

## Interrelation of Coronary Calcification, Myocardial Ischemia, and Outcomes in Patients With Intermediate Likelihood of Coronary Artery Disease

### A Combined Positron Emission Tomography/Computed Tomography Study

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**Background**—Although the value of coronary artery calcium (CAC) for atherosclerosis screening is gaining acceptance, its efficacy in predicting flow-limiting coronary artery disease remains controversial, and its incremental prognostic value over myocardial perfusion is not well established.

**Methods and Results**—We evaluated 695 consecutive intermediate-risk patients undergoing combined rest-stress rubidium 82 positron emission tomography (PET) perfusion imaging and CAC scoring on a hybrid PET-computed tomography (CT) scanner. The frequency of abnormal scans among patients with a CAC score  $\geq 400$  was higher than that in patients with a CAC score of 1 to 399 (48.5% versus 21.7%,  $P < 0.001$ ). Multivariate logistic regression supported the concept of a threshold CAC score  $\geq 400$  governing this relationship (odds ratio 2.91,  $P < 0.001$ ); however, the frequency of ischemia among patients with no CAC was 16.0%, and its absence only afforded a negative predictive value of 84.0%. Risk-adjusted survival analysis demonstrated a stepwise increase in event rates (death and myocardial infarction) with increasing CAC scores in patients with and without ischemia on PET myocardial perfusion imaging. Among patients with normal PET myocardial perfusion imaging, the annualized event rate in patients with no CAC was lower than in those with a CAC score  $\geq 1000$  (2.6% versus 12.3%, respectively). Likewise, in patients with ischemia on PET myocardial perfusion imaging, the annualized event rate in those with no CAC was lower than among patients with a CAC score  $\geq 1000$  (8.2% versus 22.1%).

**Conclusions**—Although increasing CAC content is generally predictive of a higher likelihood of ischemia, its absence does not completely eliminate the possibility of flow-limiting coronary artery disease. Importantly, a stepwise increase occurs in the risk of adverse events with increasing CAC scores in patients with and without ischemia on PET myocardial perfusion imaging. (*Circulation*. 2008;117:1693-1700.)

**Key Words:** calcium ■ ischemia ■ perfusion ■ imaging ■ prognosis

Because the signal event of cardiovascular disease is often sudden death or disability due to myocardial infarction (MI), considerable energy has been focused on developing new technologies to identify those patients at risk for ischemic heart disease. Although current prediction models based on a patient's age and sex along with modifiable coronary risk factors provide valid global risk assessments for a given population, these methods are only marginally useful in predicting individual-level risk.<sup>1-4</sup> Consequently, the measurement of coronary artery calcification (CAC) by computed tomography (CT), with either electron-beam CT or multide-

tor spiral CT, has received considerable attention, with the goal of improving the diagnostic assessment and risk stratification of patients with suspected coronary artery disease (CAD).<sup>5-12</sup> The relationship between CAC measurement by CT and myocardial perfusion, either by stress single-photon emission CT (SPECT MPI) or by positron emission tomography (PET MPI), is currently under investigation, especially in patients with an intermediate pretest likelihood of CAD, for whom effective risk stratification would be of most benefit. The decision of whether and when myocardial perfusion imaging should be coupled with CAC scoring is

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becoming increasingly relevant, because hybrid SPECT-CT and PET-CT scanners are becoming more widely available.

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Before CAC scoring can be accepted and routinely integrated with conventional stress imaging tests in the clinical assessment of patients with suspected and known CAD, a better understanding of the potential predictive relationship between the CAC score, the likelihood of stress-induced myocardial ischemia, and outcomes should be attained. Our objective was to assess the relationship between the magnitude of CAC and the presence of stress-induced myocardial ischemia, as assessed by combined PET-CT, and to define the incremental prognostic information added by integrating CAC and myocardial perfusion in a consecutive series of patients with an intermediate likelihood of CAD.

## Methods

### Study Design

We reviewed 695 consecutive patients (mean age  $61.3 \pm 13.1$  years, 40.9% male) who completed combined rest-stress rubidium 82 PET perfusion imaging and CAC scoring on a hybrid PET-CT scanner from September 2004 to July 2006. Patients were referred for stress PET MPI on clinical grounds, and CAC scoring was performed as a routine component of each study. Because the study was designed to evaluate patients without known CAD, we subsequently excluded 74 patients who had prior revascularization, history of MI, known valvular heart disease, or cardiomyopathy, which left 621 patients in the cohort (mean age  $60.9 \pm 13.1$  years, 40.1% male).

### Clinical and Historical Data

Clinical histories elicited at the time of examination ascertained the presence or absence of various cardiac symptoms and risk factors, including chest pain, dyspnea, medications, family history of premature CAD, diabetes mellitus, hypertension, hyperlipidemia, and current or past cigarette smoking. Height and weight were measured, and body mass index was calculated. Pretest likelihood of CAD was assigned according to age, sex, symptoms, and other risk factors.<sup>13</sup>

### Hybrid PET-CT Imaging

All patients were imaged with a whole-body PET-CT scanner (Discovery ST-LightSpeed 16 PET-CT, GE Healthcare, Waukesha, Wis). Patients were studied after an overnight fast, and all subjects refrained from caffeine-containing beverages or theophylline-containing medications for 24 hours before the study. The total-body effective dose from the combined PET-CT scan was 16.3 mSv.

