Prevalence and Predictors of Ischemia and Outcomes in Outpatients With Diabetes Mellitus Referred for Single-Photon Emission Computed Tomography Myocardial Perfusion Imaging

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Background—The prevalence of ischemia and its prediction of events are unclear in outpatients with diabetes mellitus in the modern era of intensive medical management. We sought to identify the prevalence of ischemia, subsequent cardiac events, and impact of sex, stress type, and symptom status on these findings in a cohort of stable outpatients with diabetes mellitus referred for single-photon emission computed tomography myocardial perfusion imaging (MPI).

Methods and Results—The study cohort included 575 consecutive outpatients with diabetes mellitus who underwent quantitative, gated single-photon emission computed tomography MPI. Clinical information, stress MPI variables, and cardiac events were prospectively collected and analyzed. The study population was at intermediate risk of coronary artery disease or had known coronary artery disease (40.3%); 29% of patients were asymptomatic at the time of stress testing. Scintigraphic ischemia and significant (≥10%) left ventricular ischemia were present in 126 patients (21.9%) and 29 patients (5.0%), respectively, and <1% of patients had early revascularization. The risk of ischemia was increased >2-fold by male sex (P<0.001), but was not impacted by pharmacological stress (P=0.15) or presence of symptoms (P=0.89). During a median 4.4 years follow-up, the rate of cardiac death/nonfatal myocardial infarction was moderate at 2.6%/y (cardiac death 0.8%/y) in the total cohort, but was 5.7%/y in those with ischemia (P<0.001). Pharmacological stress predicted a higher cardiac event rate (P<0.001) but symptoms did not (P=0.55).

Conclusions—This cohort of stable outpatients with diabetes mellitus referred for single-photon emission computed tomography had low rates of significant ischemia and early revascularization; an initially low cardiac event rate increased after 2 years. Independent predictors of cardiac death/nonfatal myocardial infarction were known coronary artery disease, pharmacological stress, and MPI ischemia. Nearly one third of those with events had a normal MPI, indicating a need for improved risk stratification. (Circ Cardiovasc Imaging. 2013;6:466-477.)

Key Words: coronary artery disease diabetes mellitus myocardial perfusion imaging prognosis

Diabetes mellitus (DM) is a highly prevalent comorbidity that affects >194 million people worldwide and is closely associated with coronary artery disease (CAD).1 CAD is the leading cause of mortality in patients with DM (accounting for 65% to 70% of deaths) and is also associated with high morbidity.2,3 The diagnosis of CAD is complicated by the often atypical presentation of patients with DM attributable to concomitant autonomic neuropathy and other disorders. Moreover, it is important to identify CAD early in these patients to optimize medical therapy and lifestyle modifications. It is especially important to identify and aggressively treat those at the highest risk of events. For these reasons, there is a high rate of referral for myocardial perfusion imaging (MPI) when symptoms develop in this population. Similarly, many asymptomatic patients with DM deemed at high risk for silent ischemia are referred for stress imaging. The prognostic impact of ischemia together with other clinical and stress variables has previously been reported.4-7 However, the prevalence of ischemia and its ability to predict those who experience future cardiac events is less clear in a consecutive group of stable outpatients with DM with or without symptoms referred for MPI in the current era.

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Accordingly, we sought to identify the prevalence and predictors of significant scintigraphic ischemia and subsequent cardiac events, and assess the impact of sex, type of stress, and symptom status on these findings in a cohort of stable outpatients with DM referred for single-photon emission computed tomography (SPECT) MPI.
Methods

This study comprised a retrospective analysis of prospectively collected data from the University of Virginia Nuclear Databank with subsequent prospective collection of outcomes data.

Study Cohort

All outpatients undergoing 99mTc-sestamibi SPECT stress MPI from February 1, 2006, to January 31, 2007, for the detection of myocardial ischemia were identified. Those referred for indications other than detection of ischemia, such as viability assessment or post-acute coronary syndromes, were excluded. As shown in Figure 1, only those patients with DM, complete data, and follow-up of ≥1 year or a known event within the first year were considered for study inclusion. The cohort was stratified by presence of symptoms. Subjects were considered symptomatic if they were experiencing chest pain or shortness of breath thought to be of possible cardiac origin. A total of 575 consecutive outpatients comprised the final study cohort. Five subjects with early revascularization were censored before outcomes analysis, leaving 570 subjects as the follow-up cohort.

Clinical Information Collection and Management

Key data including baseline demographics, comorbidities, medication usage, physical examination findings, and baseline electrocardiographic findings were collected at the time of testing. This information was entered into the University of Virginia Nuclear Databank along with exercise and stress electrocardiographic parameters and imaging results. Collected imaging parameters included myocardial volumes, regional and global function, and perfusion variables. Protocol approval and waiver of informed consent were obtained from the University of Virginia Institutional Review Board.

Stress MPI

Subjects underwent either exercise (n=200; 34.8%) or pharmacological stress (n=375; 65.2%) with either adenosine (n=364; 97.1% of those undergoing pharmacological testing, 63.3% of the entire cohort) or dobutamine (n=11; 2.9% of those undergoing pharmacological testing, 1.9% of the entire cohort). Exercise stress was treadmill based and was performed according to a Bruce or modified Bruce protocol in 99% of cases. Testing was symptom limited unless prematurely terminated for reasons recommended in the most recent guidelines on exercise testing.8 Positive electrocardiographic evidence of ischemia was defined as horizontal or downsloping ST-depression of ≥1 mm measured 80 ms after the J-point for 3 consecutive beats.

