Impact of Diabetes on the Risk Stratification Using Stress Single-Photon Emission Computed Tomography Myocardial Perfusion Imaging in Patients With Symptoms Suggestive of Coronary Artery Disease

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Background—Coronary artery disease can develop prematurely and is the leading cause of death among diabetics, making noninvasive risk stratification desirable.

Methods and Results—Patients with symptoms of coronary artery disease who were undergoing stress myocardial perfusion imaging (MPI) from 5 centers were prospectively followed (2.5±1.5 years) for the subsequent occurrence of cardiac death, myocardial infarction (MI), and revascularization. Stress MPI results were categorized as normal or abnormal (fixed or ischemic defects and 1, 2, or 3 vessel distribution). Of 4755 patients, 929 (19.5%) were diabetic. Patients with diabetes, despite an increased revascularization rate, had 80 cardiac events (8.6%; 39 deaths and 41 MIs) compared with 172 cardiac events (4.5%; 69 deaths and 103 MIs) in the nondiabetic cohort (P<0.0001). Abnormal stress MPI was an independent predictor of cardiac death and MI in both populations. Diabetics with ischemic defects had an increased number of cardiac events (P<0.001), with the highest MI rates (17.1%) observed with 3-vessel ischemia. Similarly, a multivessel fixed defect was associated with the highest rate of cardiac death (13.6%) among diabetics. The unadjusted cardiac survival rate was lower for diabetic patients (91% versus 97%, P<0.001), but it became comparable once adjusted for the pretest clinical risk and stress MPI results. In multivariable Cox analysis, both ischemic and fixed MPI defects independently predicted cardiac death alone or cardiac death/MI. Diabetic women had the worst outcome for any given extent of myocardial ischemia.

Conclusions—In this large cohort of diabetics undergoing stress MPI, the presence and the extent of abnormal stress MPI independently predicted subsequent cardiac events. Using stress MPI in conjunction with clinical information can provide risk stratification of diabetic patients. (Circulation. 2002;105:32-40.)

Key Words: imaging ■ diabetes mellitus ■ risk factors ■ trials

The percentage of patients with diabetes is increasing in the United States, from 4.9% in 1988 to 6.3% in 1994, according to a recent survey.1 Patients with diabetes develop coronary artery disease (CAD) at an accelerated rate and have a higher incidence of heart failure, myocardial infarction (MI), and cardiac death than their nondiabetic counterparts.2 Although age-adjusted mortality from CAD has declined substantially among the general population, CAD mortality rates in diabetics have not decreased to the same extent and may have even increased in diabetic women.3 With the lack of improvement in survival rates and the increasing prevalence of diabetes in the United States, risk stratification in diabetics is of clinical relevance because aggressive therapies seem to improve outcome.4–6

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The unique pathophysiology of diabetes makes traditional symptomatology and angiographic demonstration of epicardial coronary narrowing less discriminative.7 The role of radionuclide myocardial perfusion imaging (MPI) in the
general population for risk stratification is well-established.8–11 However, because diabetic patients constituted only 10% to 20% of those being evaluated in prior studies, specific information on the diabetic population is limited.12 Recently, several institutions collaborated to study the economic impact of the noninvasive diagnosis of CAD on outcomes.13 The purpose of this substudy was to evaluate the incremental role of stress single-photon emission computed tomography (SPECT) imaging in diabetic patients in the prediction of cardiac events. A secondary objective was to explore the possibility of a sex-ischemia interaction.

Methods

Patient Selection
Patients referred to enrolling facilities with symptomatology suggestive of CAD were prospectively recruited in this registry. Five hospitals participated, including Cedars-Sinai Medical Center, Duke University Medical Center, Memorial Hospital of Rhode Island, Roger Williams Medical Center, and St Louis Veterans Affairs Medical Center. Excluded were patients hospitalized for unstable angina or MI or who underwent early coronary revascularization within 3 weeks of presentation. A detailed history was taken, and a physical examination was performed on each study patient. Data were then submitted to the core laboratory at Duke University. Patients were initially identified as diabetics on the basis of their response to a questionnaire. A study physician interviewed the patients before the stress MPI procedure to verify the diagnosis of diabetes on the basis of the diagnostic criteria of a fasting blood sugar level ≥120 mg/dL or a random blood sugar level of ≥200 mg/dL.14

Stress MPI Protocols
Patients able to exercise underwent symptom-limited exercise treadmill testing by the Bruce protocol. Heart rate, blood pressure, and 12-lead ECGs were recorded during exercise and after discontinuation at standard clinical end points.15 Radiopharmaceutical injection was made at peak exercise with Tc99m or Tc99m sestamibi. Tc99m sestamibi was the predominant radiopharmaceutical agent; Tl201 alone was used in 6.8% of patients with diabetes and 5.3% of patients without diabetes.

