Stress Myocardial Perfusion Single-Photon Emission Computed Tomography Is Clinically Effective and Cost Effective in Risk Stratification of Patients With a High Likelihood of Coronary Artery Disease (CAD) But No Known CAD

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OBJECTIVES We sought to evaluate the prognostic and cost implications of stress myocardial perfusion single-photon emission computed tomography (SPECT), or MPS, in patients with a high pretest likelihood (>0.85) of coronary artery disease (CAD) with no previous CAD.

BACKGROUND Sparse data are available regarding the prognostic performance characteristics of MPS in this patient group.

METHODS We followed up 1,270 consecutive patients with no previous revascularization or myocardial infarction (MI), with a pre–exercise tolerance test (ETT) likelihood of CAD ≥0.85, who underwent exercise or adenosine stress MPS (follow-up 94.4% complete; 2.2 ± 1.2 years; 60 hard events [5.9%, 2.6%/year]). Risk adjustment of survival data was done using Cox proportional hazards analysis. Costs per reclassification of risk were calculated using assumed costs and threshold analyses.

RESULTS In patients treated medically after MPS, normal MPS had a low risk of cardiac death and hard events (0.6% and 1.3% per year, respectively). With increasing extent and severity of MPS defects, the risk of both cardiac death and hard events increased significantly (p < 0.05). Cox models indicated that the addition of MPS data resulted in incremental prognostic value over pre-MPS data (chi-square increase 48 to 87, p < 0.0001). Compared with strategies of initial referral to ETT in patients able to exercise, initial referral to MPS appeared to be a more cost-effective strategy. Similarly, compared with a strategy of direct referral to catheterization in patients with a high likelihood of CAD, initial referral to MPS is a cost-saving approach.

CONCLUSIONS In patients with a high likelihood of CAD but without known CAD, stress MPS yields incremental value and achieves risk stratification in a cost-effective manner. The current results support a strategy of initial stress imaging in this patient cohort, as a reasonable alternative to direct referral to catheterization or initial ETT. (J Am Coll Cardiol 2004;43:200–8) © 2004 by the American College of Cardiology Foundation

In light of the staggering mortality, morbidity, and cost associated with coronary artery disease (CAD) in the U.S., increasing demands have been placed on the medical community to enhance the efficiency of the valuation and care of patients with this disease. With respect to noninvasive testing, there is increasing appreciation of the importance of identifying which patients are appropriate for testing. Consequently, testing algorithms and guidelines are continuously being refined on the basis of new research.

Selection of appropriate patients for testing is the first important step in the process of cost-effective risk stratification. Traditionally, the use of noninvasive testing in patients with suspected CAD has been defined in terms of an anatomic end point and is guided by the principle that the patient’s pretest likelihood of angiographically significant CAD determines the best clinical approach (1). Using this approach for diagnosis of the presence of anatomic CAD, only patients with an intermediate likelihood of CAD are considered candidates for exercise treadmill testing, because in this range, the results would reclassify patients as having either a low likelihood (not in need of further testing) or a high likelihood (in need of angiography to determine the suitability for revascularization). This approach is embodied in multiple American College of Cardiology/American Heart Association (ACC/AHA) guidelines in which stress testing, with and without stress imaging, is considered a class IIb indication (usefulness/efficacy is less well established by evidence/opinion) for...
diagnostic testing in patients with either a high or low pretest probability of CAD (2–5).

On the other hand, for the management of patients with chronic stable angina (3), ACC/AHA/American College of Physicians-American Society of Internal Medicine (ACP-ASIM) guidelines acknowledge that stress myocardial perfusion single-photon emission computed tomography (SPECT), or MPS, can provide clinically useful information with respect to risk and prognosis in some patients with a high pretest likelihood of CAD. To date, however, guidelines suggest that this application would only achieve a class I indication when stress testing without imaging cannot be effective. Furthermore, it is not yet clear whether these patients with a high likelihood of CAD can be stratified into low- and high-risk subgroups by MPS results. To date, studies investigating the prognostic value of MPS in patients considered to have a high likelihood of CAD predominantly include patients who actually have documented CAD (3,6–10), such as patients with a previous myocardial infarction (MI) and/or revascularization. Also, the subsets of reported “high-likelihood” patients with no previous MI or revascularization are relatively small cohorts (11–13). With this in mind, the current study considers a larger cohort than those previously examined. We hypothesize that the ability of a normal stress MPS image to identify low-risk patients in a cohort of patients without known CAD but with a high likelihood of CAD will result in effective and clinically useful risk stratification in a cost-effective manner.