All subjects underwent stress gated–SPECT MPI according to a 1- (for body mass index <36) or 2-day protocol (for body mass index ≥36) as described previously.9 One-day imaging was performed with 10 mCi and 30 mCi of 99mTc Sestamibi at rest and stress, respectively. Patients with a body mass index of 36 to 45 received 30 mCi rest and stress doses for 2 days, and those with a body mass index >45 received 45 mCi at rest and with stress.

Supine images were acquired with a dual-head GE Infinia camera with low-energy, high-resolution collimators. Each camera head acquired 180° of data by 60 projections at 30 to 40 seconds per projection using a standard 99mTc energy window. The data from the 2 heads were combined to give 360° of coverage.
Radionuclide Image Processing
All radionuclide images and associated data were processed according to standard protocols using proprietary V-Quant software (Charlottesville, VA). Myocardial perfusion was calculated as the relative percent tracer uptake in each of the 17 segments of a standard model. Uptake deviating by 2 SDs from institution-derived sex-specific normal databases was flagged as abnormal in a reversible or fixed pattern. The transient ischemic dilation (TID) ratio was defined as the ratio of left ventricular (LV) volumes on un-gated images at stress and rest. A TID ratio of ≥2.14 was considered abnormal.

Gated images were used to generate systolic and diastolic volumes, end-systolic and end-diastolic volumes indexed to body surface area, segmental and global LV thickening fractions, and the LV ejection fraction (LVEF). Thickening fractions >2 SDs below the normal database mean were considered abnormal. The LVEF was measured on the poststress-gated images.

Experienced nuclear cardiology specialists used this quantitative data as well as visual image analysis to interpret each MPI study as described previously and briefly summarized here. All borderline or abnormal studies were reclassified by the consensus of 2 additional readers blinded to additional patient information. Readers assigned a score to each segment (0–4 for normal, mild, moderate, severe, and absent uptake, respectively). The semiquantitative summed stress, rest, and difference scores were calculated from these segmental values, with the 5 apical segments receiving 40% weighting (each apical segmental score × 0.4) to correct for the over-representation of the apex partially in the standard 17-segment model.

Finally, the percentage of myocardial ischemia was obtained by dividing the difference between summed stress and summed rest scores by 56, the maximum possible difference. This score, modified from Hachamovitch et al, provides a logical semiquantitative measure, which combines both extent and severity of LV inducible ischemia. LV ischemia of 1% to 9% was considered mild-moderate, >9% to 19% was considered high-severity, and ≥20% LV ischemia was considered significant.

Coronary Angiography
Coronary angiography was performed and interpreted by experienced operators using computer-assisted quantitative angiography (AGFA Heartlabs; Greenville, SC). Stenoses of ≥70% or equivocal stenoses of 50% to 69% with a fractional flow reserve of <0.8 were considered significant. Operators had access to all clinical data and SPECT results during study interpretation.

Follow-up
Data on all-cause and cardiac mortality, nonfatal myocardial infarction (MI), and both early and late revascularization were collected initially through mailed questionnaires. All subjects not responding received ≥3 follow-up telephone contact attempts, with additional calls made to their primary cardiologist and primary care physician. Intensive chart review was subsequently performed and events were confirmed when possible. A documented visit to a cardiologist or an annual visit with a primary care physician was considered sufficient to rule out an intervening event if none was described. Death certificates were obtained when available for deaths outside the healthcare system.

Events were classified by a reviewer blinded to thestress SPECT results to minimize bias. Cardiac death was defined as any death with a cardiac cause or without a clear noncardiac cause. Indeterminate deaths were classified as cardiac. A nonfatal MI was recorded for any troponin elevation ≥2× the upper limit of normal, with or without typical ischemic electrocardiographic changes, in the setting of a history consistent with an acute coronary syndrome. Coronary revascularization procedures included percutaneous coronary interventions and coronary artery bypass grafting. Late revascularization was designated as any coronary revascularization performed later than 12 weeks after the initial MPI study unless documentation linked it to the original MPI results.

Statistical Analyses
The clinical characteristics, medication usage, findings on exercise stress and MPI, and clinical outcomes were given as percentages for categorical variables and as medians with 25th and 75th percentiles for continuous variables. Continuous and categorical variables were compared using Wilcoxon rank-sum test and χ² analysis or Fisher exact testing where appropriate.