Patients unable to perform a maximal exercise test underwent intravenous vasodilator stress using adenosine (140 μg · kg−1 · min−1 for 6 minutes)16 or dipyridamole (0.56 mg/kg over 4 minutes).17 The number of patients requiring adenosine and dipyridamole (273 diabetic versus 656 nondiabetic patients) was higher among diabetics (χ2 = 113, P < 0.0001). A radiopharmaceutical agent was injected 3 minutes after the adenosine infusion and 7 to 9 minutes after dipyridamole infusion initiation. Exercise was not used in conjunction with pharmacological testing.

SPECT MPI Imaging
SPECT MPI was performed using previously described same-day or 2-day protocols. For same-day single isotope studies, 8 to 10 mCi of Tc99m sestamibi was injected at rest, and 22 to 25 mCi was injected at peak stress. For single-isotope Ti201 imaging, an average of 3 mCi was injected at peak stress. For dual isotope studies, 3 mCi of Ti201 was injected at rest and 22 to 25 mCi of Tc99m sestamibi was injected at stress. SPECT acquisition was performed using a single or dual-head gamma camera over a 180-degree, semicircular orbit extending from the 45-degree right anterior oblique to the 45-degree left posterior oblique positions. Data were acquired in a 64×64 matrix for 64 projections (20 to 25 seconds/projection) with Tc99m sestamibi and for 32 projections (40 seconds/projection) with Ti201 in a step and shoot format. All image sets were normalized to maximal myocardial activity.

Two experienced nuclear cardiologists from each institution who were unaware of the clinical data reviewed the images. Stress images were compared with rest images. Defects that were present at rest and remained unchanged during stress were considered fixed defects. New or worsening defects (≥40% activity reduction compared with the rest images) after stress were considered ischemic. The scoring system used for analysis included documentation of fixed or ischemic defects in the left anterior descending artery, right coronary artery, and circumflex vascular territories.18 The extent of perfusion defects was coded as 0, 1, 2, and 3 vascular territory involvement.

Left Ventriculography and Coronary Angiography
A total of 597 patients underwent coronary angiography with left ventriculography to determine ejection fraction and epicardial coronary disease. The results of these procedures were included in the database to evaluate their relationship with nuclear variables and clinical outcomes.

Follow-Up
Patients were prospectively followed for 2.5 ± 1.5 years (minimum, 6 months) after initial testing to check for the occurrence of the primary end points, which were defined as cardiac death or cardiac death and MI. Coronary revascularization was also documented separately as either coronary artery bypass graft surgery (CABG) or percutaneous coronary intervention (PCI). Follow-up information was obtained through yearly clinic visits or telephone interviews and submitted to the core laboratory at Duke University. More than 90% of required information was necessary for data inclusion, with active acquisition of missing data by the core laboratory. A participating physician from each site who was unaware of the patient’s clinical history or image results evaluated and confirmed each cardiac event on the basis of hospital records and death certificates, including classification of death as cardiac or noncardiac. Of the surviving patients, follow-up at 12 months was 97% complete. In the remaining 3% of patients, the reason for lack of follow-up was early revascularization.

Statistical Analysis

Univariable
Descriptive statistics were generated using percentages for discrete variables and mean ± SD for continuous variables. Demographic and clinical information were tabulated for patients with or without an event. All continuous variables were compared by outcome rates using ANOVA. Categoric variables were compared by χ2 tests. The impact of diabetes on cardiac outcomes was initially computed with the Kaplan-Meier method and compared using the log-rank χ2 test.