METHODS

Study population. We identified 1,345 consecutive patients with a pre-exercise tolerance test (ETT) likelihood of CAD (≥0.85), based on age, gender, symptoms, and CAD risk factors (1), who underwent exercise or adenosine stress dual-isotope SPECT between March 1991 and May 1998, with no history of revascularization or MI. Of these patients, 75 (5.6%) were lost to follow-up, leaving 1,270 patients with follow-up performed at least one year after the index SPECT study. Patients who were known to have valvular heart disease or primary cardiomyopathy were not considered for this study.

A 60-day time point after stress SPECT has been shown to be a temporal threshold distinguishing referrals to revascularization made on the basis of the scan results (≥60 days), as opposed to worsening of the patient’s clinical status, prompting intervention (>60 days) (14). For this reason, 249 patients (19.6%) who underwent revascularization within 60 days after their index SPECT study were also excluded from the prognostic analyses but were included in analyses of resource utilization.

Imaging and stress protocol. Patients were injected intravenously at rest with 2.5 to 3.5 mCi of thallium-201 (TI-201) with dose variation, based on patient weight. Rest TI-201 imaging was initiated 10 min after injection of the isotope (15).

EXERCISE STRESS PROTOCOL. Immediately after imaging, patients performed a symptom-limited treadmill exercise test, using standard protocols with 12-lead electrocardiographic (ECG) recording each minute of exercise and continuous monitoring of leads aVF, V1, and V5. Blood pressure was measured and recorded at rest, at the end of each exercise stage, and at peak exercise. Exercise end points included physical exhaustion, severe angina, sustained ventricular tachycardia, hemodynamically significant supraventricular dysrhythmias, and significant exertional hypotension. At near maximal exercise, a 20- to 30-mCi dose of technetium-99m (Tc-99m) sestamibi was injected (actual patient dose varied with patient weight), and exercise continued for one additional minute after injection. Technetium-99m sestamibi SPECT imaging was begun 30 min after isotope injection (15). The maximal degree of ST-segment change at 80 ms after the J point of the ECG was measured and assessed as horizontal, upsloping, or downsloping. Resting ECGs were considered interpretable for ETT if left bundle branch block, paced rhythm, or Wolff-Parkinson-White syndrome was not present (16).

ADENOSINE MYOCARDIAL PERFUSION PROTOCOL. Patients were instructed not to consume coffee or other products containing caffeine for 24 h before the test. After rest TI-201 SPECT, pharmacologic stress was applied with an adenosine infusion (140 µg/kg/min for 6 min). Technetium-99m sestamibi (20 to 30 mCi) was injected at the end of the third minute of infusion, and SPECT was initiated ~60 min after the end of the adenosine infusion (15). During both types of stress, blood pressure was measured and recorded at rest, at the end of each stress stage, and at peak stress. The maximal degree of ST-segment change at 80 ms after the J point of the ECG was measured and assessed as horizontal, upsloping, or downsloping. For patients who underwent exercise as an adjunct to adenosine infusion, low-level treadmill exercise was performed at 0% grade and 1.0 to 1.7 mph.

The SPECT acquisition protocol. The SPECT studies were performed as previously described, using a circular or elliptical 180° acquisition for 64 projections at 20 s per projection (15). During imaging, two energy windows were utilized for TI-201 (30% window centered on the 68- to
80-keV peak and 10% window centered on the 167-keV peak), and a 15% window centered on the 140-keV peak was used for Tc-99m sestamibi. No attenuation or scatter correction was used.

