Prognostic estimation of coronary artery disease risk with resting perfusion abnormalities and stress ischemia on myocardial perfusion SPECT

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Background. **The extent and severity of stress ischemia are strong predictors of coronary artery disease (CAD) events. Prognosis associated with myocardial perfusion single photon emission computed tomography (MPS) abnormalities on the resting scan as it relates to stress ischemia has been incompletely described.**

Methods and Results. **The Myoview Prognosis Registry was a prospective consecutive series of 7849 outpatients enrolled from 5 geographically diverse centers. Patients were followed up for the occurrence of CAD events (nonfatal myocardial infarction [MI] or death related to MI, heart failure, or sudden cardiac death). Time to CAD event (n = 545) was estimated by use of univariable and multivariable Cox proportional hazards models (risk adjusted by symptoms, risk factors, and comorbid conditions). For patients with no resting defects, overall CAD event rates were 1.2%, 8%, and 10% for patients with 0% ischemic myocardium, 1% to 4.9% ischemic myocardium, and 5% ischemic myocardium or greater, respectively ($P < .0001$). As the percent myocardium with resting defects worsened, overall CAD event rates increased, such that for patients with 10% or more of the rest myocardium with perfusion defects, cardiovascular death or MI rates ranged from 7% to 44% ($P < .0001$). In a model including both the percent of the myocardium with resting defects and the percent ischemia, both were highly predictive of CAD events ($P < .0001$). For every 1% increase in ischemic myocardium, there was a 7% increased risk of CAD events ($P < .0001$). A 3% increase in risk of CAD events was observed for patients with every 1% of the myocardium with resting defects ($P < .0001$).**

Conclusions. **The estimation of CAD risk may be optimally estimated by use of a combination of resting MPS, reflecting a patient's burden of disease, and MPS with provocative ischemia. (J Nucl Cardiol 2008;15:762-73.)**

Key Words: Myocardial perfusion single photon emission computed tomography • prognosis • infarction • ischemia

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There is a vast evidence base regarding the prognostic accuracy of stress myocardial perfusion single photon emission computed tomography (MPS).[1-4] In diverse patient subsets there is a directly proportional relationship between the extent and severity of stress perfusion abnormalities and accelerating risk of cardiac events.[5,6] This delineation of risk that separates low- and high-risk patient subsets was facilitated by the introduction of segmental models that detail the extent of perfusion defects as well as the severity of abnormalities across the myocardium.[5]

Despite the wide and varied evidence on outcomes after stress MPS, the associations with risk remain incompletely defined with regard to the interrelationship between rest perfusion abnormalities and inducible ischemia. Moreover, cardiac death is one of the most common endpoints used in predictive models for cardiovascular (CV) imaging yet may occur as a result of heart failure, sudden death, or fatal myocardial infarction (MI), all arising from different stages within the atherosclerotic

disease process.[7,8] As we unfold our evidence base and look to future developments in the field of nuclear cardiology and CV imaging, further exploration of associations between resting abnormalities and stress ischemia on MPS to varied outcomes may prove beneficial for targeting markers for optimal risk detection.

Thus we present an exploratory analysis that is based on expanding the boundaries of our knowledge of risk prediction models. Our primary endpoint was to explore the relationship between CV outcomes with the extent and severity of ischemia as well as perfusion abnormalities on the resting MPS. Secondarily, we propose to examine the prognostic significance of ischemia relative to the presence and extent of resting perfusion abnormalities.

METHODS

Patient Entry Criteria

Details of the Myoview Prognosis Registry have been published elsewhere.[4,9,10] However, in brief, the Myoview Prognosis Registry was a prospective, consecutive series of patients enrolled from 5 tertiary medical centers enrolling 7849 outpatients evaluated for suspected or known coronary artery disease (CAD) from 1997 through 1999. Informed consent was provided by each patient for the stress MPS procedure as well as for participation in the follow-up portion of this study. Previous reports from this registry have been published.[4,9,10]

Stress Testing Procedures

For patients capable of performing maximal stress, a graded exercise test was performed by use of the modified Bruce protocol with metabolic equivalent estimates based on the standard protocol. Before testing, resting heart rate and blood pressure were performed and a 12-lead electrocardiogram (ECG) was obtained in the supine, sitting, and standing positions. During each minute of exercise, similar measurements were obtained. Continuous monitoring of electrocardiographic changes was performed throughout the stress procedure and for several minutes into recovery. The procedures for the exercise test were in accordance with those of the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines.[11] The exercise test was discontinued for excessive fatigue or dyspnea and under the following circumstances: marked electrocardiographic changes defined as 3 mm of ST-segment depression or ST elevation of 1mm or greater in a non–Q-wave lead, ventricular tachycardia or fibrillation; chronotropic incompetence, exertional hypotension, or limiting chest pain symptoms. Patients were monitored into recovery for complete or near resolution of symptoms and electrocardiographic changes. The ECG was considered to be abnormal if there was 1 mm of horizontal or downsloping ST depression or greater at 60 milliseconds after the J point, ST elevation of 1mm or greater in a non–Q-wave lead of upsloping ST depression or greater.

Vasodilator stress by use of intravenous adenosine or dipyridamole was performed for patients unable to adequately perform exercise testing. The conduct of the pharmacologic stress procedure was in accordance with ACC/AHA/American Society of Nuclear Cardiology standards.[2,12] Specifically, dipyridamole was infused at 0.142 mg $\cdot$ kg^{-1} $\cdot$ min^{-1} over a 4-minute period. Aminophylline, 75 to 125 mg, was administered to patients with persistent side effects; nitroglycerin was administered at the discretion of the overseeing physician. Intravenous adenosine was infused per the standard dose of 140 μg $\cdot$ kg^{-1} $\cdot$ min^{-1} over a 6-minute period. For adenosine, radiopharmaceutical injection occurred at the midpoint of the infusion. However, radiopharmaceutical injection occurred approximately 3 to 4 minutes after the dipyridamole infusion.