Multivariable
The relationship between nuclear variables and the subsequent occurrence of cardiac events was analyzed using Cox’s model, with generation of survival curves adjusted for the effects of baseline characteristics.19 We compared rates of cardiac death and cardiac death and/or MI in patients with diabetes with those without diabetes. To adjust or control for known clinical confounding variables, a previously validated clinical index that considers a patient’s cardiac symptoms, CAD risk factors, age, sex, and prior history of MI was used.20 The clinical index was then entered into the model to reflect the pretest probability of cardiac survival or event-free survival. Finally, the nuclear variables were added to the model. For the nuclear stress imaging results, the number of vascular territories (0, 1, 2, or 3) was used to indicate the presence and extent of ischemia (ie, defect reversibility) and infarcted (ie, fixed) defects. The number of infarcted vascular areas was collapsed into 0, 1, and ≥2 because of the low incidence of such defects. To assess the incremental value of the nuclear test data, we calculated the difference in the model likelihood ratio χ2 statistic from the overall model with and without the nuclear variables.

Cost Analysis
The cost-analysis methodology has been described in detail previously.21 Cost data were obtained using previously developed methods22–25 that had been revised for use in noninvasive testing.
populations. Direct cost estimates from a microcost accounting system and Medicare hospital charge (adjusted by cost-charge ratio), including physician billing data, were used to estimate cost. Both the top-down and bottom-up cost data from microcost accounting systems were averaged for use in all clinical decision-making models. Hospital charges were obtained from the hospital-specific Medicare cost report and per diems from each participating hospital. Physician service costs were determined on the basis of the Medicare Fee Schedule, which provides a standardized resource-based approach for these costs. All costs were expressed in 1995 US dollars. Total costs were the sum of all costs accrued in noninvasive tests, catheterization, and cardiac hospitalizations. The cost of outpatient medical therapy was not available for this analysis. There was a standard discount rate of 3% for this analysis.

Briefly, the composite cost per patient of diagnostic testing plus follow-up medical care over a period of 3 years was calculated for both diabetic and nondiabetic patients from inflation-corrected Medicare charges and adjusted for institutional cost-charge ratios. ANOVA techniques were used to compare costs, adjusting for treatment propensity and pretest risk.

Results

Baseline Clinical History
Clinical and stress test characteristics are shown in Table 1. Of the 4755 patients, 929 (19.5%) were diabetic. Diabetic patients were similar to nondiabetic patients in age (65±11 versus 64±11 years), sex (49% versus 53% female), and number of patients ≥65 years of age (55% versus 52%). There were 80 cardiac events (8.61%; cardiac death in 39 patients and nonfatal MIs in 41 patients) in the diabetic patients and 172 events (4.50%; cardiac death in 69 patients and nonfatal MIs in 103 patients) in the nondiabetic patients during the 2.5±1.5 years of follow-up. The significantly (P<0.001) higher cardiac event rate in diabetics was noted despite a higher rate of revascularization (CABG and PCI; Figure 1). An abnormal MPI image was a significant predictor of cardiac death and MI in both diabetic and nondiabetic populations (Table 2). An increasing number of ischemic defects was associated with a stepwise increase in the death rate (diabetic, χ²=15.1, P=0.002; nondiabetic; χ²=38.8, P<0.0001 for cardiac death). However, a stepwise increase was more evident among nondiabetic patients because in diabetic patients, even single-vessel ischemia significantly increased the risk of death. The presence of ischemic defects was significantly associated with cardiac events in diabetic patients, whereas the strongest predictor of MI was the presence of an ischemic defect in all 3 vascular territories. In the nondiabetic population, the presence of ischemic defects was also significantly associated with higher cardiac event rates, with the greatest number of events for both MI and cardiac death in those with 3 ischemic territories.

The presence of fixed defects also predicted cardiac events in diabetic patients. Cardiac events increased if ≥2 fixed defects were present (Table 2). The cardiac death rate was significantly greater in both diabetic and nondiabetic populations with multivessel, fixed defects than in similar patients with multivessel ischemic defects.

In an unadjusted analysis, diabetics had a χ²=30.7 and P<0.0001 for death and a χ²=1.1 and P=0.78 for MI. Nondiabetic patients had a χ²=51.7 and P<0.0001 for death and a χ²=29.2 and P<0.0001 for MI. However, in a Cox model, the interaction of diabetes with the extent of fixed defects was χ²=26.1 and P<0.0001. In a death or MI model, a significant interaction also existed (χ²=19.5, P<0.0001). Therefore, these results reveal that there is a significant difference in the risk of death and death or MI in diabetic and nondiabetic patients by the extend of fixed defect(s).