**Image interpretation.** A semiquantitative visual interpretation was performed using 20 segments for each rest and stress image (15). Each segment was scored by the consensus of two experienced observers using a 5-point scoring system (0 = normal; 1 = equivocal; 2 = moderate; 3 = severe reduction of radioisotope uptake; and 4 = absence of detectable tracer uptake in a segment), as previously described.

**Scintigraphic indexes.** The summed stress score (SSS) was obtained by adding the scores of the 20 segments of the stress images (17). Summed stress scores <4 were considered normal; 4 to 8 = mildly abnormal; and >8 = moderately to severely abnormal. A summed rest score (SRS) was obtained by similarly adding the scores of the 20 segments of the rest thallium images. The sum of the differences between each of the 20 segments on the stress and rest images was defined as the summed difference score (SDS), a variable representing the amount of ischemia present. Each of these variables incorporates both the extent and severity of perfusion defects, both of which independently add prognostic information (18). Summed difference scores <2 were considered as no ischemia; 2 to 4 = mild ischemia; 5 to 8 = moderate ischemia; and >8 = severe ischemia.

**Patient follow-up.** Patient follow-up was performed by scripted telephone interview by individuals blinded to the patients’ test results. Hard events included both cardiac death and nonfatal MI. The latter was said to have occurred if a patient presented with signs and symptoms suggestive of MI and enzyme elevations (creatine kinase-MB fraction or lactate dehydrogenase), in addition to any of the following conditions: 1) emergent treatment with percutaneous transluminal coronary angioplasty or thrombolysis; 2) development of new Q waves on the resting ECG in the setting of either delayed or silent presentation, so that enzymatic diagnosis was not possible; or 3) new Q waves or enzymatic increase sufficient to diagnose perioperative MI. Cardiac death was defined as death due to any cardiovascular cause, as noted and confirmed by a review of the death certificate and hospital chart or physician’s records. Patients undergoing revascularization within 60 days after MPS were censored from all analyses, and subsequent events were not considered unless specified. Patients undergoing revascularization >60 days after MPS were considered in all analyses, and events subsequent to this revascularization were considered in analyses. Patients included in this report were not contacted until at least one year after their index SPECT study.

**Statistical analysis.** Comparisons between patient groups were performed using one-way analysis of variance with Bonferroni correction, as appropriate, for continuous variables and the chi-square test for categorical variables. All continuous variables are described as the mean value ± SD. A p value <0.05 was considered statistically significant.

**Survival analysis.** To determine the incremental prognostic value of MPS, risk-adjusted, multivariate survival analysis was performed with a Cox proportional hazards model (19) in a stepwise fashion, using S-plus 2000 (Mathsoft, Cambridge, Massachusetts). Incremental prognostic value was assessed by first considering prescan information in an initial model and forcing it into the model before considering MPS data. The primary end point for all models was the occurrence of hard events. Secondary analyses of cardiac death and all-cause death were also performed. A statistically significant increase in the global chi-square value of the model after the addition of nuclear variables defined incremental prognostic value. The threshold for entry of variables into all models was p < 0.05, and the threshold for removal of variables was p > 0.10. Based on these models, risk-adjusted survival curves were determined. Assumptions of proportional hazards, linearity, and additivity were examined (20,21).

**Logistic regression.** Logistic regression was performed using S-plus 2000. Assumptions of linearity and additivity were examined (20,21). The threshold for entry of variables into all models was p < 0.05, and the threshold for removal of variables was p > 0.10. This type of modeling was used in cost analyses to determine one-year predicted risk and in resource utilization analyses to determine the most predictive model of referral to revascularization. The c index is reported as a measure of model robustness, and bootstrap analyses (80 iterations) were employed, as appropriate.