### PET Perfusion Study Protocol

Myocardial perfusion was assessed at rest and during vasodilator stress with dipyridamole, with <sup>82</sup>Rb used as a flow tracer. Initial scout (120 kV; 10 mA) and transmission (140 kV; 20 mA) CT scans were obtained for orientation and attenuation correction. Regional myocardial perfusion was then assessed at rest, after the administration of 40 to 60 mCi (1480 to 2220 MBq) of <sup>82</sup>Rb. Approximately 90 seconds after completion of radionuclide injection, a 5-minute rest emission scan was acquired. Patients then received a standard intravenous infusion of dipyridamole ( $0.142 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  for 4 minutes). Approximately 3 minutes after completion of the dipyridamole infusion, a second dose of <sup>82</sup>Rb (40 to 60 mCi) was administered, and a stress emission scan was acquired in the same manner. A second transmission CT scan was obtained for attenuation correction of the stress perfusion data. The rest and stress myocardial perfusion studies were completed in  $\approx 25$  minutes. Images were acquired with simultaneous ECG gating (8 frames/cycle). Patient motion was minimized by fastening a Velcro strap across the

patient's chest. The heart rate, systemic blood pressure, and 12-lead ECG were recorded at baseline and every minute during and after the infusion of dipyridamole.

### CAC CT Acquisition and Reconstruction

After myocardial perfusion imaging, all patients underwent a third CT scan for CAC scoring on the integrated 16-slice multidetector spiral CT scanner (collimation  $16 \times 1.25$  mm; pitch 0.563; gantry rotation time 500 ms; effective temporal resolution 250 ms) with retrospective ECG gating. Breath-holding instructions were given to minimize misregistration. This gated CT scan (120 kV; 300 mA) was acquired and reconstructed with filtered back-projection and a standard convolution kernel to 2.5-mm slices with a  $512 \times 512$  matrix and a fixed 25-cm field of view. Gated CT scans for calcium scoring were acquired without the use of  $\beta$ -blockers, and the average heart rate during the study was  $68.1 \pm 12.7$  bpm.

## Analysis of Imaging Data

### Assessment of Myocardial Perfusion

Semiquantitative visual interpretation of the rest and stress perfusion images was performed with a 17-segment model. Segments were scored by 2 experienced observers using a standard 5-point scoring system (0=normal, 1=mild defect, 2=moderate defect, 3=severe defect, and 4=absence of detectable uptake). PET images were evaluated without knowledge of the CAC score. Left ventricular ejection fraction, end-diastolic volume, and end-systolic volume were computed at both rest and stress with commercially available software (Emory Cardiac Toolbox, Emory University, Atlanta, Ga).

Stress and rest segmental perfusion scores were added together to obtain the summed stress score and summed rest score. The sum of the differences between each of the 17 segments was defined as the summed difference score. The summed difference score was converted to a percent ischemic myocardium by dividing the summed difference score by the maximum potential score ( $4 \times 17 = 68$ ) and multiplying by 100%. For the purpose of the present analysis, a summed difference score  $\geq 2$  was considered abnormal, given the increased sensitivity and specificity of PET for detecting myocardial ischemia compared with SPECT.<sup>14</sup>

### CAC Scoring

Scoring was performed by an experienced independent observer who was blinded to the patients' clinical history, outcomes, and PET scan results. Agatston scores were computed with commercially available software (SmartScore, GE Healthcare).<sup>15</sup> Artery-specific scores were summed across lesions identified in the left main, left anterior descending, left circumflex, and right coronary arteries to provide a total CAC score for each patient. CAC percentile scores were then assigned based on age and sex.

### Assessment of Outcomes

Patients were followed up for the occurrence of serious clinical outcomes (death or MI) by review of the electronic longitudinal medical records at our institution and in the Social Security Death Index with a prescribed follow-up data sheet. MI was defined according to American College of Cardiology/European Society of Cardiology criteria. Events were adjudicated by review of hospital records and data from the Social Security Death Index by consensus of 2 experienced investigators blinded to the test results. The follow-up was terminated either with the patient's death, occurrence of a nonfatal MI, or the end of the follow-up period (January 31, 2007). All patients undergoing "early" revascularization procedures within 60 days of imaging were excluded.