Survival Analyses
Cardiac survival over time was compared using the Kaplan-Meier method and multivariate Cox models. The unadjusted cardiac survival was 91% for diabetic patients and 97% for nondiabetic patients (P<0.001). However, once risk-adjusted

### Table 1. Clinical and Stress Test Characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Diabetic Patients (n=929)</th>
<th>Nondiabetic Patients (n=3826)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cardiac Death, %</td>
<td>MI, %</td>
</tr>
<tr>
<td>----------------------------</td>
<td>------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Total patients</td>
<td>929 (19.5)</td>
<td>4.2</td>
</tr>
<tr>
<td>Age ≥65 years</td>
<td>506 (55)</td>
<td>5.0</td>
</tr>
<tr>
<td>Female sex</td>
<td>451 (49)</td>
<td>4.0</td>
</tr>
<tr>
<td>Smoking</td>
<td>396 (43)</td>
<td>3.0*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>738 (79)</td>
<td>3.8</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>559 (60)</td>
<td>3.2</td>
</tr>
<tr>
<td>Prior MI</td>
<td>329 (35)</td>
<td>5.5*</td>
</tr>
<tr>
<td>CHF</td>
<td>77 (8)</td>
<td>13.0*</td>
</tr>
</tbody>
</table>

CHF indicates congestive heart failure.

*P≤0.05 outcomes in patients with vs those without diabetes.

![Figure 1](https://example.com/figure1.png)

Figure 1. Outcomes of cardiac death, MI, PCI, and CABG in diabetic and nondiabetic patients.
for pretest clinical risk and extent of perfusion abnormalities, cardiac survival was comparable (Figure 2). Similarly, the unadjusted cardiac event–free survival rate was significantly lower for diabetics (83% versus 91%, \( P < 0.0001 \)). When risk-adjusted, the cardiac event–free survival rate was similar for diabetics and nondiabetics (86% versus 89%, \( P = 0.3 \); Figure 3).

A separate survival analysis was performed comparing patients with and without diabetes who had normal stress MPI images (Figure 4). For the first 2 years of the study follow-up, patients with normal stress MPI images had virtually identical survival curves, irrespective of their diabetic status. Beyond 2 years, patients with diabetes demonstrated a sharp increase in the incidence of cardiac events (log-rank statistic, 18.28; \( P = 0.0001 \)).

We developed a survival score estimating all-cause mortality as a surrogate for diabetic comorbidity. We then included this variable in several models. First, this all-cause survival score, which included age, risk factors (hypertension, diabetes, hypercholesterolemia, family history, and smoking), past medical history of congestive heart failure, vascular disease, MI, sex, and other comorbidity, was independently associated with cardiac death, even after controlling for pretest clinical risk index\(^{20} \left( \chi^2 = 13.2, P = 0.0003 \right) \). Even after controlling for all-cause mortality risk and pretest clinical risk index, diabetes was not an independent estimator of cardiac death (\( \chi^2 = 0.93, P = 0.33 \)). Both the extent of infarcted defects and ischemic defects were independent estimators of cardiac death (\( \chi^2 = 186.6, P < 0.0001 \) for infarct and \( \chi^2 = 76.9, P < 0.0001 \) for ischemia).

### Multivariable Risk-Adjusted Cox Model

Multivariable analysis for cardiac events or cardiac death alone demonstrated a significant association with pretest clinical risk but not with diabetes alone. After risk adjustment, the number of ischemic and fixed MPI defects demonstrated the strongest association with clinical outcomes (Table 3). Relative risks for clinical outcomes in the Cox analyses were highest for the extent of ischemic/fixed MPI defects in both diabetic and nondiabetic groups. An abnormal

<table>
<thead>
<tr>
<th>Table 2. Cardiac Event Rates (2.5 Years) by Diabetic Status and Results of Stress Perfusion Scan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>Abnormal image</td>
</tr>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>Abnormal</td>
</tr>
<tr>
<td>No. of ischemic defects</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>No. of fixed defects</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>( \geq 2 )</td>
</tr>
</tbody>
</table>

*\( P \leq 0.05 \) for outcomes in patients with vs without diabetes. All nuclear variables were predictive of both cardiac death and MI end points, except the increasing number of fixed defects, which was associated with cardiac death but not MI in diabetics.