**Cost analysis.** The cost implications of MPS in patients after ETT was performed were calculated by determining the number of patients who were reclassified with respect to their risk of adverse outcomes by the addition of MPS data to prescan information (high vs. low risk after ETT as defined by a logistic model of hard events; reclassification based on a logistic model incorporating MPS data) (3,22,23). Correct reclassification was defined as: 1) a post-MPS risk ≤1% in patients at >1% risk by ETT who had no event; or 2) a post-MPS risk >1% in patients at ≤1% risk by ETT who had an event on follow-up. Incorrect reclassification was defined as: 1) a post-MPS risk >1% in patients at ≤1% risk by ETT who had no event; or 2) a post-MPS risk >1% in patients at ≤1% risk by ETT who had no event on follow-up. The net change in reclassifications with MPS results was defined as the number of correct reclassifications minus the number of incorrect reclassifications. Costs per reclassification of risk were calculated as noted earlier. The cost of MPS used for all cost analyses was $840 and that of catheterization $2,800, as in previous studies, to permit direct comparisons with previous work (24). Threshold analyses were performed to compare the relative cost effectiveness of MPS and catheterization. The comparison between costs with MPS and costs with direct referral to catheterization was made with respect to the cost per hard event detected.
factoring in the costs of MPS and catheterization, as noted earlier.

**Resource utilization.** Analyses of resource utilization employed referral to catheterization and revascularization within 60 days after the index SPECT study as the end points of interest.

**Quantifying the impact of early revascularization on observed event rates.** Based on the variables presented in the aforementioned Cox proportional hazards model, logistic regression analysis was performed also modeling hard events in patients not undergoing early revascularization. Using this model, the predicted probabilities for hard events were then calculated for patients both with and without early revascularization (20,21).

**RESULTS**

**Patient characteristics.** The pre-ETT likelihood of CAD in the patients included in the current study was 0.94 ± 0.04. The characteristics of the patients in the study cohort are shown in Table 1. Overall, the patients were middle-aged to elderly, about half were women, and two-thirds underwent exercise stress. With respect to cardiac risk factors, about one-fifth of patients had diabetes mellitus or had a history of smoking, one-quarter had a family history of CAD, about half had hypertension or hypercholesterolemia, and 95% presented with typical angina. One-fifth of patients had previous catheterization, and 94% had a resting ECG interpretable for ETT. About one-fifth of patients had ischemic ECG results on their stress studies. With respect to MPS results, the average SSS was 5.5, with most of the defects being reversible (SDS = 4.8).

**Outcome events.** In the cohort of 1,021 patients used for the prognostic analysis, over a mean follow-up of 2.2 ± 1.2
years, 60 hard events occurred (28 cardiac deaths [1.2% per year] and 32 MIs [5.9% hard event rate, 2.6% per year]). In addition, 65 all-cause deaths occurred during this period (6.4%, 2.8% per year). The subset of 384 patients who underwent pharmacologic stress experienced 34 hard events (3.9% per year), and of the 662 patients who underwent exercise stress, 26 experienced hard events (3.9% per year). Furthermore, 371 early catheterizations (29.2%), 249 early revascularizations (19.6%), and 142 late (1.9% per year). Furthermore, 371 early catheterizations who underwent exercise stress, 26 experienced hard events (3.9% per year), and of the 662 patients who underwent pharmacologic stress experienced 34 hard events (3.9% per year). The subset of 384 patients who underwent catheterization who went on to revascularization also tended to revascularization between pharmacologic and exercise stress, but no significant difference was present across MPS categories (p < 0.0001). In the setting of severe, inducible ischemia, a statistically significant difference was found in referral rates to early catheterization and revascularization between pharmacologic and exercise stress, but no such differences were present between the other SDS categories or with respect to referral rates to early revascularization.

### Performance of Inducible Ischemia

The relationship between scan results and annualized frequencies of all-cause death, cardiac death, and hard events for all patients and patients undergoing exercise and adenosine stress is shown in Table 2. In all patient groups, the annual frequencies for each of these end points increased significantly across scan categories, thus indicating successful risk stratification in all groups toward all end points examined.

### Survival analysis

Cox proportional hazards analysis was performed using hard events, cardiac death, and all-cause death as end points. After adjusting for prescan data (type of stress, age, previous catheterization), the addition of MPS data resulted in a significant increase in the global chi-squared value (48 to 87, p < 0.0001) for prediction of hard events. Adenosine stress, increasing age, SRS, and SDS were identified as the model most predictive of hard events (p < 0.0001, chi-square = 87), with the analysis stratified by SDS due to violation of the proportional hazards assumption. Risk-adjusted survival curves based on this model are shown for the subsets of patients undergoing exercise and pharmacologic stress (Figs. 1A and 1B). For both patient subsets, a statistically significant survival difference was present across MPS categories (p < 0.0001), even after adjusting for other confounding variables, again indicative of incremental prognostic value. With respect to both cardiac death and all-cause death, this same model was predictive (chi-square = 60 and 99, respectively; both p < 0.0001).