Although nearly half of the patients underwent vasodilator stress testing; only 8% underwent dobutamine stress MPS. Dobutamine was infused via standard incremental dosing ranging from 5 to 40 μg $\cdot$ kg^{-1} $\cdot$ min^{-1}. The procedure for the discontinuation of dobutamine was similar to that for exercise testing. This procedure was terminated after attainment of target heart rate. For patients who failed to reach the predicted maximal heart rate levels, 1 mg of atropine was administered. For all of the pharmacologic stress procedures, continuous monitoring for clinical signs and symptoms of ischemia were performed and ECGs were obtained. Similar to the exercise procedures, a 12-lead ECG and heart rate and blood pressure measurements were obtained for each minute of the procedure and for several minutes into recovery.

Gated MPS Protocol and Image Interpretation

All MPS scans were interpreted by experienced nuclear cardiologists blinded to the patient's clinical history or exercise test results, with the exception of the patient's gender. MPS procedures were standardized to protocols set forth by ACC/AHA/American Society of Nuclear Cardiology.[2] MPS protocols were predefined to be similar across each of the participating sites. Specifically, rest (thallium or technetium 99m Myoview [GE Healthcare, Buckinghamshire, England]) and stress Tc-99m Myoview imaging was performed. MPS imaging was performed immediately at rest and after exercise with a gamma camera, where acquisitions were performed over a 180° semicircular orbit. Data acquisition included a 64 $\times$ 64 matrix for 32 and 64 projections for thallium and Tc-99m by use of a step-and-shoot format. Horizontal and vertical long-axis and short-axis image sets were normalized to maximal myocardial activity.

Poststress gated left ventricular ejection fraction (LVEF) measurements were available in 4575 patients.

All scans were interpreted locally by use of a 20-segment myocardial model for image interpretation. This interpretation was performed separately from the clinical reading and with blinding to all data but patient gender. Each of the 20 segments was scored as normal to abnormal on a 5-point scoring system, with 0 indicating normal and 4 indicating absent perfusion. Total scores for the rest and stress images were summed. Percent rest myocardium was calculated as (Total rest score/80) $\times$ 100. Percent ischemic myocardium was calculated as [(Stress score $-$ Rest score)/80] $\times$ 100. For this analysis, 0% was normal or low risk, 1% to 4.9% was minimal, 5% to 9.9% was mildly abnormal, and 10% or more was moderately to severely abnormal.

Ascertainment of Follow-Up Outcome Status

The follow-up portion of this study was approved by each institution's institutional review board. For this study, patients were initially contacted at 6 months and then at yearly intervals. A skilled research nurse or coordinator performed each patient interview using a scripted follow-up form for ascertainment of death status, CV hospitalizations, or invasive procedure use. In the case in which a patient was unavailable, the interview could be performed with a family member. All identified CV events were confirmed by review of the patient's death certificate or medical records (including confirmation from the referring physician). With regard to death, specific rules were applied to the defining of etiology. A witnessed cardiac arrest as a cause of death listed on a death certificate was defined as sudden cardiac death. Fatal MI was defined if it occurred within 24 hours of patient admission for acute MI. Death due to heart failure was defined by use of the medical record or death certificate as the preceding circumstance. Death during hospitalization for a cerebrovascular accident (CVA) was defined as a fatal CV event. A nonfatal CVA was classified with confirmation of the patient's hospital records. Our case report form indicated that the remaining subset of CV deaths were related to peripheral arterial disease. Deaths related to peripheral arterial disease were also confirmed by medical records. All other deaths were classified as all cause related. A nonfatal MI was defined based on admission for acute MI meeting electrocardiographic and enzymatic criteria for myocardial necrosis. Documentation of the date and occurrence of coronary revascularization procedures was also performed for censoring in the survival analysis. All death certificates and medical records were reviewed by experienced cardiologists blinded to the patient's stress test, clinical history, and MPS results. Only 1% of patients were lost to follow-up. The total time to follow-up for surviving patients was a median of 1.6 years (interquartile range, 1.2-2.0 years).

For this analysis, CAD events were defined as fatal or nonfatal MI combined with the occurrence of sudden cardiac death or heart failure–related death. Total CV events included CAD events plus fatal CVAs or death related to peripheral arterial disease.

Statistical Analyses

Initial comparisons of the frequency of clinical history, risk factor, and symptom data were performed in ischemic MPS subsets of patients by use of a χ^2 statistic, with the exception that in ischemic MPS subsets, we compared the mean differences ($\pm$SD) in age (in years) using analysis-of-variance techniques. A comparison of the observed frequency of types of death and MI was performed by use of a χ^2 statistic. A receiver operating characteristic (ROC) curve area, including 95% confidence interval (CI), was plotted for CAD and CV events including the percent rest myocardium with abnormalities, percent ischemic myocardium, and poststress LVEF.

Our primary endpoint was time to CAD events including the combined outcome of fatal or nonfatal MI, heart failure death, or sudden cardiac death (n = 545). Although we included heart failure deaths in this endpoint, we could not discern the underlying etiology of this event (diastolic or systolic dysfunction) in every case. However, the exclusion of these events in ensuing risk models did not affect the results presented herein. Secondary endpoints included the total CV outcome that included fatal stroke and deaths related to peripheral arterial disease (n = 752). Univariable and multivariable Cox proportional hazard models were calculated to estimate time to the previously mentioned CAD and CV events. Model overfitting procedures were considered and included the consideration of 1 variable in a model for every 10 outcomes. The proportional hazards assumption was visually evaluated. Additional regression diagnostics were performed including examination of residuals. In each case the proportional hazards assumption was met. Patients were followed up until the occurrence of the primary endpoint or coronary revascularization and then censored at the time of the procedure.

Unadjusted or univariable Cox survival curves were calculated to estimate time to CAD and CV events by the percent ischemic myocardium including subsets with no (0%), minimal (1%-4.9%), mild (5%-9.9%), and moderate to severe ($\geq$10%) ischemia. All survival curves were plotted through 2 years of follow-up. We evaluated this model in patients presenting for evaluation of de novo chest pain symptoms and no prior history of CAD (n = 2992) as well as in a cohort of patients with prior MI (n = 1094). A stratified Cox model was also used to assess risk assessment with the percent ischemic myocardium on MPS by subsets of patients with varying degrees of resting perfusion defects. The rest MPS scan was divided by percent myocardium, with 0% indicating normal or no abnormalities; 1% to 4.9%, minimal abnormalities; 5% to 9.9%, mildly abnormal; and 10% or greater, moderately to severely abnormal. Separate Cox models for rest thallium 201 and Tc-99m did not influence the results presented herein. We also attempted to include the rest agent as a covariate within our prognostic models, and it was nonsignificant.