Event rates were calculated through person-year analysis. The total events in a subgroup during the entire study period were divided by the sum of the years of follow-up for all patients in that subgroup. This value was adjusted for 1 person-year of follow-up to give an annualized rate. Subjects with an event within the first year were included in the analysis. Subjects with noncardiac death were censored at the time of death. Unadjusted survival analysis was performed using Kaplan–Meier methodology. Survival end points included freedom from cardiac death, cardiac death/nonfatal MI, and cardiac death/nonfatal MI/late revascularization. Survival free of cardiac death/nonfatal MI was also stratified by the %LV ischemia on SPECT imaging, presence or absence of ischemia, and type of stress. Cox proportional hazards modeling was performed to identify the significant predictors of cardiac death or nonfatal MI. Candidate variables with P<0.10 on univariable analysis were entered into a multivariable Cox proportional hazards model using forward stepwise selection with age and sex forced into the model. Previous MI was not included in the multivariable model because a similar variable, known CAD, had a higher χ² on univariable analysis. The incidences of cardiac death and nonfatal MI by degree of ischemia were compared by χ² analysis or Fisher exact testing where appropriate. Incremental χ² analysis was performed by assessing the change in global χ² with the stepwise addition of symptoms and ischemia to a Cox proportional hazards model of the following clinical variables found to be significant univariable predictors of cardiac death/nonfatal MI: age, sex, dyslipidemia, known CAD, history of MI, previous revascularization, and type of stress. All analyses were completed using SAS version 9.2.2. (Cary, NC) and MedCalc version 12.3 (Mariakerke, Belgium).

Results

Study Population
The study population consisted of 575 outpatients with DM referred for SPECT imaging for the evaluation of ischemia. Of these, 409 patients were symptomatic; the majority with chest pain (74.0%). Dyspnea was the sole presenting symptom in the remaining 26.0% of patients, and 42.5% of patients had it as one of their presenting complaints. Angina was classified as typical in 58.4% of those with chest pain. In the symptomatic subgroup, preoperative risk assessment was an additional reason for referral in 34 patients (8.3%), whereas it was a much more frequent reason in asymptomatic subjects (58.2%). The clinical characteristics of this cohort are provided in Table 1 stratified by presence of symptoms of chest pain or shortness of breath. Symptomatic subjects were more often women but had a higher prevalence of CAD risk factors, including hyperlipidemia, obesity, and tobacco use. They were more likely to be on aspirin, statins, and oral hypoglycemic agents. Only 3 symptomatic patients (0.6%) were considered low pretest probability for CAD by the Diamond and Forrester criteria. The remaining symptomatic patients were at intermediate or high probability. The majority of patients had type 2 DM (97.3%), with a mean HgA1c of 7.5. The aggregate rate of microvascular complications was 32.7%, with 6.3% of patients having retinopathy, 13.6% neuropathy, and 22.0% of patients having nephropathy.
**Stress and Perfusion Imaging Findings**

Stress parameters and imaging findings by symptom status are provided in Table 2, separated into exercise versus pharmacological stress. Asymptomatic patients undergoing exercise stress were more likely to achieve a high exercise workload of ≥10 metabolic equivalents (METS; 58.3% versus 23.1%; P=0.007). Despite being able to attain a higher workload, asymptomatic patients were more likely to have a summed stress score >3 (29.7% versus 12.9%; P=0.011). There were no significant differences in summed stress or rest scores by symptom status in subjects undergoing pharmacological stress.

In the total cohort, ischemia was present in 126 individuals (21.9%). The majority of these (97/126; 77.0% of the ischemic subgroup, 16.9% of the overall cohort) had mild-moderate ischemia (<10% of the LV). Significant LV ischemia of ≥10% was present in 29 patients (23.0% of those with ischemia, 5.0% of the entire cohort). Of these 29, 14 patients had ≥15% LV ischemia, of which 10 patients had known angiographic CAD and 9 patients had a history of previous revascularization. Only 6 subjects (4.8% of those with ischemia and 1.5% of the entire cohort) had high levels of LV ischemia defined as ≥20%. Fixed perfusion defects were found in 62 patients (10.8%). No perfusion defects were observed in the remaining 412 patients (71.7% of the entire cohort).

An abnormal resting ECG leading to nondiagnostic stress electrocardiography was present in 80 (13.9%), of whom 16 patients (2.8%) had a left bundle–branch block, 8 (1.4%) had a paced rhythm, and 56 patients (9.7%) had resting ST-depression ≥1 mm. Seventeen patients (3.0%) had ECGs with LV hypertrophy but minimal baseline ST-changes that were still considered diagnostic.

**Nonperfusion Imaging Variables**

In patients without perfusion defects, 90 patients (21.8%) had ≥1 high-risk nonperfusion markers for CAD on their imaging study. These markers included a poststress LVEF <50% in 19 subjects (4.6%) and an end-systolic volume index ≥25 mL/m² in 29 subjects (7.0%). Of the 412 patients, 337 patients had both stress and rest images for the measurement of TID (the remainder had stress-only imaging). Of these, 14 patients (4.2%) had TID by quantitative criteria. The most prevalent nonperfusion finding was the presence of segmental wall-motion abnormalities involving ≥4 segments, which occurred in 71 patients (17.2%). Of note, 12 of these 71 patients (16.9%) had a paced rhythm or left bundle–branch block that may explain the abnormal findings.