### Referral rates to catheterization and revascularization after SPECT

Rates of referral to catheterization and revascularization early (<60 days) after the index MPS study are shown in Table 3. In the overall patient cohort, as well as in the subsets of patients undergoing exercise and pharmacologic stress, referral rates to catheterization and revascularization were relatively low in the absence of inducible ischemia, although these referral rates increased significantly with increasing extent and severity of stress-induced ischemia (p < 0.0001). In the setting of severe, inducible ischemia, a statistically significant difference was found in referral rates to early catheterization and revascularization between pharmacologic and exercise stress, but no such differences were present between the other SDS categories or with respect to referral rates to early revascularization. The proportion of patients referred to catheterization who went on to revascularization also tended to increase across SDS categories. Using logistic regression, the model most predictive of referral to revascularization included SDS, type of stress, patient gender, diabetes mellitus, and ischemic ECG response to stress, with significant interactions between SDS and type of stress, patient gender, and diabetes mellitus, as well as between SDS and patient gender (chi-square = 239, c index = 0.85, p < 0.0001).

### Table 3. Rates of Referral to Early Catheterization and Revascularization as a Function of the Extent and Severity of Inducible Ischemia

<table>
<thead>
<tr>
<th></th>
<th>None (SDS 0–1)</th>
<th>Mild (SDS 2–4)</th>
<th>Moderate (SDS 5–8)</th>
<th>Severe (SDS &gt;8)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early catheterization</td>
<td>3.0%</td>
<td>19.9%</td>
<td>36.5%</td>
<td>65.3%*</td>
<td>29.2%</td>
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<tr>
<td>Early revascularization</td>
<td>0.9%</td>
<td>6.0%</td>
<td>21.0%</td>
<td>49.8%*</td>
<td>19.6%</td>
</tr>
<tr>
<td>Revascularized†‡</td>
<td>31%</td>
<td>30%</td>
<td>57%</td>
<td>76%</td>
<td>67%</td>
</tr>
<tr>
<td>n</td>
<td>537</td>
<td>166</td>
<td>167</td>
<td>400</td>
<td>1,270</td>
</tr>
</tbody>
</table>

**Pharmacologic stress**

<table>
<thead>
<tr>
<th></th>
<th>Early catheterization</th>
<th>Early revascularization</th>
<th>Revascularized†‡</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early catheterization</td>
<td>4.3%</td>
<td>26.2%</td>
<td>37.0%</td>
<td>56.9%*</td>
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<tr>
<td>Early revascularization</td>
<td>1.1%</td>
<td>6.6%</td>
<td>17.8%</td>
<td>39.4%*</td>
</tr>
<tr>
<td>Revascularized†‡</td>
<td>25%</td>
<td>25%</td>
<td>48%</td>
<td>69%</td>
</tr>
<tr>
<td>n</td>
<td>186</td>
<td>61</td>
<td>73</td>
<td>137</td>
</tr>
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</table>

**Exercise stress**

<table>
<thead>
<tr>
<th></th>
<th>Early catheterization</th>
<th>Early revascularization</th>
<th>Revascularized†‡</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early catheterization</td>
<td>2.3%</td>
<td>16.2%</td>
<td>36.2%</td>
<td>69.6%*†</td>
</tr>
<tr>
<td>Early revascularization</td>
<td>0.9%</td>
<td>5.7%</td>
<td>23.4%</td>
<td>55.1%*‡</td>
</tr>
<tr>
<td>Revascularized†‡</td>
<td>38%</td>
<td>35%</td>
<td>65%</td>
<td>79%</td>
</tr>
<tr>
<td>n</td>
<td>351</td>
<td>105</td>
<td>94</td>
<td>263</td>
</tr>
</tbody>
</table>

* p < 0.01 across categories of SDS. 1p < 0.01 within SDS category between exercise and pharmacologic stress. ‡Percentage of patients who underwent catheterization who were referred to revascularization.