For the purposes of these analyses, initial multivariable models included the percent ischemic myocardium as well as the percent rest myocardium with reduced perfusion or abnormalities. Subsequent models included risk adjustment by (1) age, stress type (exercise or vasodilator stress), gender, and ethnicity and (2) peripheral arterial disease, known CAD, chronic obstructive lung disease, prior cancer, heart failure, cardiac risk factors (smoking, family history of premature coronary heart disease, hypertension, diabetes, and hyperlipidemia), and typical angina, as well as variables noted in the first model. Although known CAD was left in this model, it was nonsignificant (P = .52) when the percent rest myocardium was in the model. Finally, we plotted the predicted risk of CAD events using the predicted rates from the final multivariable model.

RESULTS

Clinical Characteristics

Patients with more extensive ischemia were generally older, more often male, had a greater risk factor burden, and a greater prevalence of noncardiac atherosclerosis (Table 1). Patients with no ischemia on MPS, however, also had a demonstrable risk, with 29% having

Table 1. Clinical characteristics of study cohort (N = 7849)

	% Ischemic myocardium				
	0% (n = 5722)	1%–4.9% (n = 859)	5%–9.9% (n = 717)	≥10% (n = 551)	*P* value
Age (y)	62 ± 12	63 ± 11	64 ± 10	65 ± 9	<.0001
Female gender	42%	28%	23%	21%	<.0001
Ethnicity other than white	32%	41%	41%	32%	<.0001
Current smoker	25%	35%	34%	30%	<.0001
Smoking history	19%	27%	29%	34%	<.0001
Family history of premature CAD	32%	33%	31%	29%	.45
Hypertension	52%	59%	61%	62%	<.0001
Hyperlipidemia	38%	49%	56%	63%	<.0001
Diabetes					<.0001
Non–insulin dependent	10%	21%	29%	30%	
Insulin dependent	8%	9%	10%	11%	
Obese	23%	32%	40%	42%	<.0001
Known CAD	29%	37%	36%	43%	<.0001
Prior stroke	2%	3%	3%	3%	<.0001
Prior PAD	4%	7%	6%	5%	<.0001
Prior valve surgery	0.3%	1%	.7%	.7%	<.0001
Heart transplant	0.2%	0%	0%	0%	.122
Other transplant	8%	5%	3%	0%	.011
COPD	1%	1%	1%	0.2%	.019
Renal failure	2%	0.6%	0.3%	0.2%	<.0001
Liver disease	0.1%	0.1%	0%	0%	.58
Prior cancer	1%	0%	0.6%	0%	<.0001
Typical angina	23%	38%	37%	31%	<.0001
Heart failure symptoms	6%	9%	9%	6%	.001
Medications					
β-Blocker	22%	31%	30%	28%	<.0001
Calcium channel blocker	21%	22%	26%	19%	.25
ACE inhibitor	14%	13%	11%	15%	.46
Nitroglycerin	9%	12%	9%	13%	.024
Statin	26%	46%	53%	65%	<.0001

Except for age, which is presented as mean ± SD, all data are presented as frequencies (%), rounded to the whole percent, except when the percent was less than 1.
PAD, Peripheral arterial disease; *COPD*, chronic obstructive pulmonary disease; *ACE*, angiotensin-converting enzyme.

known CAD, 52% being hypertensive, and 29% having presented with suspected cardiac symptoms.

Stress Test Characteristics

Patients with more extensive and severe ischemia more often underwent pharmacologic stress MPS ($P < .0001$), with a smaller proportion having poststress LVEF of 60% or greater (Table 2). By comparison, nearly three fourths of patients with no ischemia on MPS had poststress LVEF measurements of 60% or greater ($P < .0001$).

CV Outcomes

During 2 years of follow-up, the observed frequency of death was 3.5% (n = 274), with an additional 5.6% having an acute nonfatal MI (n = 430). Of the deaths, 29 were fatal MIs, 72 resulted from sudden cardiac death, and 14 were related to heart failure; in addition, 16 fatal CVAs were reported. Figure 1*A* details the frequency of percent ischemic myocardium on MPS by observed events. Approximately 35% to 40% of patients having acute MI had no ischemia. Of the patients with acute MI or sudden cardiac death, more than one third had at least mild ischemia. Of the 14 patients who died from heart

Table 2. Electrocardiographic and stress myocardial perfusion results by percent ischemic myocardium patient subsets

	% Ischemic myocardium				
	0% (n = 5722)	1%–4.9% (n = 859)	5%–9.9% (n = 717)	≥10% (n = 551)	*P* value
Pharmacologic stress	42%	48%	49%	60%	<.0001
Heart rate (beats/min)					
Rest	71 ± 31	69 ± 39	69 ± 12	68 ± 12	.31
Peak exercise	128 ± 44	123 ± 33	113 ± 32	120 ± 31	<.0001
Systolic/diastolic blood pressure (mm Hg)					
Rest	145/79	144/76	150/78	145/79	<.0001*
Peak exercise	169/79	160/75	159/76	171/76	<.0001
Abnormal rest ECG	32%	56%	59%	62%	<.0001
Electrocardiographic evidence of Q-wave MI	5%	16%	13%	18%	<.0001
ST depression ≥1 mm†	14%	18%	24%	33%	<.0001
Exertional angina	5%	6%	7%	7%	<.0001
Summed score					
Rest	1.0 ± 3.9	4.0 ± 6.0	3.8 ± 6.0	4.0 ± 6.1	<.0001
Stress	1.0 ± 3.9	6.0 ± 5.9	9.0 ± 5.8	16.3 ± 7.6	<.0001
% Rest defects					<.0001
0%	89%	45%	46%	45%	
1%–4.9%	3%	21%	21%	19%	
5%–9.9%	3%	15%	14%	19%	
≥10%	5%	19%	19%	18%	
Poststress LVEF‡					<.0001
≥60%	74%	17%	8%	15%	
50%–59%	7%	29%	28%	25%	
40%–49%	9%	30%	36%	38%	
<40%	10%	24%	28%	21%	

*$P < .0001$ for all blood pressure comparisons, except for rest systolic blood pressure ($P = .99$).
†Upsloping ST depression of 1.5 mm or greater was included in this category.
‡Poststress LVEF measurements were available in 4575 patients.

failure, only 14.3% had moderate to severe ischemia. By comparison, nearly two thirds of patients with deaths from all causes had no ischemia. A similar relationship between events and resting perfusion abnormalities was observed (Figure 1*B*). In univariable Cox models, rest and ischemic defects on MPS were highly significant estimators of the combined endpoint of CAD-related events, including fatal or nonfatal MI, and sudden cardiac death ($P < .0001$ for both rest and ischemic MPS).

