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 ≥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 ≥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 ≥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 ≥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.1-4 Consequently, the measurement of coronary artery calcification (CAC) by computed tomography (CT), with either electron-beam CT or multidetector 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).5-12 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
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±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±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.

**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 \(^{82}\)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 \(^{82}\)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 mg · kg\(^{-1}\) · min\(^{-1}\) for 4 minutes). Approximately 3 minutes after completion of the dipyridamole infusion, a second dose of \(^{82}\)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 ~25 minutes. Images were acquired with simultaneous ECG gating (6 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 16×1.25 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 512×512 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±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 (4×17=68) and multiplying by 100%. For the purpose of the present analysis, a summed difference score ≥2 was considered abnormal, given the increased sensitivity and specificity of PET for detecting myocardial ischemia compared with SPECT.

**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). 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 prescriptive 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±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
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).16–18 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 cut point (ie, CAC $\geq$500) were explored
systematically,16–21 because no optimal cut point has been estab-
lished 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 heterosce-
dasticity. 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 confirm
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 statisti-
cally 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 (Spear-
man rank correlation coefficient $r=0.28, P<0.001$). 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

Table 1. Characteristics of the Study Population

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

*One-tailed t test.
patients with CAC ≥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 Illinois24 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 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 ≥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.

| Predictor                  | OR   | P>|z| | 95% CI     |
|---------------------------|------|------|----------|
| CAC≥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|

### Table 2. Multivariate Predictors of Ischemic PET MPI
specified. When treated as a continuous variable, a 1-unit increase in log(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,16–21 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. Among 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 CAD17–18 and with a stepwise increase in coronary risk that is independent of that afforded by conventional coronary risk factors.5–12 The present results extend these observations in 2 important ways: by demonstrating the relationship between CAC and the frequency of myocardial

![Figure 3. Receiver operating characteristic curve analysis illustrating the incremental value of CAC score for predicting ischemic PET MPI.](http://circ.ahajournals.org/)

![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).](http://circ.ahajournals.org/)
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 calcium score criteria by dividing the patients into tertiles (CAC<1000, 1000–4000, and >4000 HU) and calculating the event rate in each tertile, we observed a dose-response relationship between CAC and PET MPI result.

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

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>CVD Events</th>
<th>Event Rate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic</td>
<td>165</td>
<td>60</td>
<td>0.036</td>
<td>0.024–0.050</td>
</tr>
<tr>
<td>CAC=0</td>
<td>34</td>
<td>4</td>
<td>0.082</td>
<td>0.031–0.219</td>
</tr>
<tr>
<td>1–399</td>
<td>61</td>
<td>10</td>
<td>0.172</td>
<td>0.085–0.326</td>
</tr>
<tr>
<td>400–999</td>
<td>33</td>
<td>4</td>
<td>0.121</td>
<td>0.033–0.338</td>
</tr>
<tr>
<td>≥1000</td>
<td>37</td>
<td>9</td>
<td>0.221</td>
<td>0.115–0.424</td>
</tr>
<tr>
<td>Nonischemic</td>
<td>441</td>
<td>49</td>
<td>0.011</td>
<td>0.059–0.258</td>
</tr>
<tr>
<td>CAC=0</td>
<td>179</td>
<td>7</td>
<td>0.026</td>
<td>0.012–0.054</td>
</tr>
<tr>
<td>1–399</td>
<td>178</td>
<td>11</td>
<td>0.060</td>
<td>0.023–0.144</td>
</tr>
<tr>
<td>400–999</td>
<td>42</td>
<td>3</td>
<td>0.070</td>
<td>0.033–0.155</td>
</tr>
<tr>
<td>≥1000</td>
<td>42</td>
<td>7</td>
<td>0.123</td>
<td>0.059–0.258</td>
</tr>
<tr>
<td>Total</td>
<td>606</td>
<td>55</td>
<td>0.063</td>
<td>0.049–0.082</td>
</tr>
</tbody>
</table>

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).

Cox proportional hazards regression model for freedom of the significance of this observation is prone to error. The use of a threshold value without concern for percentile
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. This was especially true in the present study, because only 8 patients (6.3%) under 50 years old had CAC scores ≥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 may miss a significant portion of intermediate likelihood patients under 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, 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 ≥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 ≥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., 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 β-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 symptomatological 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.

**References**

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 physiologic 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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