SDS = summed difference score.
The most predictive model of prescan data consists of ETT exercise stress. The risk of hard events occurring in the first year of follow-up was modeled using logistic regression. The initial risk classification by ETT was evaluated in a subset of 617 patients with ECGs interpretable for ETT who underwent exercise stress. The cost per reclassification versus MPS.

Cost effectiveness of stress perfusion imaging: ETT versus MPS. The cost per reclassification for MPS after initial risk classification by ETT was evaluated in a subset of 617 patients with ECGs interpretable for ETT who underwent exercise stress. The risk of hard events occurring in the first year of follow-up was modeled using logistic regression analysis. The most predictive model of prescan data consisted of the Duke treadmill score alone (p < 0.003, c index = 0.74, bootstrap c index = 0.72) and the model incorporating MPS data included SSS and age (p < 0.0001, c index = 0.91, bootstrap c index = 0.89). On the basis of the prescan model, 275 patients (5 hard events) were identified as <1% risk and 342 patients (17 hard events) as ≥1% risk. The results of the postscan model identified 49 of the former as ≥1% risk, in whom three hard events occurred, and 187 of the latter as <1% risk, in whom no events occurred. Hence, 190 patients were correctly reclassified and 46 were incorrectly reclassified, for a net change of 144 reclassifications. Assuming a cost of $840 per MPS, this resulted in a cost of $3,599 per reclassification, which decreased to $2,999 for a cost of $700 per MPS and increased to $3,856 for a cost of $900 per MPS.

Given the cost effectiveness of MPS in both the low- and intermediate- to high-risk groups, as well as the risk in the low prescan risk group (1.8% hard event rate in the first year), it is possible that direct referral of patients with a high pre-ETT likelihood of CAD to MPS rather than ETT would be advantageous.

Cost effectiveness of stress perfusion imaging: MPS versus catheterization. We compared two strategies in patients with a high pre-ETT likelihood of CAD—direct referral to catheterization versus referral to MPS with subsequent referral to catheterization in patients with an abnormal MPS image. Based on one-year follow-up in our cohort of 1,021 patients, direct referral to catheterization resulted in a cost of $95,293 per hard event detected (assuming that all 30 hard events would be identified by catheterization) versus $81,435 per hard event detected (assuming all 1,021 patients had MPS and 428 had subsequent referrals to catheterization, with 26 hard events detected). Threshold analysis revealed that assuming a cost for catheterization of $2,800 initial MPS as a strategy remained superior to referral to catheterization for all MPS costs up to $1,200. Assuming a cost of $900 per MPS, initial MPS as a strategy remained superior to referral to catheterization for catheterization costs of $2,100 or higher. Conversely, direct referral to catheterization is a superior strategy to referral to MPS at costs below $2,100.

Impact of early revascularization on observed event rates. Logistic regression analysis was performed using the variables in the final Cox model described to model hard events in patients not undergoing early revascularization (c index 0.77, p < 0.0001). In these patients, the observed and predicted hard event rates were very similar (Table 4). Based on this model, the hard event rate in patients undergoing early revascularization would have been markedly greater than those observed had no early revascularization been performed (10.9% vs. 4.4%). Also based on this model, the hard event rate in the overall study cohort, if no patients had undergone early revascularization, would have been 19% higher (5.9% vs. 4.8%).

