LVEF minus rest LVEF; heart rate reserve = stress heart rate minus rest heart rate.

Table 2
Summary of Studies Evaluating Prognostic Value of PET Perfusion Defects and Ejection Fraction

	Marwick ³	Sdringola ⁵¹	Yoshinaga ⁴	Lertsurapa ²	Dorbala ²⁵	PET Registry ²⁸
Number of patients	657	326	367	1441	1432	7061
Age (years)	62±12	58±9	59±10.9	69.5±12	63±12	63±13
Women (%)	29	9	54.2	58.2	52	47
Prior CAD (%)	85	100	40.3	53.6	30.6	
Prior MI (%)	48	30	30.9	NA	10	27
Prior PCI/CABG (%)	37	29	32.5	NA	24	27
Prior angiogram (%)	88	NA	NA	NA	NA	NA
Mean follow-up (yrs.)	3.4	5	3.1±0.9	2.5±0.9	1.7±0.7	2.5±1.5
Normal MPI (%)	24	NA	70.6	64.8	54	44
Mean rest LVEF%	N/A	57±11	NA	59±15.6	60±14	60±16
Total Events (N)	151	62*	62	132	184	570
All cause death	NA	NA	11	132	140	570
Cardiac death	81	NA	NA	NA	43	169 [†]
MI	16	NA	6	NA	44	NA
UA/Hospitalization	7	NA	16	NA	NA	NA
Late coronary revascularization	47	16	29	NA	NA	NA
Annualized event rate – Normal scan	0.9%: CD 1.2%: CE	NA	0.4%: ACD/MI 1.7%: AER	2.4%: ACD	0.7%: CD/MI 3.5%: ACD	0.8%: CD 5.1%: ACD
Annualized event rate – Abnormal scan	4.3%: CD 7%: CE	NA	4.2%: ACD/MI 13%: AER	5.7%: ACD	6%: CD/MI 8%: ACD	4.3%: CD 10.2%: ACD
Independent predictors of survival	Diabetes Functional class Angio CAD extent PET results	Size and severity of perfusion defects; worsening scan risk factors treatment	Age > 65 Hx MI > 2 risk factors SSS	Age, Diabetes stress LVEF SSS	Rest LVEF Hx CAD PVD Insulin % myo ischemic % myo scarred LVEF reserve	Age Male Diabetes Dyslipidemia Smoking Angina Rest HR % myo ischemic % myo scarred

* Including stroke;

[†] data from 3 centers;;

UA = unstable angina; MPI = myocardial perfusion imaging; LVEF = left ventricular ejection fraction; ACD = all-cause death rate; CE = cardiac events; AER = annual event rate (ACD, MI, late revascularization and hospitalization); MI = non-fatal myocardial infarction; Hx = history of; CAD = coronary artery disease; PCI/CABG = percutaneous coronary intervention/coronary artery bypass graft; PVD = peripheral vascular disease; HR = heart rate; SSS = summed stress score; Angio = angiographic; myo = myocardium; NA = not available.