**Relationship of Symptoms, Type of Stress, Sex, and Exercise Workload to Ischemia**

The prevalence and degree of scintigraphic ischemia are stratified by symptom status, type of stress, sex, and exercise workload achieved as shown in Figure 2. There were no significant differences in any or significant ischemia (≥10%) based on either presence or absence of symptoms (Figure 2A) or type of stress (Figure 2B). However, male sex was associated with a >2-fold increase in the prevalence of both any and significant LV ischemia (Figure 2C). We have previously shown that high cardiac workload is associated with a low risk of significant LV ischemia. In the subgroup of 200 patients who underwent exercise stress, there were 1.6-fold and 3.8-fold increases in any and ≥10% LV ischemia in those unable to reach 10 METS of exercise workload (Figure 2D). These differences were not statistically significant, likely because of decreased power from the low absolute number of individuals who achieved ≥10 METS on exercising testing.
Follow-up and Outcomes

Early catheterization within 12 weeks as a result of the stress findings occurred in 12 of 575 patients (2.1%), of whom 8 patients had obstructive CAD (66.7%). Of these 8, 5 patients had early revascularization (percutaneous coronary interventions in 4, bypass surgery in 1). Thus, the rate of early revascularization in the entire cohort was 0.9% (5/575). These 5 patients were censored from the subsequent outcomes analysis. However, it should be noted that 2 of the 5 patients (40%) undergoing early revascularization had subsequent nonfatal MIs.

The remaining 570 patients comprised the follow-up cohort; the median follow-up time was 4.4 years (25th and 75th percentiles for 2.5 and 5.1 years, respectively). Median follow-up time was slightly longer for the asymptomatic cohort (4.9 versus 4.3 years). There were 60 total deaths, of which 18 deaths were classified as cardiac (30.0%). The remaining 42 deaths were attributable to cancer (60%) or other noncardiac causes. The incidences of cardiac death, nonfatal MI, and late revascularization during the median 4.4-year follow-up period are provided in Table 3 stratified by the presence or absence of chest pain or shortness of breath. There were 92 total cardiac events. No difference in incidence of events was observed between symptomatic and asymptomatic patients. The annualized rate of cardiac death/nonfatal MI was 10-fold higher in those receiving pharmacological (6.1%/y) versus exercise stress (0.6%/y).

Survival Analysis

The annualized rate of cardiac death or nonfatal MI was 2.6%/y. Total cardiac events (cardiac death, nonfatal MI, and late revascularization) occurred at a rate of 4.2%/y. The majority of these events were nonfatal MIs, with an annual cardiac death rate of only 0.8%. Kaplan–Meier analyses of the cumulative incidences of cardiac death, cardiac death/nonfatal MI, and cardiac death/nonfatal MI/late revascularization are depicted in Figure 3. There is a visually apparent low rate of each of these events through the first 2 years of follow-up, at which time the rate seems to increase. The majority of events (77.2%) occurred ≥2 years after the index MPI study.

Predictors of Hard Cardiac Events

The results of the univariable and multivariable Cox proportional hazards analyses predicting cardiac death or nonfatal MI are given in Table 4. The predictors that remained significant after multivariable adjustment were known CAD, pharmacological stress, and a 5% increase in LV ischemia. When age and sex were not forced into the model, a 5% decrease in LVEF became significant (P=0.036) with a hazard ratio of 1.12 (1.01–1.25). Kaplan–Meier survival curves stratified by presence of symptoms and type of stress are given in Figure 4. Symptoms were not a significant predictor of cardiac death/nonfatal MI on Cox analysis (P=0.55), and the Kaplan–Meier curves are closely aligned (Figure 4A). In contrast, the Kaplan–Meier curves stratified by type of stress show an early divergence (P<0.001; Figure 4B).

### Table 2. Findings on Exercise and Pharmacological Stress and Myocardial Perfusion Imaging Dichotomized by Presence or Absence of Chest Pain or Shortness of Breath

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Exercise Stress (n=200)</th>
<th>Pharmacological Stress (n=375)</th>
<th>P Value</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>163</td>
<td>246</td>
<td></td>
<td></td>
</tr>
<tr>
<td>METS achieved, median (25th, 75th percentiles)</td>
<td>8.0 (6.6–10.0)</td>
<td>8.6 (7.0–10.1)</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>≥10 METS achieved</td>
<td>37 (23.1)</td>
<td>7 (58.3)</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>Peak exercise heart rate</td>
<td>144 (133–157)</td>
<td>140 (132–151)</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td>Maximum systolic BP</td>
<td>199 (180–222)</td>
<td>204 (178–223)</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>Maximum diastolic BP</td>
<td>85 (75–97)</td>
<td>89 (73–100)</td>
<td>0.49</td>
<td></td>
</tr>
<tr>
<td>Chest pain during stress</td>
<td>23 (14.1)</td>
<td>1 (2.7)</td>
<td>0.054</td>
<td></td>
</tr>
<tr>
<td>≥1 mm stress ST-depression</td>
<td>19 (11.7)</td>
<td>7 (18.9)</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>LVEF</td>
<td>63 (59–67)</td>
<td>62 (58–67)</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>LVEF&lt;45%</td>
<td>8 (4.9)</td>
<td>5 (15.3)</td>
<td>0.068</td>
<td></td>
</tr>
<tr>
<td>ESV index ≥25 mL/m*</td>
<td>19 (12.0)</td>
<td>8 (22.9)</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>Summed stress score</td>
<td>0.023</td>
<td></td>
<td>0.51</td>
<td></td>
</tr>
<tr>
<td>0–3</td>
<td>142 (87.1)</td>
<td>26 (70.3)</td>
<td></td>
<td>102 (82.1)</td>
</tr>
<tr>
<td>4–8</td>
<td>9 (5.5)</td>
<td>6 (16.2)</td>
<td></td>
<td>16 (6.5)</td>
</tr>
<tr>
<td>&gt;8</td>
<td>12 (7.4)</td>
<td>5 (13.5)</td>
<td></td>
<td>28 (11.4)</td>
</tr>
<tr>
<td>Summed rest score</td>
<td>0.084</td>
<td></td>
<td>0.51</td>
<td></td>
</tr>
<tr>
<td>0–3</td>
<td>154 (94.5)</td>
<td>33 (89.2)</td>
<td></td>
<td>219 (89.0)</td>
</tr>
<tr>
<td>4–8</td>
<td>7 (4.3)</td>
<td>1 (2.7)</td>
<td></td>
<td>13 (5.3)</td>
</tr>
<tr>
<td>&gt;8</td>
<td>2 (1.2)</td>
<td>3 (8.1)</td>
<td></td>
<td>14 (5.7)</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; ESV, end-systolic volume; LVEF, left ventricular ejection fraction; and METS, metabolic equivalents.