CAD Event–Free Survival by Ischemia in Patients with No Prior CAD History and Patients After MI

Our initial analysis examined historical measures of CAD including patients with de novo chest pain evaluation and patients after MI or with known CAD. Overall, the CAD event–free survival rate was 98.3% in a subset of patients presenting with de novo chest pain evaluation and no prior CAD history. Incident CAD event rates were 1.4%, 8.6%, and 19.7% in patients with 0% ischemic myocardium, 1% to 4.9% ischemic myocardium, and 5% ischemic myocardium or greater, respectively ($P < .0001$) (Figure 2). In this same cohort the addition of total CV deaths or MI as the endpoint resulted in 2-year event rates that ranged from 3.8% to 20.5% for patients with 0% to 5% ischemic myocardium or greater ($P < .0001$) (Figure 2).

In a similar analysis of patients with prior MI, the cumulative CAD event–free survival rate (eg, free from fatal or nonfatal reinfarction or sudden cardiac death) was 84.6%. For this analysis of CAD events, the overall rates were 5%, 10%, 19%, and 29% for patients with 0% ischemic myocardium, 1% to 4.9% ischemic myocardium, 5% to 9.9% ischemic myocardium, and 10% ischemic myocardium or greater, respectively ($P <$

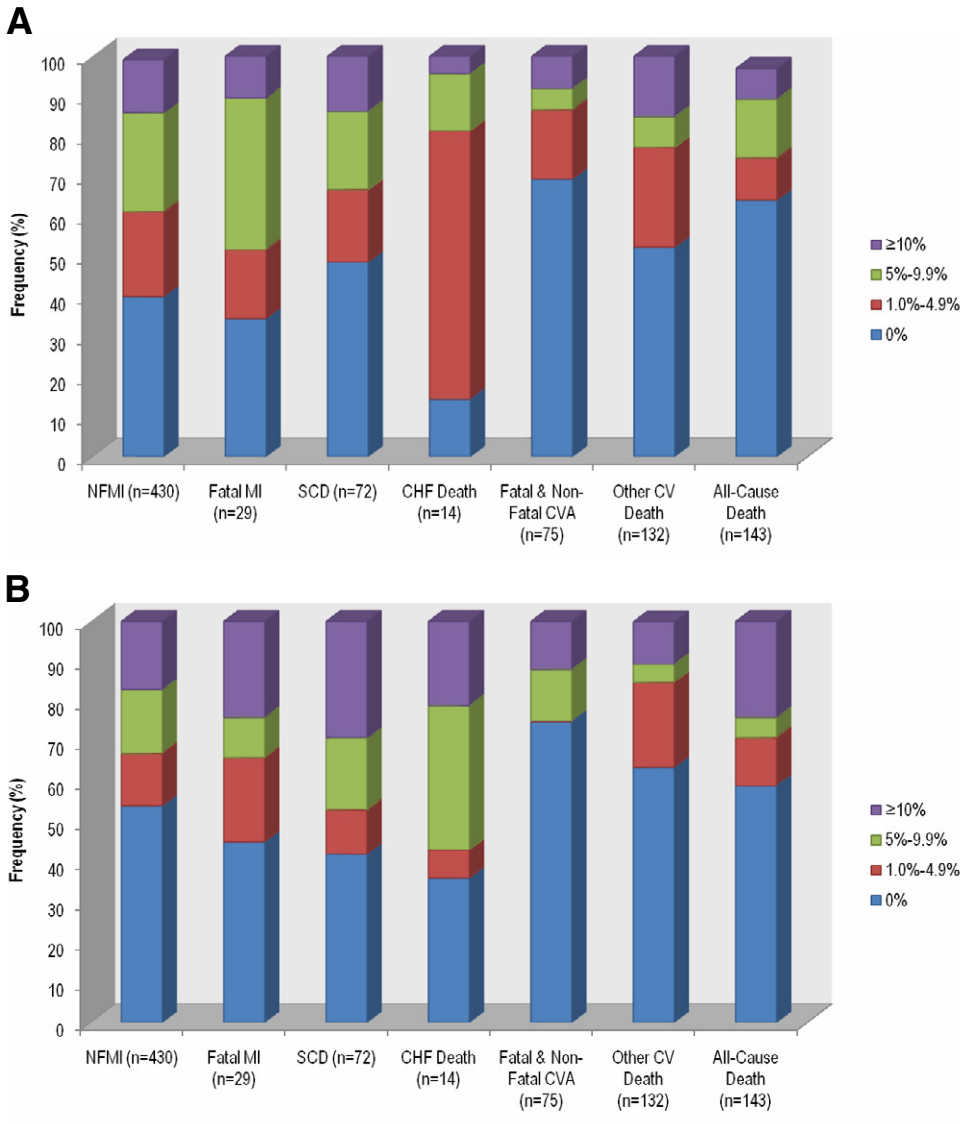

Figure 1. Observed frequency of nonfatal and fatal CV events by percent ischemic myocardium **(A)** and percent rest myocardium with defects **(B)**. $P < .00001$ for fatal MI versus nonfatal MI (*NFMI*), and $P < .0001$ for cause of death. *SCD*, Sudden cardiac death; *CHF*, congestive heart failure; *CVA*, cerebrovascular accident.

.0001) (Figure 3). Lower rates of event-free survival were reported for patients with no ischemia on MPS when the endpoint of total CV death or MI was used, although overall risk stratification by percent ischemic myocardium was highly significant ($P < .0001$) (Figure 3).