**DISCUSSION**

The goals of the current study were to determine whether in a cohort of patients with a high likelihood of but no known CAD, MPS could identify patients at low risk of adverse outcomes and achieve clinically applicable risk stratification in a cost-effective manner. With respect to MPS, unadjusted results indicated that MPS achieved excellent risk stratification in the overall cohort, as well as in the subgroups that underwent exercise and adenosine stress. Normal MPS results were present in 47% of the overall population of the current study (n = 1,270) and in 58% of patients who were treated medically (n = 1,021). In the latter, normal MPS was associated with low risk (cardiac death rates of 0.6%/year, 0.2%/year, and 1.3%/year; hard event rates of 1.3%/year, 0.8%/year, and 2.3%/year, in the

**Table 4. Observed and Predicted Hard Event Rates in Patients With and Without Revascularization After Stress Myocardial Perfusion Single-Photon Emission Computed Tomography**

<table>
<thead>
<tr>
<th>SSS</th>
<th>Normal</th>
<th>Mildly Abnormal</th>
<th>Moderate to Severely Abnormal</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No early revascularization</td>
<td>3.2%</td>
<td>5.6%</td>
<td>12.6%</td>
<td>5.9%</td>
</tr>
<tr>
<td>Predicted</td>
<td>3.9%</td>
<td>4.3%</td>
<td>14.6%</td>
<td>5.9%</td>
</tr>
<tr>
<td>Observed</td>
<td>2.9%</td>
<td>4.3%</td>
<td>12.6%</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>593</td>
<td>188</td>
<td>240</td>
<td>1,021</td>
</tr>
<tr>
<td>Early revascularization Predicted</td>
<td>3.7%</td>
<td>4.7%</td>
<td>10.9%</td>
<td>9.8%</td>
</tr>
<tr>
<td>Observed</td>
<td>0.0%</td>
<td>8.1%</td>
<td>4.4%</td>
<td>4.8%</td>
</tr>
<tr>
<td>n</td>
<td>8</td>
<td>37</td>
<td>204</td>
<td>249</td>
</tr>
</tbody>
</table>

*Predicted hard event rate based on model derived in patients with no early revascularization applied to patients with early revascularization to estimate the number of events that would have occurred had revascularization not been performed. Predicted hard event rates are those based on a logistic regression model derived in patients not undergoing early revascularization. SSS = summed stress score.
overall exercise stress and adenosine stress cohorts, respectively). With worsening defect extent and severity, the frequency of both cardiac death and hard events increased significantly, particularly in the setting of moderate to severely abnormal scans. Similar stratification was present for all-cause death. Cox proportional hazards analyses revealed that MPS results yielded incremental prognostic value, even after adjusting for the most predictive pre-SPECT data. With respect to cost effectiveness, MPS appeared to be a superior strategy compared with initial referral to ETT (in patients who are ETT candidates), as well in the overall population of patients referred to MPS, when compared with catheterization as an alternative strategy. With respect to resource utilization, referral rates to catheterization and revascularization increased in parallel to increasing patient risk in all patient subgroups.

**Previous studies.** Although a number of previous studies address the prognostic value of MPS in patients with a high likelihood of CAD, these reports are dominated by reports that include patients with a previous MI and/or revascularization (3,6–10). Limited data exist regarding post-MPS risk in patients without a previous MI and/or revascularization with a high pretest likelihood of CAD. In a first study evaluating incremental prognostic value, we described (13) a limited subset of patients with a high pre-ETT likelihood of CAD (211 patients with normal and 35 patients with abnormal rest ECGs), but this study utilized planar Tl-201 imaging. We have also previously shown in a cohort of patients with no previous MI, revascularization, or catheterization undergoing exercise stress, albeit a very small cohort (n = 79), that patients with a high pre-ETT likelihood of CAD had no risk of hard events after normal MPS and increasing risk with worsening MPS abnormalities (3.3% and 15% hard event rates in patients with mildly and moderate to severely abnormal scans, respectively) (12). Of note, however, each of these previous studies was limited with respect to the number of high-likelihood patients included. With respect to observed hard event rates after normal MPS, we have previously shown that the risk associated with a normal MPS image, and its “warranty period,” is adversely affected by increasing patient risk and use of adenosine stress (25). However, this last study only reported normal MPS; hence, no risk stratification could be surmised. Therefore, the current study is the first to examine, with sufficient power, the ability of stress MPS results to risk-stratify patients with a high likelihood of CAD, as well as the cost implications of this approach.