*End-systolic volume index is missing in 3 asymptomatic and 5 symptomatic patients in the exercise cohort and in 1 asymptomatic and 1 symptomatic patient in the pharmacological cohort.
Only 8 of the 57 cardiac deaths and nonfatal MIs (14.0%) occurred in patients undergoing exercise stress. Exercise variables were not included in the Cox model, as only 197 of 570 patients (34.6%) underwent exercise stress, and there were only 8 events in the exercise subgroup versus 49 events in the pharmacological stress patients. Although there is limited power attributable to the low event rate in the exercise subgroup, SPECT ischemia was not a significant predictor of cardiac death/nonfatal MI in univariable Cox proportional hazards analysis. The annual cardiac death or MI rate was 1.4% for those with exercise-induced ischemia versus 0.9% for those without ischemia \((P = 0.63)\). Moreover, only 1 nonfatal MI and no cardiac deaths occurred in patients achieving \(\geq 10\) METS of exercise workload. If late revascularization is included in a combined end point with cardiac death and nonfatal MI, then ischemia becomes a significant predictor of this end point (hazard ratio 5.2 [1.1–26.0; \(P = 0.043\)).

**Relationship Between Events and Ischemia**

Incremental \(\chi^2\) analysis showed that the presence or absence of symptoms did not provide incremental prognostic value \((P = 0.24)\), whereas the presence of ischemia on the index SPECT MPI study did have incremental value \((P = 0.007)\). Kaplan–Meier survival analysis of cardiac death/nonfatal MI stratified by degree of ischemia shows increased events for patients with both mild \((1\% \text{ to } 9\%)\) of the LV) ischemia and significant \((\geq 10\%)\) LV ischemia on the initial MPI study \((P < 0.001)\; \text{Figure 5)}\). Compared with no ischemia on the index MPI, the annualized rate of cardiac death/nonfatal MI was significantly higher for 1% to 9% LV ischemia \((6.0\% \text{ versus } 1.8\%; P < 0.001)\) and trended higher for \(\geq 10\%\) LV ischemia \((4.5\% \text{ versus } 1.8\%; P = 0.05)\), but did not differ significantly between the 2 ischemia subgroups \((P = 0.57)\). The annualized rate for patients with any ischemia was 5.7%/y \((P < 0.001 \text{ versus no ischemia)}\).

Despite the higher event rates in those with ischemia, 56.1% of the cardiac death/nonfatal MIs \((32/57)\) occurred in the 446 patients without any ischemia. Some had nonischemic scan abnormalities as discussed below. Only 2 of the 18 \((11.1\%)\) patients had a subsequent cardiac death with significant \((\geq 10\%)\) LV ischemia present on their index MPI. Some deaths...
in these patients may be attributed to acute plaque ruptures in the absence of high-grade stenoses.

**High-Risk Findings Other Than Reversible Perfusion Defects**

Of the 32 patients without ischemia who experienced a cardiac death or nonfatal MI, 3 patients had fixed perfusion defects. In the remaining 29 patients with normal perfusion and a subsequent hard cardiac event, a moderate number (12 patients, 41.3%) had a high-risk nonperfusion finding on their index MPI study. One patient (3.4%) had ischemic ST-depression on his stress ECG. An LVEF<50% was measured in 3 of these 29 subjects (10.3%). Segmental wall-motion abnormalities were more common but still infrequent, with 7 patients (24.1%) having ≥4 segments with abnormal wall motion. An end-systolic volume index ≥25 mL/m² was present in 4 patients (13.8%). Finally, 2 (6.9%) subjects had a TID ratio ≥1.24. Thus, of all 57 patients who experienced cardiac death/nonfatal MI in the follow-up cohort, 17 patients (29.8%) had completely normal stress MPI scans without perfusion defects or other high-risk nonperfusion findings.