Relationship Between Resting Defects and Ischemia

In an ROC analysis estimating CAD events, the C-index was 0.55 (95% CI, 0.53-0.58; $P < .0001$) for poststress LVEF. By comparison, the C-index was 0.64 (95% CI, 0.61-0.66) for resting perfusion abnormalities ($P < .0001$).

Extending prior analyses, we performed stratified Cox proportional hazard models examining the predictive value of stress ischemia within subsets of resting perfusion defects including 0%, 1% to 4.9%, 5% to 9.9%, and 10% or greater, respectively. For patients with no resting defects, overall CAD event rates were 1.2%, 8%, and 10% for patients with 0% ischemic myocardium, 1% to 4.9% ischemic myocardium, and 5% isch-

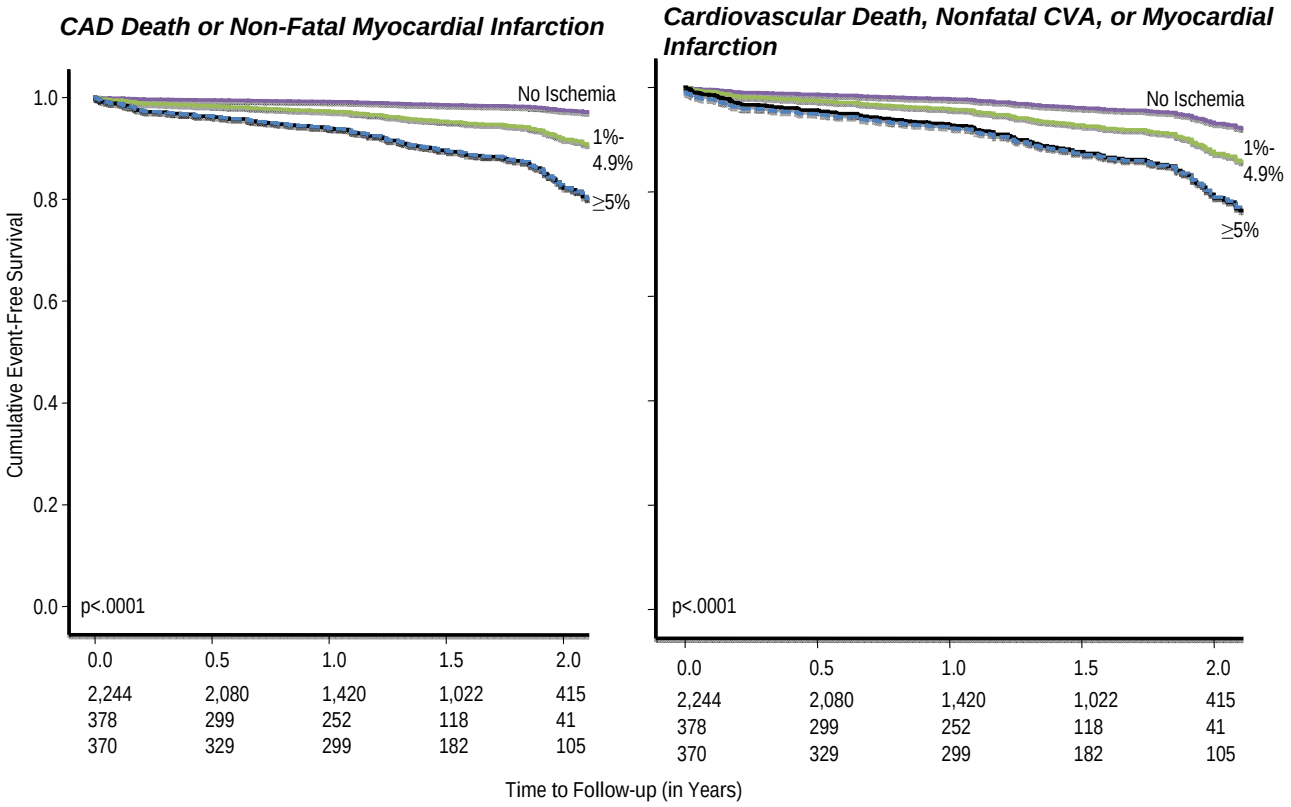

Figure 2. Cumulative CV event–free survival rate in 2992 patients with suspected CAD presenting with de novo cardiac symptoms. For this suspected CAD patient cohort, survival for 5% ischemia or greater and 10% ischemia or greater was the same, so these latter 2 subsets were combined.

emic myocardium or greater, respectively ($P < .0001$) (Figure 4). Of those with no resting defects, 81% had a normal poststress LVEF of 55% or greater, whereas only 25% of patients with severely abnormal rest MPS had normal systolic function ($P < .0001$).

As the percent myocardium with resting defects worsened, overall CAD event rates increased, such that for patients with resting perfusion defects comprising 10% of the myocardium or greater, CV death or MI rates ranged from 7% to 44% ($P < .0001$).

In a combined model that included both the percent of the myocardium with resting defects as well as the percent ischemia, both variables were highly predictive of CAD events (Table 3). The full model including clinical and nuclear variables is included in Appendix Table 1. In this combined model, for every 1% increase in ischemic myocardium, there was a 7% increased risk of CAD events ($P < .0001$). A 3% increase in risk of CAD events was observed for patients with every 1% of the myocardium with resting defects ($P < .0001$). Both the percent ischemia and percent with resting defects within the myocardium remained highly significant in risk-adjusted models (Table 3). It is interesting to note that the percent rest myocardium added to a model that contained both percent ischemic myocardium and LVEF. Moreover, the χ^2 for a model containing the percent rest and ischemic myocardium was significantly higher than that of percent stress myocardium or for a model that included percent rest and stress myocardium ($P < .05$ for all comparisons). The risk-adjusted or predicted risk of CAD events by rest defects and ischemic myocardium on MPS based on models reported in Table 3 are plotted in Figure 5.