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**Figure 2.** Cox regression survival plots for diabetic and nondiabetic patients, unadjusted and adjusted for clinical and stress MPI variables.

**Figure 3.** Cox regression event-free (cardiac death and MI) survival plots for diabetic and nondiabetic patients, unadjusted and adjusted for clinical and stress MPI variables.
stress MPI result was also the greatest contributor (incremental \( \chi^2 \)) to the total model \( \chi^2 \) for predicting either death or death/MI among diabetics (Figure 5).

**Ejection Fraction and Disease Extent**

Left ventricular ejection fraction was determined by ventriculography at the time of coronary angiography in 597 patients. A significant negative correlation was observed between ejection fraction and fixed MPI defects (\( r = -0.52 \), \( P < 0.0001 \)). To evaluate this relationship further, we created a separate multivariate model that included left ventricular ejection fraction, the results of coronary angiography, and clinical variables.

In a death or MI multivariable model, left ventricular ejection fractions (\( \chi^2 = 5.4, P = 0.02 \)), ischemic defects (\( \chi^2 = 6.4, P = 0.01 \)), and fixed defects (\( \chi^2 = 6.7, P = 0.0095 \)) were significant estimators (after controlling for all-cause mortality risk, pretest clinical risk, and diabetes), whereas the catheterization-determined disease extent and severity were not (\( \chi^2 = 0.5, P = 0.47 \)) significant estimators.

In a cardiac death multivariable model, left ventricular ejection fractions (\( \chi^2 = 7.1, P = 0.008 \)), ischemic defects (\( \chi^2 = 8.9, P = 0.003 \)), and fixed defects (\( \chi^2 = 6.1, P = 0.01 \)) were significant estimators (after controlling for all-cause mortality risk, pretest clinical risk, and diabetes), whereas the catheterization-determined disease extent and severity was of borderline significance (\( \chi^2 = 1.8, P = 0.18 \)).

**Value of Stress MPI in Specific Patient Subsets**

Several stratified models were created to evaluate the role of stress MPI and diabetic status in key patient subsets. In patients with no history of CAD, MI, or revascularization, both ischemic (\( \chi^2 = 76.9, P < 0.0001 \)) and fixed (\( \chi^2 = 186.6, P < 0.0001 \)) defects were independent predictors of death but diabetes was not (\( \chi^2 = 0.2, P = 0.68 \)) after controlling for all-cause mortality survival risk and pretest clinical risk (model \( \chi^2 = 294.7, P < 0.0001 \)).

In patients who had known CAD or a history of MI or revascularization, ischemic (\( \chi^2 = 14, P = 0.0002 \)) and fixed (\( \chi^2 = 68.8, P < 0.0001 \)) defects were independent estimators of death but diabetes was not (\( \chi^2 = 0.0, P = 0.95 \)) after controlling for all-cause mortality survival risk and pretest clinical risk (model \( \chi^2 = 404.2, P < 0.0001 \)).

For the combined end point of death or MI in patients with no history of CAD, MI, or revascularization, ischemic (\( \chi^2 = 198.1, P < 0.0001 \)) and fixed (\( \chi^2 = 232.3, P < 0.0001 \)) defects were independent estimators of death/MI outcome and diabetes was not (\( \chi^2 = 0.6, P = 0.43 \)) after controlling for all-cause mortality survival risk and pretest clinical risk (\( \chi^2 = 105.4, P < 0.0001 \)).

In patients with known CAD, a history of MI, and revascularization, ischemic (\( \chi^2 = 26.7, P = 0.0001 \)) and fixed (\( \chi^2 = 77.2, P < 0.0001 \)) defects were independent estimators of outcome but diabetes was not (\( \chi^2 = 0.0, P = 0.93 \)) after controlling for all-cause mortality survival risk and pretest clinical risk (model \( \chi^2 = 102.9, P < 0.0001 \)).

**Sex-Ischemia Interaction**

Cardiac event rates were significantly higher among the 451 diabetic women (36 events, 8%) than in the 1635 nondiabetic women (53 events, 3.2%; \( P < 0.01 \)). In risk-adjusted Cox regression analysis, a significant interaction between sex and ischemia was noted (relative risk, 0.30 ± 0.14; \( P < 0.01 \)). The 3-year survival rates for diabetic women were 97%, 89%, and 85% for 0, 1, and ≥2 vessel territory ischemia, respectively. These survival rates for diabetic women were the lowest for any given amount of ischemia compared with others (Table 4).