### Statistical Analyses

Descriptive data are presented as mean  $\pm$  SD or simple proportions as appropriate. The null hypothesis was that no association exists between CAC and myocardial perfusion. The null hypothesis was initially tested with  $\chi^2$  analysis of the association between age- and sex-stratified CAC percentiles and PET MPI results. To facilitate comparison with prior studies, we used the existing literature to

**Table 1. Characteristics of the Study Population**

Parameter	Overall (n=621)	Normal PET MPI (n=442)	Ischemic PET MPI (n=179)	P
Age, y	60.9±13.1	60.2±13.7	62.5±11.3	0.026*
Sex, n (%)				
Women	372 (59.9)	293 (66.3)	79 (44.1)	<0.001
Men	249 (40.1)	149 (33.7)	100 (55.9)	<0.001
Symptom class, n (%)				
Dyspnea	171 (27.5)	115 (26.0)	56 (31.3)	0.187
Nonanginal pain	158 (25.4)	124 (28.1)	34 (19.0)	0.017
Atypical angina	49 (7.9)	33 (7.5)	16 (8.9)	0.542
Typical angina	41 (6.6)	28 (6.3)	13 (7.3)	0.676
Risk factors, n (%)				
Hyperlipidemia	336 (54.1)	233 (52.7)	103 (57.5)	0.274
Hypertension	459 (73.9)	317 (71.7)	142 (79.3)	0.047
Family history	231 (37.2)	169 (38.2)	62 (34.6)	0.399
Diabetes mellitus	175 (28.2)	113 (25.6)	62 (34.6)	0.024
Smoking	88 (14.2)	55 (12.4)	33 (18.4)	0.058
Body mass index	32.4±9.1	32.6±9.1	31.9±8.7	0.382
Mean likelihood of CAD	59.4±29.9	59.0±30.1	60.6±29.4	0.527
CAC score	429±869	299±652	750±1195	<0.001

\*One-tailed *t* test.

inform the ordinal and binary cut points of the CAC score used in the analysis, because some have been shown to be associated with a higher frequency of ischemia (ie, CAC  $\geq$ 400).<sup>16–18</sup> The frequency of abnormal PET MPI was compared across these cut points with the  $\chi^2$  test of trend. Historical and clinical variables were subsequently tested with  $\chi^2$  and bivariate tests of association to examine the unadjusted effects of these variables on the PET MPI result. This was also used to inform the variable selection for the multivariate analysis.

Multivariate logistic regression was then performed to examine whether the CAC score was independently associated with an abnormal PET MPI result after adjustment for the effects of age, sex, symptoms, body mass index, and conventional coronary risk factors. For the purpose of multivariate analysis, the CAC score was tested both as a dichotomous and continuous independent variable. When treated as a dichotomous variable, various thresholds thought to be associated with a higher risk of obstructive CAD were explored systematically,<sup>16–21</sup> because no optimal cut point has been established by means of clinical or biological criteria. When treated as a continuous variable, a log transformation of the CAC score was used to adjust for the rightward skew of the data and to reduce heteroscedasticity. These analyses were also run with stratification by age and sex percentiles. Several post-estimation regression diagnostics were then applied. The Hosmer-Lemeshow test was used to determine goodness-of-fit. Link tests were conducted to confirm that the dependent variable was specified correctly. Correlation coefficients and variance inflation factors were calculated to check for the presence of multicollinearity. Receiver operating characteristic curves were generated to compare the different predictive models of ischemic PET MPI with use of age and sex, age, sex, and conventional risk factors, as well as the combination of these with the CAC score.

We then calculated annualized cardiac event rates by PET MPI result and CAC score and used Cox proportional hazard regression to analyze the association between clinical outcomes and imaging results. Patients undergoing revascularization within 60 days of follow-up were excluded from outcomes analysis. In the outcomes analysis, the CAC score was again analyzed as a binary value but with a higher cut point (ie, CAC  $\geq$ 1000) based on an extensive body of literature reporting a higher clinical risk in these patients.<sup>10,22</sup> We also included a variable for an ischemic PET MPI result (summed

difference score  $\geq$ 2) and 2 other variables that are well-known predictors of prognosis (ie, age and diabetes mellitus). We then examined the discriminatory power of the Cox regression by means of Harrell's concordance probability statistic (c-statistic). The c-statistic is a rank-based measure in which a value of 1 indicates perfect concordance of the prediction and the outcome, whereas a value of 0.5 indicates only chance agreement.<sup>23</sup> For all analyses, a probability value  $<$ 0.05 was used to define statistical significance. The Institutional Review Board of Partners Research Management approved this study.

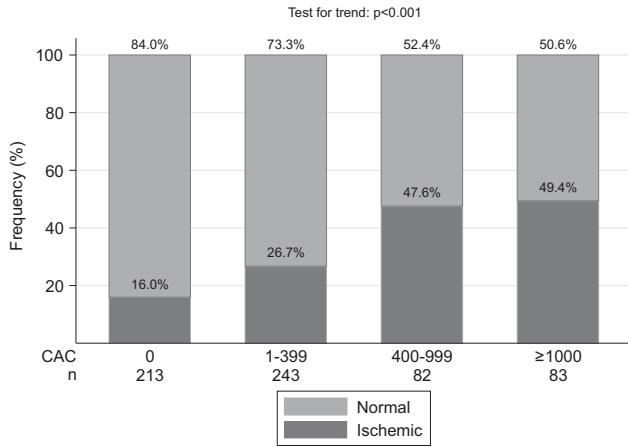
The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

## Results

Relevant clinical characteristics of the study population are listed in Table 1. Among 179 patients with abnormal PET MPI, 134 (74.9%) had small defects (1% to 10% ischemic myocardium), 30 (16.8%) had medium defects (10% to 20%), and 15 (8.4%) had large defects ( $>$ 20%). In general, coronary risk factors were prevalent in patients with and without ischemia, and the mean likelihood of CAD was not statistically different between the 2 groups; however, bivariate evaluation of individual risk factors showed that patients with ischemia were more likely to be older, male, diabetic, and hypertensive and to have a tendency to smoke. Interestingly, patients with ischemia had much higher calcium scores on average than patients without ischemia ( $P<$ 0.001).