DISCUSSION

A diverse body of evidence supports the direct relationship between the extent and severity of perfusion abnormalities on MPS and accelerating risk of CV events.[13,14] Although prior investigations have generally relied on the prognostic accuracy of the sum of stress defects using a semiquantitative score or the percent myocardium with perfusion abnormalities, this measure incorporates both ischemia and infarction into a global measure of risk.[5,13,14] Our report shows that the combination of resting perfusion abnormalities and ischemic MPS may provide a unique method for stratification of

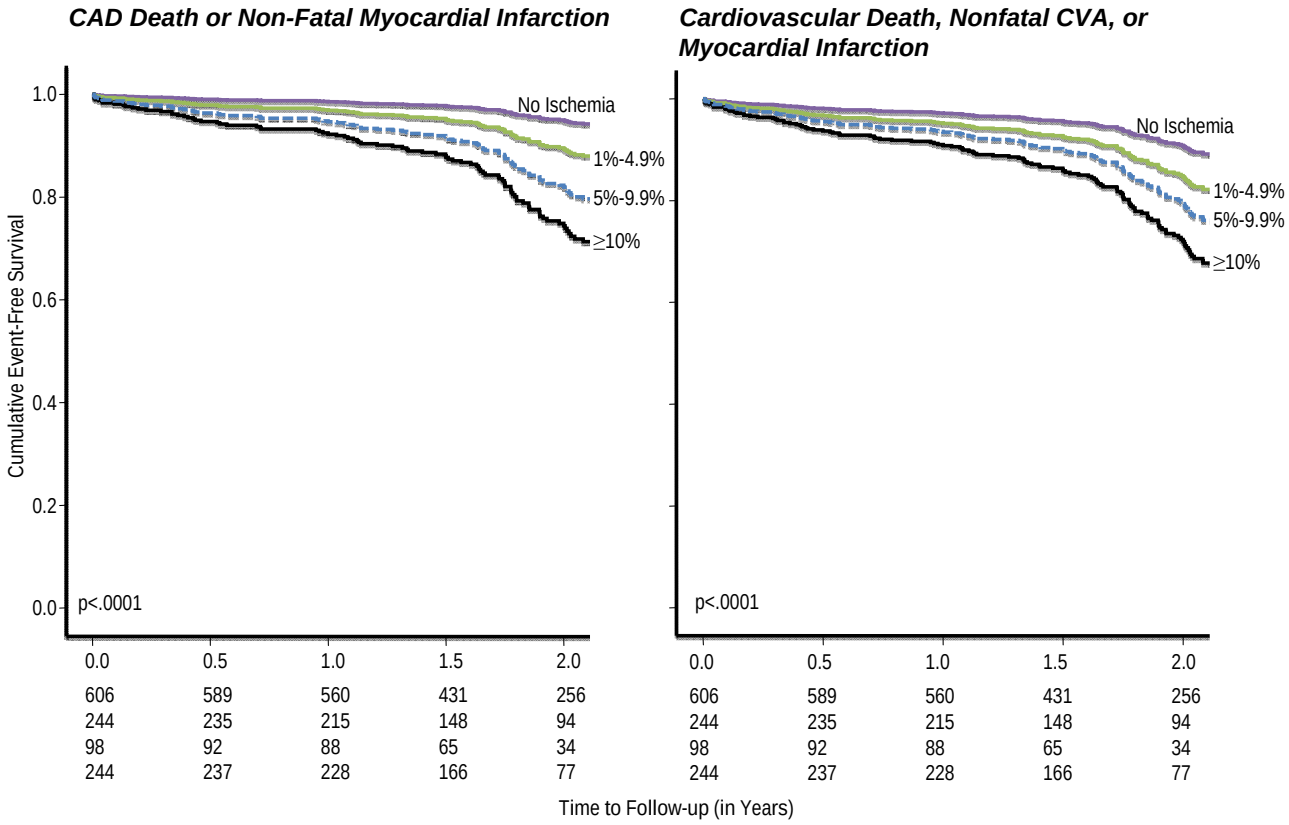

Figure 3. Cumulative event-free survival rate in 1094 patients with prior MI.

cardiac event risk. This combination of infarcted myocardium, defined by use of resting defects, with stress-induced ischemia provides accurate global risk estimation by integrating the role of either disease marker. That is, in a patient with a prior infarct with a moderately abnormal rest MPS scan, even minimal ischemia is associated with increasing risk. Thus one may envision the rest MPS scan as reflective of a patient's baseline CAD risk or underlying hazard for clinical events whereas stress ischemia defines a patient's risk encumbered in his or her presenting symptomatic burden. Moreover, in the absence of a precise CAD history, the percent resting defects may serve as a surrogate for the burden of disease.

Our results further indicate that an improved stratification of ischemic risk was possible by limiting our endpoints to those directly related to CAD including fatal or nonfatal MI or sudden cardiac death. Throughout all of the comparative subsets of patients including those with de novo chest pain and those with prior MI or across the range of rest MPS abnormalities, a more specific ischemic or CAD-specific endpoint provided improved delineation of risk. Notably, cardiac event rates in patients with no ischemia were lower than those from a broader endpoint of total CV events. For example, in suspected CAD patients with no ischemia on MPS, annual CAD event rates were lower than 1% but approached 2% when total CV events were included. It should also be noted that more than one third of CAD events occur in patients with no ischemia or no resting perfusion defects. Thus future developments in the field of nuclear cardiology should seek to improve on current risk prediction accuracy levels.

Ischemia for Prognostication or Therapeutic Decision Making

There are numerous publications on the prognostic value of the summed stress score (or sum of all perfusion defects on the stress scan incorporating both ischemia and fixed abnormalities). However, the utility of inducible ischemia has often been studied with regards to therapeutic decision making.[15,16] Our data show in a large cohort of patients that the extent and severity of ischemia, measured semiquantitatively by use of stress MPS, is a prominent factor influencing cardiac events. Importantly, a threshold of 5% ischemic myocardium or greater and 10% ischemic myocardium or greater signified high-risk status for patients presenting for de novo