The presence and the extent of perfusion abnormalities were the strongest predictors of cardiac events among diabetic women (total model \( \chi^2 = 65.61, P < 0.0001 \)). Once risk-adjusted for the nuclear variables, sex alone (odds ratio, 0.32; 95% confidence interval, −0.54 to 1.06; \( P = 0.32 \)) was no longer independently predictive of cardiac events in diabetics.

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**TABLE 3. Multivariable Cox Proportional Hazard Model Demonstrating the Total Model \( \chi^2 \) Values**

<table>
<thead>
<tr>
<th>Predicting Variables</th>
<th>Cardiac Death</th>
<th></th>
<th></th>
<th>Cardiac Death or MI</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>0.37</td>
<td>0.55</td>
<td>2.4</td>
<td>0.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical risk</td>
<td>52.2</td>
<td>0.00001</td>
<td>16.1</td>
<td>0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of ischemic MPI defects</td>
<td>39.2</td>
<td>0.00001</td>
<td>40.9</td>
<td>0.00001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of fixed MPI defects</td>
<td>54.6</td>
<td>0.00001</td>
<td>30.8</td>
<td>0.00001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Figure 4. Kaplan-Meier survival curves comparing the subset of diabetic and nondiabetic patients with normal stress MPI results.

Figure 5. Incremental \( \chi^2 \) value of nuclear and clinical variables to the total model \( \chi^2 \) value for the prediction of cardiac death or cardiac death/MI in diabetic (DM) patients.
Cost Analysis
To evaluate the differences in the cost of care, patients were stratified by diabetes status and matched for other pretest clinical risk and the choice of diagnostic strategies (Table 5). Composite 3-year costs of care were compared for the 2 patient population using ANOVA techniques and adjusting for treatment propensity and pretest risk (Figure 6). Observational comparisons of diabetic versus nondiabetic patient populations reveal that the average costs of care were higher for diabetic patients compared with nondiabetic patients ($2705.00 versus $1688.00; \( P < 0.00001 \); Figures 7 and 8). Thus, patients with stable chest pain who are diabetic have higher diagnostic costs and greater rates of intervention and follow-up costs.

Discussion
Although stress SPECT MPI use is well-established for risk stratification in a general population, evaluation in a large diabetic population has not occurred. In this multicenter study of 4755 patients that included 929 diabetic patients who were followed prospectively for 2.5 years, the presence of multivessel ischemia was the strongest predictor of total cardiac events, and a multivessel fixed defect was the greatest predictor of cardiac death in diabetic patients. Risk stratification by stress SPECT MPI was incremental to that provided by the clinical risk assessment, and diabetes status alone and in diabetic women, it negated the sex differences observed in cardiac risk.

Correlation Between Stress MPI Results and Cardiac Events in Diabetics
Our diabetic patients were significantly younger than nondiabetic patients, but they demonstrated consistently higher overall unadjusted cardiac death/MI rates, despite higher revascularization rates. However, when the clinical information and size and extent of the perfusion abnormalities were factored in, results were similar to the nondiabetic patients. These data suggest that risk stratification with stress MPI provides a key component to the evaluation of diabetic patients beyond the assessment of clinical features alone. Previously, such data have been unavailable. In a small series of 123 diabetics undergoing stress Tl201 scintigraphy, Felscher et al\(^{12}\) demonstrated that cardiac events were independently associated with an abnormal stress MPI result (\( \chi^2 = 5.4 \)). Further analysis was not possible because of the small number of patients. Our data confirm and extend these observations of the ability of stress MPI to provide risk stratification in a much larger diabetic population with categorization of the impact of size and extent of the perfusion abnormalities.

### TABLE 4. Kaplan-Meier 3-Year Survival Rate for Patients With and Without Diabetes Stratified by Sex, Demonstrating Lowest Survival Rates for Diabetic Women for any Given Extent of Myocardial Ischemia

<table>
<thead>
<tr>
<th></th>
<th>Death</th>
<th>Death/MI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-Vessel Ischemia</td>
<td>1-Vessel Ischemia</td>
</tr>
<tr>
<td>Diabetic men</td>
<td>93.75</td>
<td>93.0</td>
</tr>
<tr>
<td>Nondiabetic men</td>
<td>99.0</td>
<td>96.5</td>
</tr>
<tr>
<td>Diabetic women</td>
<td>99.0</td>
<td>80.0*</td>
</tr>
<tr>
<td>Nondiabetic women</td>
<td>98.75</td>
<td>97.50</td>
</tr>
</tbody>
</table>

*\( P < 0.05 \).