**Discussion**

The prognosis of patients with DM and acute coronary syndromes or known ischemia has been documented in multiple previous studies, most notably the BARI-2D study.4,17–19 The prevalence of ischemia and outcomes has also been studied extensively in symptomatic and asymptomatic patients with DM.20–26 In this study of consecutive ambulatory patients with DM referred for stress SPECT MPI, we report a low overall cardiac death/nonfatal MI rate of 2.6% annually. Only 5% of this cohort with DM had ≥10% LV ischemia. As expected, the event rate of patients with ischemia was significantly greater than that seen in patients with normal scans. The event rate was lower than that observed in patients with DM with normal or abnormal scans as reported in a pooled analysis of studies published before 2004, many of which were performed in the 1990s.7 One presumed explanation for this lower event rate is that more patients with DM without known CAD are now placed on medications, such as statins, ACE-inhibitors, and β-blockers, than in previous years. Another potential explanation for the difference in our event rates versus those reported in the pooled analysis7 is that our cohort solely comprised outpatients, and the event rates analyzed were for ischemia versus nonischemia rather than normal versus abnormal scans. Furthermore, our study showed no difference in prevalence of ischemia or event incidence in symptomatic versus asymptomatic patients. Patients who underwent pharmacological stress had a higher event rate than those undergoing exercise stress.

**Population Makeup**

This study population was evenly split between the sexes with an intermediate age range and high levels of cardiovascular risk factors, as seen in both Detection of Ischemia in Asymptomatic Diabetics (DIAD) and BARI-2D.17,21,27 Approximately 30% were asymptomatic at the time of testing. A moderate number had known CAD and previous revascularization. Because 23% had previous MI, 40% had known CAD, and nearly one third had previous revascularization, the study cohort can be considered at intermediate pretest risk. Only 3 patients (0.6%) were deemed low risk by the Diamond and Forrester criteria, indicating that this cohort either had known CAD or was at intermediate-to-high risk for CAD. Of those who were symptomatic, 42.5% had dyspnea, a high-risk marker in patients with DM.28 The majority of subjects were taking appropriate medications, such as statin in 61% and ACE-inhibitor or angiotensin-receptor blocker in 68%.
Table 4. Univariable and Multivariable Cox Proportional Hazards Analyses Predicting Cardiac Death or Nonfatal Myocardial Infarction

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Univariable</th>
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<th>Multivariable</th>
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<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>X²</td>
<td>Hazard Ratio (95% CI)</td>
<td>P Value</td>
<td>X²</td>
<td>Hazard Ratio (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Age (increase by 10)</td>
<td>9.6</td>
<td>1.31 (1.10–1.56)</td>
<td>0.002</td>
<td>1.2</td>
<td>1.14 (0.91–1.43)</td>
<td>0.27</td>
</tr>
<tr>
<td>Male sex</td>
<td>5.5</td>
<td>1.93 (1.12–3.36)</td>
<td>0.008</td>
<td>1.9</td>
<td>1.51 (0.85–2.69)</td>
<td>0.16</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.0</td>
<td>1.05 (0.59–1.86)</td>
<td>0.86</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>6.1</td>
<td>2.05 (1.16–3.63)</td>
<td>0.013</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tobacco use</td>
<td>0.1</td>
<td>0.72 (0.69–1.71)</td>
<td>0.72</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic symptoms</td>
<td>0.3</td>
<td>1.14 (0.72–1.81)</td>
<td>0.58</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index ≥30</td>
<td>1.8</td>
<td>0.70 (0.41–1.18)</td>
<td>0.18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Known CAD</td>
<td>33.4</td>
<td>3.75 (2.40–5.88)</td>
<td>&lt;0.001</td>
<td>10.6</td>
<td>2.76 (1.50–5.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous MI*</td>
<td>13.5</td>
<td>2.20 (1.44–3.34)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous revascularization</td>
<td>19.9</td>
<td>2.56 (1.69–3.87)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacological stress</td>
<td>9.7</td>
<td>3.65 (1.62–8.24)</td>
<td>0.002</td>
<td>11.7</td>
<td>3.76 (1.76–8.03)</td>
<td>0.001</td>
</tr>
<tr>
<td>ST-depression ≥1 mm</td>
<td>0.2</td>
<td>1.17 (0.54–2.52)</td>
<td>0.70</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF, 5% decrements†</td>
<td>18.1</td>
<td>1.19 (1.10–1.29)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV ischemia, 5% increments†</td>
<td>15.1</td>
<td>1.46 (1.21–1.77)</td>
<td>&lt;0.001</td>
<td>6.5</td>
<td>1.32 (1.07–1.62)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease; CI, confidence interval; EF, ejection fraction; LV, left ventricular; and MI, myocardial infarction.

*Previous MI was considered to provide redundant information to known CAD and was not included in the multivariable model.

†LVEF and LV ischemia are coded in 5% increments, so that the hazard ratio represents the increased risk of events with a 5% decrease in LVEF and a 5% increase in LV ischemia, respectively.

Prevalence of Ischemia

The prevalence of ischemia in this cohort of stable symptomatic outpatients with DM referred for SPECT MPI was somewhat lower than expected, with only 5% having significant LV ischemia of ≥10%. Seventy-eight percentage of the entire group had no evidence of ischemia by MPI. This finding suggests a reduction in inducible ischemia in stable patients with DM compared with those in previously published studies. The total prevalence of ischemia of 21.9% in our cohort of symptomatic and asymptomatic patients with DM is similar to the 22% prevalence of ischemia in the DIAD study of asymptomatic patients with DM, the 21% prevalence of ischemia in asymptomatic patients with DM studied by De Lorenzo et al., and the 17% prevalence of ischemia in asymptomatic patients with DM in the J-ACCESS 2 study. The rate of ischemia is also lower than the 47% rate seen in an analysis of patients with DM with stable symptoms recruited in the discontinued MERIDIAN trial (performed in 2002–2004) and the 59.5% prevalence of an abnormal SPECT study in symptomatic patients with DM from the Mayo Clinic cohort.