### Relationship Between CAC and Ischemia

The correlation between the frequency of ischemic PET MPI and total CAC was modest but statistically significant (Spearman rank correlation coefficient  $\rho=$ 0.28,  $P<$ 0.001). Overall, the frequency of ischemia increased with the CAC score (Figure 1). Consistent with prior studies, we also observed a significantly higher frequency of abnormal scans among



**Figure 1.** Bar graph illustrating the frequency of ischemic PET MPI by CAC score.

patients with CAC  $\geq 400$  (48.5%,  $P < 0.001$  for trend). However, patients with mild or no CAC had a relatively high frequency of ischemia (16% to 27%; Figure 1). Consequently, the negative predictive value (NPV) of a negative CAC scan was only 84.0% (95% CI 81.2 to 86.9%; NPV 85.7% for patients  $< 50$  years old and 83.0% for patients  $> 50$  years old).

Because age and sex are both known to impact CAC burden, we analyzed the frequency of abnormal PET results according to age- and sex-adjusted CAC percentile scores. Two comparisons were made, one with a widely cited electron-beam CT database of 35 246 patients from the University of Illinois<sup>24</sup> and another based on a yet-unpublished 16-slice multidetector spiral CT database of 8231 patients from the Tennessee Heart & Vascular Institute (Tracy Q. Callister, MD, unpublished data, 2005). The results were comparable. Thus, only the multidetector spiral CT database comparison is listed because of its relevance to the methodology used in the present study (Figure 2). Although a significant overall trend was observed, with higher CAC percentile groups being associated with a greater frequency of

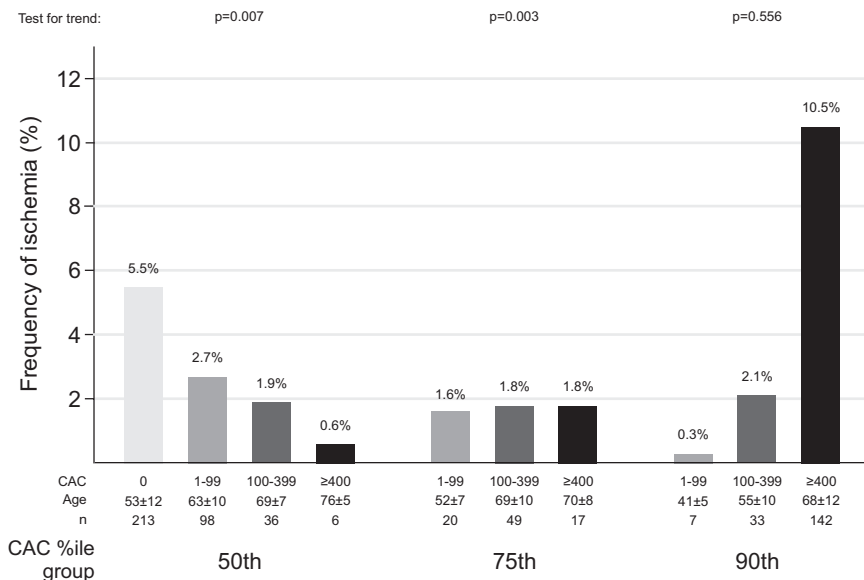
**Table 2. Multivariate Predictors of Ischemic PET MPI**

Predictor	OR	$P > z$	95% CI
CAC $\geq 400$	2.91	0.000	1.89–4.47
Age	1.00	0.784	0.98–1.01
Female	0.43	0.000	0.29–0.64
Hypertension	1.46	0.109	0.92–2.31
Diabetes mellitus	1.39	0.128	0.91–2.12
Hyperlipidemia	1.03	0.863	0.71–1.52
Family history of CAD	0.94	0.775	0.64–1.40
Smoking	1.40	0.190	0.85–2.32
Body mass index	1.00	0.981	0.98–1.02
Symptoms	1.21	0.342	0.81–1.81