Extent of ischemia was determined by the number of vascular territories (0, 1, or \( \geq 2 \) vessel) involved in the reversible perfusion defect.

### TABLE 5. Risk-Adjusted Model for Predicting Cost after Controlling for Pretest Clinical Risk, Infarct Extent, and Ischemia Extent

<table>
<thead>
<tr>
<th>Predicting Variables</th>
<th>Unstandardized Coefficient B</th>
<th>Standard Error</th>
<th>Standardized Coefficients (( \beta ))</th>
<th>t</th>
<th>Significance (( P ))</th>
<th>95% Confidence Interval for B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>-43.5</td>
<td>187.3</td>
<td>...</td>
<td>-0.232</td>
<td>0.816</td>
<td>-410 to 324</td>
</tr>
<tr>
<td>Diabetes</td>
<td>56.5</td>
<td>97.4</td>
<td>0.008</td>
<td>0.580</td>
<td>0.562</td>
<td>-134 to 247</td>
</tr>
<tr>
<td>Clinical risk</td>
<td>81.7</td>
<td>49.5</td>
<td>0.023</td>
<td>1.651</td>
<td>0.099</td>
<td>-15 to 179</td>
</tr>
<tr>
<td>No. of ischemic MPI defects</td>
<td>97.8</td>
<td>41.9</td>
<td>0.034</td>
<td>2.333</td>
<td>0.020</td>
<td>16 to 180</td>
</tr>
<tr>
<td>No. of fixed MPI defects</td>
<td>159.4</td>
<td>59.3</td>
<td>0.036</td>
<td>2.689</td>
<td>0.007</td>
<td>43 to 276</td>
</tr>
<tr>
<td>Catheterization</td>
<td>3303.2</td>
<td>138.7</td>
<td>0.418</td>
<td>23.802</td>
<td>0.0001</td>
<td>3031 to 3575</td>
</tr>
<tr>
<td>Revascularization</td>
<td>4950.3</td>
<td>175.6</td>
<td>0.477</td>
<td>28.193</td>
<td>0.0001</td>
<td>4606 to 5295</td>
</tr>
</tbody>
</table>

Amount of explained variability: \( r^2 = 0.68, P < 0.00001 \).

Although the unadjusted costs of care for diabetics were substantially higher, diabetes per se only accounted for 1% of the explained variability in cost. Even considering the SPECT results and pretest clinical risk, the \( r^2 \) increased to only 18%. However, this final model, which accounts for nearly 68% of the variability in cost, reveals that diabetes no longer predicted cost when nuclear results, catheterization, and revascularization were considered.
Prognostic Value of Fixed MPI Defects
The relationship between the presence and extent of reversible MPI defects in predicting cardiac events in the diabetic population in the present study is consistent with most prior observations. However, we also identified the extent of fixed MPI defects as a predictor of cardiac events, especially cardiac death in diabetics. Although several previous studies do not show this relationship, others have, particularly if the study included a high-risk population. For example, in cardiac patients with ischemic events, Miller et al demonstrated similar predictive values of both fixed and reversible MPI defects. Stratmann et al evaluated 285 patients before nonvascular surgery and found a fixed MPI defect was associated with a cardiac event rate of 17%, compared with a rate of 12% with a reversible defect. Moreover, in that study, a fixed MPI defect in high-risk (Goldman class II) patients was associated with a 37% cardiac event rate compared with a rate of 24% in patients with reversible defects. In the largest series to date, Brown et al demonstrated a strong relationship between cardiac survival and the extent of fixed defects in patients with recent MI. Thus, the finding in our study regarding fixed defects is not unique, and it may reflect the higher absolute risk associated with the diabetic population.