As suggested previously, it is possible that the contemporary increased aggressive use of medications that suppress ischemia or lower low-density lipoprotein cholesterol or blood pressure may be attenuating the degree of ischemia, both macrovascular and microvascular. Similarly, many patients with DM currently take aspirin although they have not experienced a previous cardiac event. Accordingly, a contemporary assessment of silent ischemia may even show a lower prevalence of ischemia in asymptomatic patients with DM than perceived in the past. In accordance with the low ischemia rate, the rates of catheterization as a result of the index MPI study (2.1%) and early revascularization (0.9%) were extremely low. Another explanation for the low early revascularization rate is that 10 of the 14 patients with ≥15% LV ischemia had known CAD and 9 had a previous history of revascularization. The imaging studies in this subgroup were ordered to assess any significant changes in perfusion, presumably to guide therapy.

Symptom State and Mode of Stress

The prevalence of any ischemia and significant ischemia (≥10% of the LV) was similar in symptomatic and asymptomatic patients. We found no difference in the incidence of cardiac death, nonfatal MI, or late revascularization between symptomatic and asymptomatic patients; and symptom state was not a significant variable predicting cardiac death or nonfatal MI by univariable or multivariable Cox Proportional Hazards analysis. Event-free survival (Figure 4) was comparable in symptomatic and asymptomatic patients with DM. These findings are different from those of Zellweger et al who reported a higher event rate for symptomatic patients with DM with abnormal scans. In that study, patients with dyspnea and abnormal MPI studies had a higher event rate than asymptomatic patients or patients presenting with angina. It should be emphasized that the asymptomatic patients in our study were judged to be so at the time of testing. They may have had symptoms in the past. The asymptomatic subgroup with DM in our study was at significantly higher clinical baseline risk before testing than asymptomatic patients in the DIAD study.

This is evidenced by a 43% prevalence of known CAD, a 23% prevalence of previous MI, and a 33% prevalence of previous revascularization. More than 50% were referred for preoperative risk assessment, further suggesting a high baseline risk...
as compared with the DIAD cohort of asymptomatic patients. Thus, it is not surprising that the event rates and prevalence of high-risk scans were similar between asymptomatic and symptomatic patients in our study.

We found a higher rate of cardiac death/nonfatal MI in patients who had pharmacological stress versus exercise stress, as previously reported in related populations undergoing stress imaging. The higher risk is not surprising because pharmacological stress is often performed in patients with comorbidities, such as older age, physical deconditioning, and other causes of weakness or gait instability, which may be unapparent but increase the risk of cardiac events. In addition, patients initially referred for exercise testing with imaging are not injected with tracer if they fail to achieve ≥85% of their maximum age-predicted heart rate. Such patients are switched to pharmacological stress imaging if no ischemic symptoms or ST-depression is noted. This is 1 explanation for the larger number of patients undergoing pharmacological versus exercise imaging (375 versus 200). In the setting of the low event rate in the exercise subgroup and questionable predictive

Figure 4. Kaplan–Meier analysis of survival free from cardiac death/nonfatal myocardial infarction (MI) during 5 years of follow-up stratified by the presence of symptoms (A) and the type of stress (B).

Figure 5. Kaplan–Meier analysis of survival free from cardiac death/nonfatal myocardial infarction (MI) during 5 years of follow-up stratified by the degree of left ventricular (LV) ischemia.
ability of SPECT ischemia, the usability of SPECT imaging in stable patients with DM able to exercise to target heart rates may be limited. Further research in a larger number of patients with DM will be necessary to identify which subset of patients able to undergo exercise stress will benefit from the addition of MPI imaging to exercise electrocardiography (eg, older age, known previous MI, poor exercise workload, eGFR<60, and long duration of DM). In a recent study, 20% of patients with known or suspected CAD and normal exercise ECG testing had reversible perfusion defects on SPECT MPI.31

Outcomes and Impact of Ischemia
The low prevalence of ischemia in this population corresponded with a low incidence of cardiac death, nonfatal MI, and late revascularization during a long-term follow-up (median 4.4 years). The rate of cardiac death was very low at 0.8% per year. A composite of all cardiac events had a similarly low incidence of 4.2% per year. The 2.6% yearly incidence of cardiac death or nonfatal MI in the total cohort was intermediate between that of the DIAD study (0.6%/y) and both BARI-2D (4.7%/y, including stroke) and a prospective cohort of symptomatic patients with DM undergoing stress MPI assembled by Giri et al5 (5.7%/y).17,22 Given that patients were asymptomatic in DIAD and had ischemia by design in BARI-2D, this is not unexpected. The symptomatic cohort reported by Giri et al5 predated the more widespread practice of statin therapy to lower low-density lipoprotein cholesterol to below 100 mg/dL for primary prevention of CAD in patients with DM. The annual rate of cardiac death/nonfatal MI in this study in those with ischemia was 5.7%, which is 1.5- to 2-fold lower than that reported in a pooled analysis of studies in the literature by Shaw and Iskandrian,7 which included an analysis of individuals with DM undergoing SPECT MPI. The potential explanations for the difference in event rates were previously discussed. The >2-fold increase in events in those with ischemia in our cohort (Figure 4) is comparable with that observed in previous studies.5,28,34