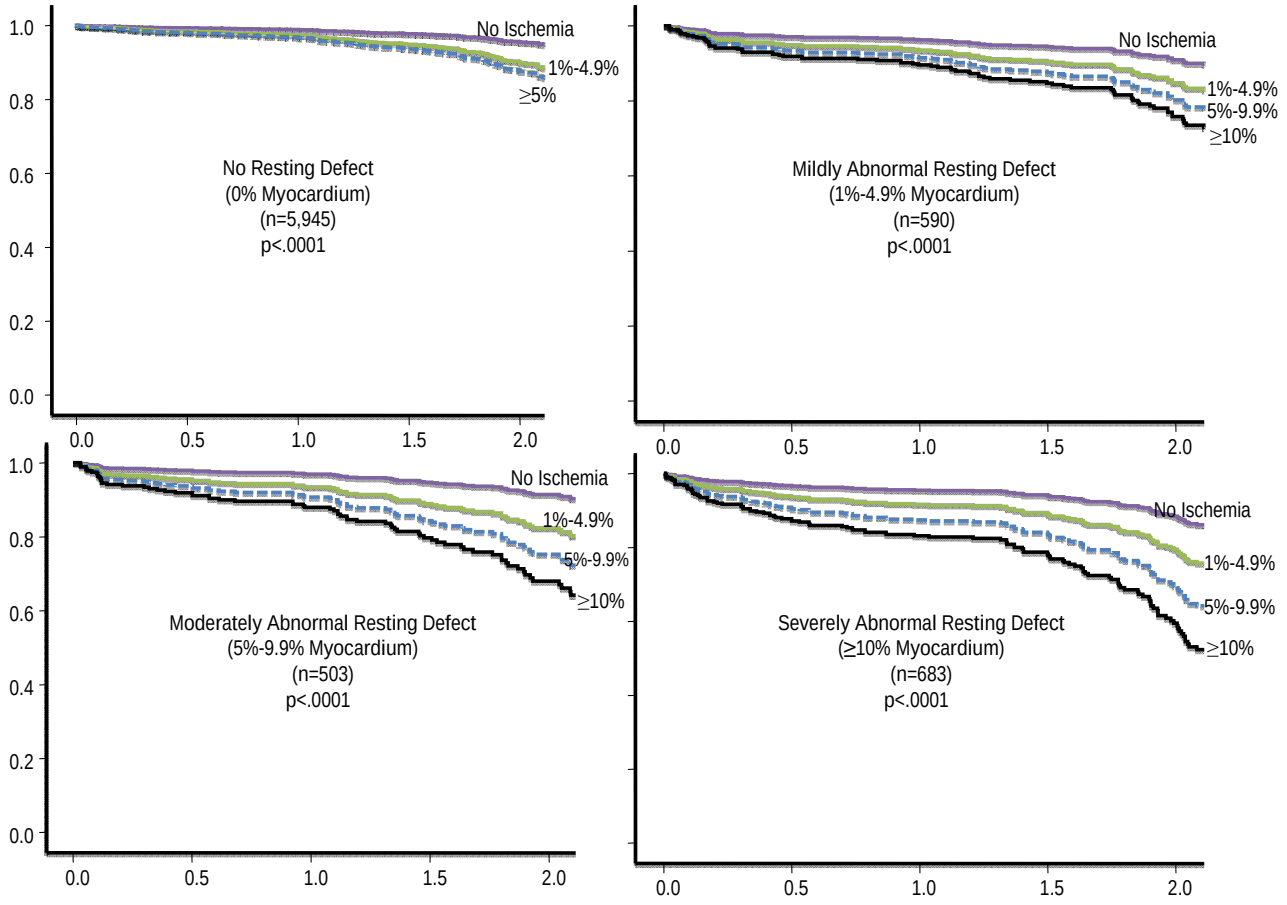

Figure 4. Cumulative CAD event–free survival rate by percent ischemic myocardium with stratification by percent rest myocardium with defects.

chest pain evaluation and for those with known CAD. Similarly, in one recent report of 1988 patients, the summed difference score or extent/severity of ischemia was one of the greatest predictors of acute MI or unstable angina.[17]

Similarities between the relationships of resting perfusion defects with LVEF would be expected.[18-22] However, we hypothesized a priori that an improved gradation or stratification of risk may be observed using regional differences in resting perfusion as compared with the global LVEF. Our results showed that the rest MPS scan had improved classification of risk, by use of an ROC analysis, over measures of left ventricular function. Moreover, our results extend prior work on predischarge stress MPS[19] and show a graded relationship between the extent and severity of resting defects and CAD events. For the lower-risk patient with suspected CAD or for the patient with no resting defects, CV event rates remain low, ranging from less than 1% to approximately 20% for those with no ischemia to severe ischemia. For the patient with severe rest perfusion abnormalities, even a normal scan had a CV death or MI rate of 3% per year. By comparison, nearly half of this latter subset had a CV event during near-term follow-up of 2 years ($P < .00001$). The prognostic utility of stress ischemia in higher-risk patient subsets including patients after MI has been previously reported.[19,23-25] However, our results provide evidence of effective risk stratification by use of the rest MPS scan as a marker of infarcted myocardium that may then be applied to inpatients and outpatients alike.

Two approaches for optimal risk detection have been presented thus far in the published literature. The first includes integration of the global left ventricular function measurements with stress-induced ischemia.[21,22] In a prior report by Sharir et al,[21] cardiac death was prominently estimated by measures of LVEF after stress; by comparison, ischemia provided an improved prediction of acute MI. In that report high-risk patients included those with annualized event rates of greater than 4%. However, by combining ischemia-specific event rates, we were able to define high-risk subsets of patients

Table 3. Multivariable models evaluating CAD death or nonfatal MI by rest perfusion defects and inducible ischemia by stress MPS

	Wald χ^2	*P* value	Hazard ratio	95% CI
Model 1 (χ^2 = 228)				
% Rest myocardium	49	<.0001	1.03	1.02–1.04
% Ischemic myocardium	136	<.0001	1.07	1.06–1.08
Model 2 (χ^2 = 188)				
% Stress myocardium	188	<.0001	1.04	1.03–1.05
Model 3 (χ^2 = 205)				
% Rest myocardium	20	<.0001	1.03	1.01–1.04
% Stress myocardium	134	<.0001	1.07	1.06–1.08
Model 3: Risk-adjusted model* (χ^2 = 498)				
% Rest myocardium	23	<.0001	1.02	1.02–1.04
% Ischemic myocardium	27	<.0001	1.06	1.05–1.08

*The full risk-adjusted model is included in Appendix Table 1.