Sex-Ischemia Interaction
CAD mortality rates in diabetics, especially women, have not decreased to the same extent as those in the general population. In this large cohort of patients referred for coronary disease in our study, diabetic women had the highest adjusted mortality rates. However, estimate of ischemic burden with stress MPI significantly improved risk stratification in diabetic women compared with clinical risk alone. Stratification by the number of ischemic vessels demonstrated a significant linear increase in cardiac events with escalating ischemic burden (sex-diabetes interaction, \( P = 0.016 \)). Thus, an estimation of the ischemic burden in diabetic women can categorize high- and low-risk female diabetics and may negate the sex effect noted in previous studies.

Significance of Normal Study
Ideal risk stratification must identify patients who do not require further intervention. In a general population, a normal stress MPI possesses this value. Iskander and Iskandrian summarized the results of over 12,000 patients from the world literature with normal stress MPI results using Tc-99m sestamibi. They found an annual cardiac event rate (death/MI) of 0.6% compared with a 7.4% event rate in patients with abnormal studies. A position statement by the American Society of Nuclear Cardiology recommends that, under usual conditions, cardiac catheterization is not warranted in the presence of a normal study.26

Our study extends the observation of a low cardiac event rate associated with normal MPI results to the diabetic population. Survival during the first 2 years of follow-up was identical in the patients with normal MPI results, irrespective of their diabetic status (Figure 4). However, rates increased after 2 years in diabetics but not in nondiabetics. A more rapid progression of coronary disease in diabetics may explain these results. This discovery corroborates the findings of Nesto and colleagues, who recommended more frequent assessments in diabetics because of associated high cardiac event rates. Our data suggest that retesting of diabetic patients with normal studies should occur earlier than in a nondiabetic population.
Limitations
In this study, the diagnosis of diabetes was determined on the basis of patient self-reporting, with verification by a physician. We did not collect data on medication use and, thus, cannot determine whether diabetics taking insulin have a different event rate than those using diet alone or oral medications. However, the difficult logistics behind accurately defining diabetes has been encountered in other recent cardiovascular studies that used methods similar to ours. For example, in the Bypass Angioplasty Revascularization Investigation (BARI) analysis, 27 diabetics were defined as patients taking insulin or oral hypoglycemic drugs at baseline; the 94 diabetics without medication were assigned to the nondiabetic group. In the subgroup analysis of the Cholesterol and Recurrent Events (CARE) trial 5 and the Heart Outcomes Prevention Evaluation (HOPE) study, 6 diabetes was confirmed by history alone.

The recent 1999 revision of World Health Organization criteria for diabetes mellitus 31 lowers the threshold for diagnosis. It includes cases of early diabetes that would have been missed by prior, more stringent criteria. However, our study enrolled patients from 1992 through 1995, a period when the older criteria were still applicable. The impact of a new definition of diabetes in research may be that more former fruste cases of diabetes will now be identified, and comorbidity in such a cohort may be less than in those studies conducted using the older definition.

Patients in the present study represent referrals for symptoms suggestive of CAD but not limited to chest pain alone. Thus, our data may not be applicable to entirely asymptomatic diabetic patients in whom silent myocardial ischemia is still a concern. The follow-up time of 2.5 years is relatively short; MPI might be less predictive over longer periods in diabetics because of their more rapid progression of coronary disease.

Nuclear cardiologists at the individual centers interpreted the results of the perfusion study semiquantitatively, which may be subject to interobserver variability among the centers. The rates of site-specific positive result responses for the recruiting centers were analyzed using the overall \( \kappa \) statistic was 0.54 (95% confidence interval, 0.39 to 0.69), thus demonstrating no significant interobserver variability that would have influenced the clinical outcomes.

Although 2 radiopharmaceuticals were used in this study (Tl 201 and Tc 99m sestamibi), the majority of patients were studied with the latter. Similar prognostic data are available for both; therefore, results were combined. Equivalent information regarding risk stratification with exercise and pharmacological stress are also documented, thus justifying combined analysis.

This study represents the largest cohort of diabetic patients (n=929) undergoing stress MPI thus far. Stress MPI results independently predict future cardiac events in diabetic patients. Incorporating the stress MPI results in the risk stratification process provides more information than clinical risk assessment alone. Using both the clinical information and stress MPI results can improve the prediction of cardiac events in diabetics to the same levels as those achieved in nondiabetic subjects in both sexes.

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Impact of Diabetes on the Risk Stratification Using Stress Single-Photon Emission Computed Tomography Myocardial Perfusion Imaging in Patients With Symptoms Suggestive of Coronary Artery Disease

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