The multivariable predictors of cardiac death/nonfatal MI in this cohort (Table 4) were not unexpected. Multiple previous studies have shown ischemia to be a significant predictor of cardiac events, and it remained so in this cohort of outpatients with DM.29,35 Patients with known CAD are much more likely to have progressive disease and, thus, subsequent events. Not unexpectedly, referral for pharmacological stress was an independent predictor of cardiac death or nonfatal MI. Duration of DM and type of therapy (insulin versus oral agents) have been reported to provide independent and incremental prognostic information to perfusion and functional variables.36 These variables were not investigated in the present study.

Impact of Exercise Capacity
High exercise workload (≥10 METS) was associated with a low risk of significant ischemia and cardiac events in this cohort with DM. No patient achieving this high workload had ≥10% LV ischemia, and there was only 1 hard cardiac event. These findings are consistent with multiple previous studies showing the powerful positive impact of exercise capacity on prognosis.9,37–39

Other High-Risk Findings
It is possible that some patients without evidence of regional ischemia on their nuclear MPI study are falsely negative, with unappreciated balanced ischemia or microvascular disease. We therefore closely examined variables other than perfusion defects that might identify underlying ischemia.60,61 The prevalence of these other high-risk findings was also relatively low. Only 21.8% had evidence of a reduced LVEF (<50%), an elevated end-systolic volume index (≥25 mL/m²), TID, or ≥4 segments with abnormal thickening fractions. Moreover, only 6.7% had ischemic ST-depression on their stress ECG.

Study Limitations
The data in this study emanate from a single center and may apply only to this specific referral cohort. It may be that some of the higher risk patients were directly referred for cardiac catheterization rather than first undergoing noninvasive imaging. A larger median follow-up may have yielded a higher cardiac event rate with more patients crossing over to revascularization strategies. The use of chart review to identify follow-up in some patients prevented precise adjudication of events. However, documentation was available in the majority of subjects.

Conclusions
The prevalence of significant (≥10%) LV ischemia was only 5% in this cohort of stable, predominately asymptomatic outpatients with DM. The increased use of aggressive risk-factor modification by primary care physicians and cardiovascular specialists and use of evidence-based medicines may be partly responsible for the lower event rates in patients with and without ischemia in the present study. Reaching a high cardiac workload of ≥10 METS predicts a very low risk of significant ischemia on SPECT imaging in this population of patients with DM, similar to what was observed in a mixed population of patients referred for exercise testing.5

The event-free survival was similar in patients with mild-to-moderate ischemia and those who exhibited ≥10% LV ischemia. Thus, any inducible ischemia on stress SPECT should be of concern. The rate of cardiac death/nonfatal MI in patients with no ischemia was 1.8% yearly, which is higher than that seen in patients without DM without ischemia. Interestingly, the prevalence of ischemia and the cardiac event rates were similar in asymptomatic and symptomatic patients with DM, although the asymptomatic patients in this study were at intermediate pretest risk.

Finally, compared with those who underwent exercise stress, patients who underwent pharmacological stress had a worse event-free survival. An increased risk of hard events in those with ischemia undergoing exercise stress could not be demonstrated. Further studies in a large population of patients with DM referred for stress imaging might indicate which patients would benefit from SPECT imaging (eg, markedly abnormal Duke Treadmill Score). Because 30% of the patients without SPECT abnormalities had events during follow-up, other noninvasive technologies, such as quantitative PET and cardiac magnetic resonance MPI, should be explored for identifying a larger number of patients with DM at risk for an adverse outcome.
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Disclosures

None.

References

Patients with diabetes mellitus, especially those who are symptomatic, are thought to have high rates of myocardial ischemia and cardiac events. Accordingly, there is a high rate of referral for single-photon emission computed tomography myocardial perfusion imaging for risk stratification in stable outpatients with diabetes mellitus. However, the prevalence of ischemia and events is not well known in this population, especially in the setting of contemporary advances in medical therapy for coronary artery disease and its sequelae. We have identified a low rate of significant (≥10%) left ventricular ischemia in a large consecutive cohort of outpatients with DM referred for single-photon emission computed tomography myocardial perfusion imaging. Although the presence of known coronary artery disease, ischemia, and a pharmacological mode of stress predicted higher event rates, symptoms did not. These findings suggest that stable outpatients with DM referred for single-photon emission computed tomography myocardial perfusion imaging in the current era seem to be at a lower risk than reported previously. Interestingly, event-free survival was similar for patients with DM and mild-moderate versus significant ischemia. The high prevalence of events in patients with high-risk myocardial perfusion imaging findings further supports the need for enhanced risk stratification and aggressive prevention strategies in this population.
Prevalence and Predictors of Ischemia and Outcomes in Outpatients With Diabetes Mellitus Referred for Single-Photon Emission Computed Tomography Myocardial Perfusion Imaging

Jamieson M. Bourque, Chetan A. Patel, Mohamed M. Ali, Margarita Perez, Denny D. Watson and George A. Beller

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