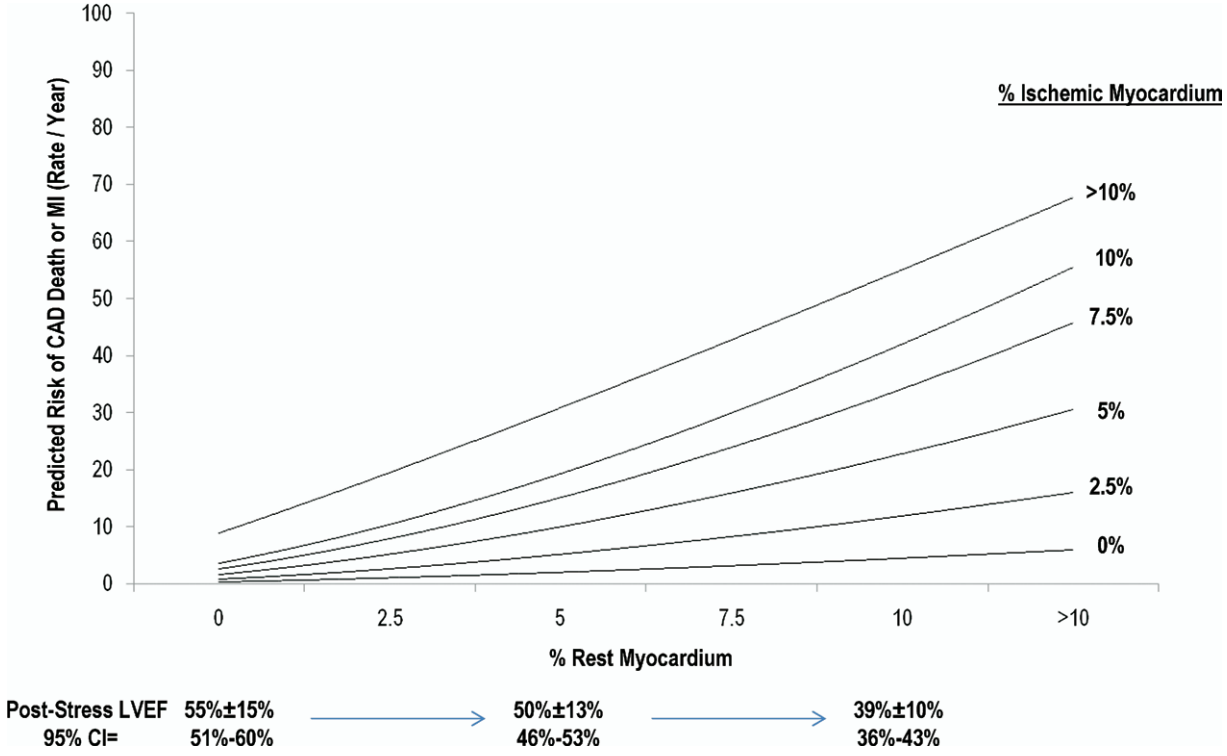

Figure 5. Predicted annual risk of CAD events by combined assessment of percent perfusion defects at rest and percent ischemic myocardium. Below the x-axis, the mean ± standard deviation and 95% CI for poststress LVEF (n = 4575), within the subsets of patients by their percent myocardium with defects at rest, are included for comparative purposes. $P < .0001$.

with annual event rates of 10%. Our approach was to use regional differences in the extent and severity of resting perfusion abnormalities, a measure that we believe provided a gradation of risk over that of the global VEF. In our report, the rest MPS scan yielded an improved estimation of CAD events when compared with the global measure of LVEF. The reason for this may lie in the fact that mild reductions in resting defects may be prognostically significant but fail to exhibit global declines in LVEF. This is evident by analysis from a recent report from the Duke group (Duke Clinical Research Institute/Duke University Health System, Durham, NC).[26]

This report evaluated the interactive relationship between the summed rest score and systolic function, noting a significant interaction suggesting that stratification of risk by decreased regional perfusion was notable within LVEF subsets ($P = .032$).

Study Limitations

Poststress LVEF data were not available in all patients and may have affected the presented results. Despite this, we believe that regional differences in reduced perfusion at rest may provide better discrimination of risk than the global LVEF; similar results were previously reported.[26] Approximately 1% of patients were lost to follow-up, with the inclusion of these patients having the potential to affect risk assessment, in particular for lower-risk patients. However, clinical characteristics of those lost patients were similar to those of the available cohort. Longer-term follow-up may have further revised our risk models. Although we imposed stringent criteria for discerning cause of death, it remains possible that a sizeable proportion of "other" deaths may also be CAD or CV in origin. Finally, we believe that the type of rest agent may have influenced our results, although analytic strategies to elucidate any effect yielded no significant results.

CONCLUSIONS

Our results extend prior results and show a strong association with CAD event risk and MPS results by isolating more ischemia-specific events including fatal or nonfatal MI as well as related deaths due to heart failure or sudden cardiac death. We further explored the interrelationship between resting MPS abnormalities and how this variable's underlying hazard influenced risk stratification with provocative ischemia measurements. Our results show that, across the range of abnormalities on the rest MPS scan, ensuing risk ranged from very low for 0% myocardial involvement to very high for patients with 10% or more of the myocardium being involved. Stratification of ischemic risk was observed within each of the rest MPS scan subsets. We believe that a combined assessment using both the rest and ischemic MPS results may prove optimal for delineation of risk across the range of patient subsets, from patients with de novo chest pain to those after MI. Thus the rest MPS scan may be seen as reflective of a patient's baseline CAD risk or underlying hazard for clinical events, whereas stress ischemia defines a patient's risk encumbered in his or her presenting symptomatic burden, with both factors acting synergistically to increase CAD event risk.

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Appendix Table 1. Full multivariable model (risk-adjusted model) ($\chi^2 = 498$)

	Wald χ^2	*P* value	Hazard ratio	95% CI
% Rest myocardium	23	<.0001	1.02	1.02–1.04
% Ischemic myocardium	27	<.0001	1.06	1.05–1.08
Age (y)	13	<.0001	1.02	1.01–1.03
Anginal symptoms on presentation	97	<.0001	1.19	1.15–1.23
History of chronic obstructive pulmonary disease	6	.013	2.31	1.19–4.47
History of peripheral arterial disease	4	.038	1.60	1.03–2.51
History of smoking	112	<.0001	2.63	2.20–3.14
Diabetes mellitus	32	<.0001	1.37	1.23–1.52