**Frequency of normal scans in patients with a high pretest likelihood of CAD.** In a cohort of patients with a high likelihood of CAD (mean 0.94), it is expected that the vast majority of patients would have abnormal scans. With this prevalence, assuming a sensitivity of 90%, we would anticipate that 85% of scans would have been abnormal. In the current study, however, abnormal MPS occurred in only 53% of the overall cohort. This 32% difference can be explained by several factors, including of the percent stenosis threshold used for defining CAD and post-MPS referral bias in which patients with abnormal scans are preferentially referred to catheterization.

**Impact on clinical practice.** As outlined in recent Bethesda Conference reports (26,27), a paradigm shift has occurred in which the basis of patient evaluation has moved from the likelihood of CAD to the risk of adverse events secondary to CAD. As we have previously shown, test performance characteristics of noninvasive imaging modalities differ dramatically when anatomic and prognostic end points are used (22). Thus, testing algorithms for the evaluation of patients with suspected CAD might be altered in a risk-based approach.

Although multiple current ACC/AHA guidelines define stress testing, with and without stress imaging, as being a class IIb indication for diagnostic testing in patients with either a high or low pretest probability of CAD (2–5), the ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina (3) indicate that in a prognostic context, both exercise and stress imaging modalities can provide clinically useful information on patient risk and prognosis, which may be useful for determining patient management. In the current study, we have shown that although the subset of patients with interpretable rest ECGs can be risk-stratified by exercise treadmill testing without imaging, only a small proportion of these patients are reclassified as sufficiently low risk so that no further testing is required. Hence, exercise testing without imaging in these patients is unlikely to be clinically efficient in practice. The findings of the present study may be useful in modifying current practice guidelines in this regard.

With respect to stress MPS, the results of the current study support the use of the stress imaging modalities described in the guidelines cited previously. In patients with a high likelihood of CAD without a history of CAD, stress MPS achieves excellent risk stratification, so that a majority of patients are identified as low risk of future events. Because sufficient numbers of patients are identified as low risk, this approach achieves significant cost effectiveness compared with a strategy of direct catheterization of these patients. The current study also suggests that direct referral to MPS is a superior strategy with respect to both cost and identification of risk compared with a strategy of initial referral to ETT.

**Impact of early revascularization on observed event rates.** Prognostic studies commonly remove from analyses those patients undergoing early revascularization, a procedure known to reduce mortality in high-risk subsets of patients. Because referral to catheterization and revascularization rates increase as a function of the extent and severity of inducible ischemia, patients expected to have the highest event rates are excluded from prognostic analysis. The observed event rates in patients with a high likelihood of CAD will thus be expected to decrease with increasing utilization of MPS results. As MPS results are increasingly incorporated into clinical management, and patients more
commonly receive intervention based on these results, in observational studies evaluating the prognostic value, MPS will appear to be less predictive, as the observed risk of patients with abnormal scans will be reduced by these revascularizations. We observed that the hard event rate in patients undergoing early revascularization would have been markedly greater than that observed had no early revascularization been performed (10.9% vs. 4.4%), and the hard event rate in the overall study cohort, if no patients had undergone early revascularization, would have been 11% higher (5.9% observed vs. 6.6% predicted).

Although this impact of referral to revascularization on reducing the apparent prognostic strength of MPS has been previously postulated (28,29), to our knowledge, the current study represents the first time this phenomenon has been quantified.

**Study limitations.** The principal limitation of the current study is that the patients with a high likelihood of CAD who we have examined are those preselected for stress MPS. It is possible that these patients are not representative of patients with a high likelihood of CAD referred directly to catheterization. Furthermore, the patients in this study are those referred to a university-affiliated community hospital in a major urban area, limiting the degree to which the results of this study should be generalized. The scintigraphic studies in the current work were interpreted by experienced observers using a standardized, semiquantitative approach to visual interpretation, which we have developed and documented to be highly reproducible (30,31). These form the basis for existent quantitative analysis programs that have been shown to correlate strongly with those of semi-quantitative analysis (31).

**Conclusions.** In patients with a high likelihood of CAD but without known CAD, stress MPS yields incremental value and achieves risk stratification in a cost-effective manner. The current results support a strategy of initial stress imaging in this patient cohort as a reasonable alternative to direct referral to catheterization or initial ETT.

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