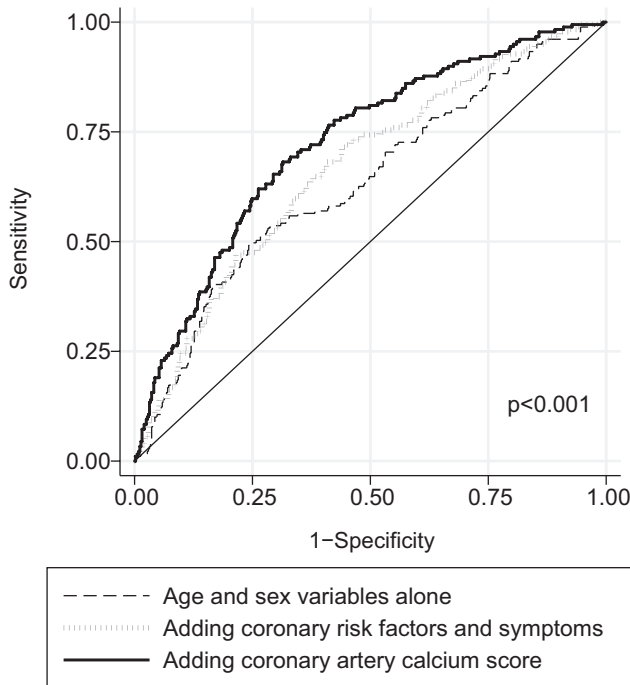
ischemic PET MPI, the relationship within percentile groups was more complex. Figure 2 demonstrates that total CAC did not have an appreciable effect in low- and intermediate-percentile groups, which contain patients who were older on average within each subgroup of the calcium score. Only within the 90th percentile group did a seemingly positive trend exist between total CAC and frequency of ischemic PET results, especially for the subgroup of patients with CAC  $\geq 400$ ; however, many patients in the 90th percentile group who had high CAC scores also had normal PET MPI results, so the test of trend was not significant ( $P = 0.556$ ).

**Multivariate Predictors of Myocardial Ischemia**

Multivariate logistic regression analysis that controlled for age, sex, conventional risk factors, and symptoms showed that the CAC score was the strongest independent predictor of an abnormal PET result when treated either as a dichotomous variable (Table 2) or a continuous variable (results not shown). However, the size of this effect was modest, and statistics that measured predictive power showed that a large portion of the variance was not explained by the predictors included in the model (pseudo  $R^2 = 0.12$ ). The size of the effect also varied according to how the variable for CAC was



**Figure 2.** Bar graph illustrating the frequency of ischemic PET MPI by CAC score and CAC percentile ranking. Within each of the 3 percentile groups, patients are subdivided by their absolute calcium score.

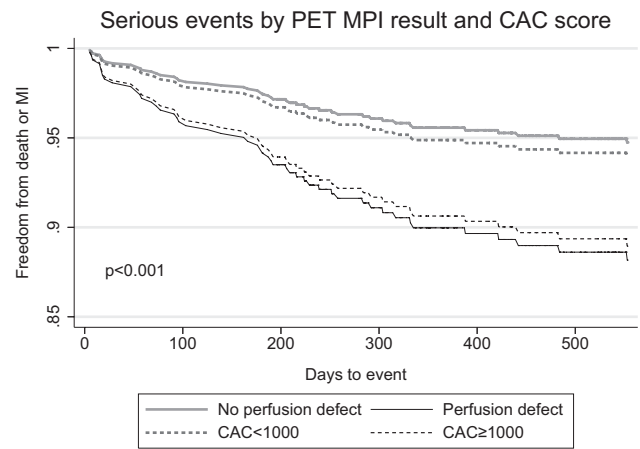


**Figure 3.** Receiver operating characteristic curve analysis illustrating the incremental value of CAC score for predicting ischemic PET MPI.

specified. When treated as a continuous variable, a 1-unit increase in  $\log(\text{CAC} + 1)$  increased the odds of abnormal PET MPI 1.61 times ( $P < 0.001$ ). For example, the odds of an individual with a calcium score of 1000 having ischemia were 61% greater than for an individual with a calcium score of 100, controlling for other variables in the model. After a systematic exploration of various threshold values mentioned in the literature,<sup>16–21</sup> we found the largest effect at a CAC score  $\geq 400$  (OR 2.91,  $P < 0.001$ ). That is, a patient with a calcium score  $> 400$  was roughly 2.9 times more likely to have ischemia than a patient with a calcium score  $< 400$ , after controlling for other variables in the model. Among patients less than 50 years old ( $n = 128$ , 20.6%), only 8 (6.3%) had a CAC score  $\geq 400$ . When this subgroup was excluded from the model, the effect of the CAC score became slightly larger (OR 3.07,  $P < 0.001$ ).

In all models, the only other significant predictor was sex, showing males to be  $\approx 2.3$  times more likely to have ischemia, after controlling for all other variables ( $P < 0.001$ ). To explore any potential relationships that may have been masked by the effect of total calcium, we performed a subanalysis of patients without this variable in the model (results not shown). When analyzed in this way, adjusted models revealed that a history of diabetes contributed to an increased likelihood of ischemia (OR 1.55,  $P = 0.035$ ). Interestingly, if only patients over the age of 50 years were analyzed in this way ( $n = 493$ ), a history of diabetes became increasingly relevant (OR 1.71,  $P = 0.018$ ).

To further assess the potential incremental value of CAC scoring in predicting abnormal PET MPI, we performed receiver operating characteristic curve analysis of 3 multivariate models, beginning with age and sex (area under the



**Figure 4.** Cox proportional hazards regression model for freedom from death or MI adjusted for age, sex, symptoms, and conventional CAD risk factors (median follow-up 553 days).

receiver operating characteristic curve  $0.63 \pm 0.025$ , 95% CI 0.58 to 0.68), and then adding, in a stepwise fashion, conventional risk factors and symptoms (area under the curve  $0.67 \pm 0.024$ , 95% CI 0.62 to 0.71), and CAC variables (area under the curve  $0.72 \pm 0.022$ , 95% CI 0.68 to 0.77; Figure 3). The relative increase in area under the curve with each subsequent model was small but highly significant ( $P < 0.001$ ).

### Survival Analysis

Fifteen of the 621 patients underwent “early” revascularization (within 60 days of PET/CT imaging) and were excluded from survival analysis. The mean follow-up duration was  $524 \pm 212$  days (maximum 866 days, minimum 15 days, median 553 days). A total of 55 cardiovascular events were observed (33 deaths and 22 nonfatal MIs). By Cox regression, an ischemic PET MPI result (hazard ratio 2.34,  $P = 0.002$ , 95% CI 1.36 to 4.03) and a CAC score  $\geq 1000$  (hazard ratio 1.88,  $P = 0.048$ , 95% CI 1.01 to 3.55) were shown to be predictors of adverse events (Figure 4). A history of diabetes was marginally significant (hazard ratio 1.71,  $P = 0.053$ , 95% CI 0.99 to 2.95), and age did not exert a sizable effect (hazard ratio 1.03,  $P = 0.036$ , 95% CI 1.00 to 1.05). The discriminatory power of this model was fairly high (c-statistic = 0.728). Table 3 summarizes the annualized event rates for patients stratified by PET result and CAC score. Patients with and without ischemia on PET showed a stepwise increase in cardiac event rates with increasing CAC scores. Separate risk-adjusted survival analyses demonstrated increased risk stratification from CAC information in patients with and without ischemia on PET MPI (Figure 5).

### Discussion

The presence and magnitude of CAC in screening asymptomatic subjects have been associated with an increased risk of incident CAD<sup>17–18</sup> and with a stepwise increase in coronary risk that is independent of that afforded by conventional coronary risk factors.<sup>5–12</sup> The present results extend these observations in 2 important ways: by demonstrating the relationship between CAC and the frequency of myocardial

**Table 3. Annualized Cardiovascular Event Rates Stratified by PET MPI Result and CAC Score**

Group	n	CVD Events	Event Rate	95% CI
Ischemic	165			
CAC=0	34	4	0.082	0.031–0.219
1–399	61	10	0.127	0.068–0.236
400–999	33	4	0.090	0.033–0.238
$\geq 1000$	37	9	0.221	0.115–0.424
Nonischemic	441			
CAC=0	179	7	0.026	0.012–0.054
1–399	178	11	0.041	0.023–0.074
400–999	42	3	0.050	0.016–0.155
$\geq 1000$	42	7	0.123	0.059–0.258
Total	606	55	0.063	0.049–0.082

perfusion abnormalities in patients with intermediate likelihood of CAD and by describing the interrelation of CAC, myocardial ischemia, and clinical outcomes.

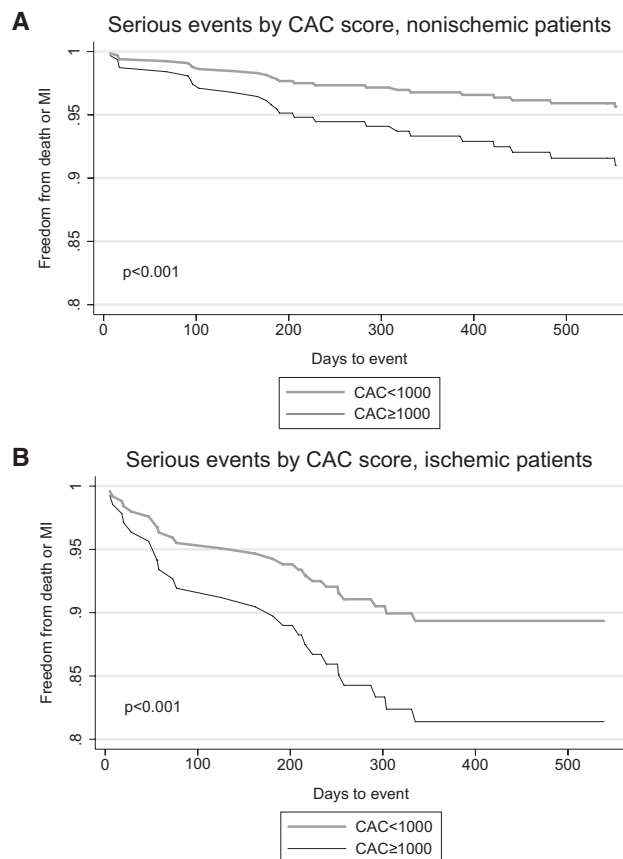
### Relationship Between CAC and Ischemia

The present results showed that CAC scores are generally predictive of a higher likelihood of ischemia on PET MPI, and multivariate analysis supported the concept of a threshold phenomenon governing this relationship. Grouping by cal-

cium score clearly revealed a trend toward ischemia on PET MPI in patients with increasing CAC scores, especially among patients with  $CAC \geq 400$ . However, unlike previous studies in largely asymptomatic screening populations, CAC scores  $<400$  in this intermediate-likelihood diagnostic population were less effective in predicting a normal PET MPI result. In fact, the absence of CAC only afforded an NPV of 84.0%. This was not surprising given the wide distribution of calcium scores among patients with normal and abnormal PET MPI, which thus limited the predictive value of CAC scoring. The present results also showed that the likelihood of myocardial ischemia as measured by PET MPI was related to age- and sex-adjusted CAC percentile scores, but when grouped according to CAC percentile scores, the independent effect of total CAC was less strong than described previously,<sup>16</sup> again owing to the wide distribution of CAC among patients with and without ischemia. Consequently, CAC percentile ranking is not likely to help define which patients with an intermediate pretest likelihood of CAD might need subsequent perfusion imaging for the diagnosis of obstructive CAD.

Only 2 prior studies have assessed the relationship between CAC and myocardial ischemia as measured by SPECT, and these primarily used screening populations.<sup>16,17</sup> In both studies, the frequency of ischemia was very low ( $<3\%$ ) in patients with CAC scores  $<100$ , and the frequency increased with higher CAC, albeit to different degrees. The present study showed a much larger distribution of CAC among patients with both normal and abnormal perfusion studies. We attribute this to differences in technology, because PET is more sensitive and specific than SPECT,<sup>14</sup> and to the fact that our study group was composed of patients with intermediate likelihood of CAD referred for evaluation of chest pain or nonclassic symptoms with multiple risk factors. Unlike prior studies that recruited patients who were referred for a single test (SPECT or CAC) to undergo a second test, patients in the present study underwent both CAC and ischemia assessments in a single setting, and thus, no selection biases were introduced. Finally, we found the frequency of ischemia among patients with no CAC was 16.0%, and its absence only afforded an NPV of 84.0% to exclude flow-limiting CAD, which was lower than in prior studies. A number of reports have described the incremental value of clinical data over imaging information as manifested by an increase in the likelihood of CAD or risk of any specific imaging result as a function of the underlying patient risk.<sup>25,26</sup> Hence, although a negative calcium scan ( $CAC=0$ ) affords a high NPV, its precise value probably varies with the cohort examined, eg, 99% in a very low likelihood cohort but  $<85\%$  in patients with an intermediate likelihood of CAD.

Multivariate analysis that controlled for age, sex, other conventional risk factors, and symptoms showed the CAC score to be the strongest predictor of ischemia, but the size of this effect was modest and varied according to how the variable for CAC was specified. The magnitude of CAC had a stronger effect when treated as a dichotomous threshold variable than as a continuous variable, but the interpretation of the significance of this observation is prone to error. The use of a threshold value without concern for percentile



**Figure 5.** Cox proportional hazards regression model for freedom from death or MI adjusted for age, sex, symptoms, and conventional CAD risk factors in patients without ischemia (top) and with ischemia (bottom).

ranking may overestimate the likelihood of ischemia in older patients, who generally have higher average calcium scores, and underestimate this risk in younger patients, who may have an elevated risk despite comparatively low average calcium scores.<sup>24</sup> This was especially true in the present study, because only 8 patients (6.3%) <50 years old had CAC scores  $\geq 400$ , but 23 (18.0%) of these patients had ischemia on PET MPI. The assignment of a cut point for high risk of obstructive CAD at this level without regard for age misses a significant portion of intermediate likelihood patients <50 years old with flow-limiting disease.

Although the models used in the present study are consistent with previous publications, indicating that CAC score incrementally enhances prediction of myocardial ischemia,<sup>17,18</sup> our regression diagnostics also show that CAC only accounts for a small portion of the overall risk for inducible ischemia in the present intermediate-likelihood population. Interestingly, in the present cohort, only patient sex was significantly predictive of ischemia when the CAC score was also considered in the model. It is possible that the CAC score provides redundant or overlapping information with other conventional risk factors. This assertion is supported by the subanalyses in the present study that excluded the CAC score, which showed a history of diabetes mellitus was significantly correlated with an increased risk of ischemia.

### Interaction of Ischemia, CAC, and Clinical Outcomes

An important finding in the present study is that CAC scores added incremental prognostic information over myocardial perfusion. Risk-adjusted analysis demonstrated a stepwise increase in cardiac event rates with increasing levels of CAC score. This was true overall (Figure 4), as well as in patients with and without evidence of ischemia on PET MPI (Table 3; Figure 5). Indeed, the annualized event rate in patients with normal PET MPI and no CAC was substantially lower than among those with a CAC score  $\geq 1000$  (2.6% versus 12.3%). Likewise, the annualized event rate in patients with ischemia on PET MPI and no CAC was also substantially lower than among those with a CAC score  $\geq 1000$  (8.2% versus 22.1%). These findings suggest incremental risk stratification can be achieved by the incorporation of anatomic information on the extent of CAD as measured by CAC with the physiological information gleaned from myocardial perfusion imaging.

The present findings contrast those by Rozanski et al,<sup>27</sup> who reported no interaction between CAC scores and the results of SPECT imaging. In their largely asymptomatic screening cohort, 11 events (death/MI) occurred among 1153 patients (0.95%) over a mean follow-up of 4 years. In contrast, the present study group consisted of a diagnostic cohort with intermediate likelihood of CAD among whom we confirmed 55 events (death/MI) in 606 patients (9.1%) over a mean follow-up of 1.4 years. This apparent discrepancy most likely reflects the different underlying clinical risk profiles of the 2 patient populations. The present findings suggest that evaluation of the anatomic burden of disease by means of CAC scores does add incremental prognostic information over the delineation of myocardial ischemia alone in patients with an intermediate pretest likelihood of CAD. If confirmed

by other studies, the present findings may be of high clinical relevance, especially among symptomatic patients without evidence of myocardial ischemia, in whom the CAC score may serve as a more rational basis for personalizing the intensity and goals of medical therapy in a more cost-effective manner.

### Study Strengths and Limitations

The present study consisted of an entirely physician referral-based diagnostic population with patients at intermediate likelihood of CAD. As such, the study did not have self-referral bias, but it was limited by the selection of patients for testing within our own institution, a limitation of all single-center studies. Similarly, this study design and the nature of patients referred for stress imaging limit the generalizability of the present results and our ability to examine the interrelation of conventional risk factors, CAC, ischemia, and clinical outcomes. Also, gated CAC CT scans were acquired without the use of  $\beta$ -blockers, which could have contributed to error in the Agatston score computation in some patients with higher heart rates. However, by assessing perfusion and CAC simultaneously, we eliminated a significant source of potential referral bias that may have limited previous studies of this type. We also had a relatively high frequency of patients with inducible ischemia overall (n=179, 28.8%), which makes our findings robust. Larger prospective studies investigating the interrelation of myocardial perfusion, calcium scores, and outcomes could help confirm or extend the present findings. An obvious strength of the present study over previous studies that used SPECT MPI was the use of PET MPI to assess for inducible ischemia.

### Conclusions and Clinical Implications

The wide range of CAC scores in patients with normal PET MPI suggests that stress perfusion imaging is limited in its ability to detect subclinical atherosclerosis. Conversely, the wide distribution of CAC scores in patients with abnormal PET MPI suggests that CAC scoring cannot reliably serve as a screening tool for obstructive CAD in a largely symptomatic intermediate-likelihood population. Indeed, the absence of coronary calcium does not eliminate the possibility of flow-limiting CAD, so a negative CAC score in this patient group must be interpreted with caution. More importantly, patients with and without ischemia on PET MPI exhibit a stepwise increase in their risk of cardiac events with increasing CAC scores. These findings suggest that imaging approaches that combine quantitative information on the anatomic burden of CAD with its physiological consequences offer improved risk stratification over conventional approaches that use myocardial perfusion alone. If confirmed in larger prospective studies, it is possible that the use of combined imaging technologies may offer improved risk assessment and management in a cost-effective manner.

### Disclosures

None.

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### CLINICAL PERSPECTIVE

The measurement of coronary artery calcification (CAC) by computed tomography (CT) has received considerable attention for diagnosis and risk stratification of patients with suspected coronary artery disease. The decision of whether and when myocardial perfusion imaging should be coupled with CAC scoring is becoming increasingly relevant because hybrid single-photon emission computed tomography/CT and positron-emission tomography/CT scanners are becoming more widely available. The goals of the present study were to assess the relationship between CAC scoring and stress-induced myocardial ischemia, as assessed by combined positron-emission tomography CT, and to define the incremental prognostic information added by the integration of CAC scoring and myocardial perfusion imaging in patients with intermediate likelihood of coronary artery disease. The frequency of ischemia among patients with a CAC score  $\geq 400$  was high (48%), and multivariable analysis supported the concept of a threshold CAC score  $\geq 400$  governing this relationship. Conversely, the absence of CAC only afforded a negative predictive value of 84% to rule out ischemia. Survival analysis demonstrated a stepwise increase in event rates (death and myocardial infarction) with increasing CAC scores. Among patients with normal myocardial perfusion, the annualized event rate in patients with no CAC was lower than in those with a CAC score  $\geq 1000$  (2.6% versus 12.3%). Similar differences were observed in patients with inducible ischemia. The study suggests that imaging approaches that combine quantitative information on the anatomic burden of coronary artery disease with its physiological consequences offer improved risk stratification over conventional approaches that use myocardial perfusion alone. If confirmed in larger prospective studies, it is possible that the use of combined imaging technologies may offer improved risk assessment and a more rational risk-based approach to management.



**Interrelation of Coronary Calcification, Myocardial Ischemia, and Outcomes in Patients With Intermediate Likelihood of Coronary Artery Disease: A Combined Positron Emission Tomography/Computed Tomography Study**

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