Association Between Coronary Vascular Dysfunction and Cardiac Mortality in Patients With and Without Diabetes Mellitus

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Background—Diabetes mellitus increases the risk of adverse cardiac outcomes and is considered a coronary artery disease (CAD) equivalent. We examined whether coronary vascular dysfunction, an early manifestation of CAD, accounts for increased risk among diabetics compared with nondiabetics.

Methods and Results—A total of 2783 consecutive patients (1172 diabetics and 1611 nondiabetics) underwent quantification of coronary flow reserve (CFR; CFR = stress divided by rest myocardial blood flow) by positron emission tomography and were followed up for a median of 1.4 years (quartile 1–3, 0.7–3.2 years). The primary end point was cardiac death. Impaired CFR (below the median) was associated with an adjusted 3.2- and 4.9-fold increase in the rate of cardiac death for diabetics and nondiabetics, respectively ($P=0.0004$). Addition of CFR to clinical and imaging risk models improved risk discrimination for both diabetics and nondiabetics ($c$ index, 0.77–0.79, $P=0.04$; 0.82–0.85, $P=0.03$, respectively). Diabetic patients without known CAD with impaired CFR experienced a rate of cardiac death comparable to that for nondiabetic patients with known CAD (2.8%/y versus 2.0%/y; $P=0.33$). Conversely, diabetics without known CAD and preserved CFR had very low annualized cardiac mortality, which was similar to patients without known CAD or diabetes mellitus and normal stress perfusion and systolic function (0.3%/y versus 0.5%/y; $P=0.65$).

Conclusions—Coronary vasodilator dysfunction is a powerful, independent correlate of cardiac mortality among both diabetics and nondiabetics and provides meaningful incremental risk stratification. Among diabetic patients without CAD, those with impaired CFR have event rates comparable to those of patients with prior CAD, whereas those with preserved CFR have event rates comparable to those of nondiabetics. (Circulation. 2012;126:1858-1868.)

Key Words: cardiac imaging techniques ▪ coronary disease ▪ diabetes mellitus ▪ myocardial perfusion imaging ▪ vasodilation

Despite advances in medical therapy, cardiovascular disease remains the leading cause of mortality among patients with diabetes mellitus. Indeed, diabetes mellitus has been classified as a coronary heart disease equivalent. For any degree of myocardial ischemia on noninvasive testing, diabetics are at considerably higher risk of cardiac mortality than those without diabetes mellitus. This may be due in part to a higher prevalence of high-risk coronary anatomy among diabetics. However, the absence of myocardial ischemia on noninvasive testing in patients with diabetes mellitus does not necessarily identify a lower-risk cohort. This may be related, at least in part, to the observation that diffuse coronary vascular dysfunction in diabetics precedes overt atherosclerosis. Abnormalities of vascular dysfunction may help identify additional high-risk populations for therapy who are missed by current risk stratification methods. Indeed, there is growing, consistent evidence that impaired coronary vascular function is associated with adverse prognosis. However, the link between coronary vascular dysfunction and adverse outcomes has been established in predominantly nondiabetic populations. Whether the strength of these associations is maintained in the setting of diabetes mellitus is unknown.

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This study was designed to test the hypothesis that the presence of impaired coronary vasodilator function helps...
explain the observed excess risk of cardiac mortality among patients with diabetes mellitus and to compare the strength of this association with nondiabetics.

Methods

Study Population
All patients referred for rest/stress cardiac positron emission tomography (PET) at the Brigham and Women’s Hospital (Boston, MA) between January 1, 2006, and June 30, 2010, were included in this study; those whose images were missing or were uninterpretable owing to poor image quality were excluded (n=254). In cases of repeat PET scans during the study period, only the earliest evaluable study was included. Patients with diabetes mellitus were identified by interview, medical records, and laboratory results (hemoglobin A1c ≥6.5% or fasting plasma glucose ≥126 mg/dL). A combined analysis of all of the diabetic and nondiabetic patients in this study was previously published.11 The study was approved by the Partners Healthcare Institutional Review Board and conducted in accordance with institutional guidelines.

Risk Factor Assessment
Demographic factors and key elements of the patients’ histories, including risk factors and medication use, were ascertained at the time of the study by patient interview and review of medical records. Diabetic nephropathy was identified from medical records and laboratory results (urine total protein ≥500 mg/dL, spot urine albumin/creatinine ratio ≥30 μg/mg, or 24-hour urine albumin ≥30 mg). Microalbuminuria was identified on the basis of spot urine albumin/creatinine ratio ≥30 μg/mg or 24-hour urine albumin ≥30 mg. Diabetic neuropathy and retinopathy were identified from medical records.

PET Imaging
Patients were studied with a whole-body PET/computed tomography scanner (Discovery RX or STE LightSpeed 64, GE Healthcare, Milwaukee, WI) after an overnight fast. Patients refrained from caffeine- and methylxanthine-containing substances and drugs for 24 hours before their scans. Myocardial blood flow (MBF) was measured during rest and peak stress with rubidium-82 as a perfusion tracer as described previously.12 Briefly, after transmission imaging and beginning with the intravenous bolus administration of rubidium-82 (1480–2200 MBq), list-mode images were acquired for 7 minutes. Then, a standard intravenous infusion of dipyridamole, adenosine, regadenoson, or dobutamine was given. At peak stress, a 7-minute data set was acquired. Quantitative MBF was performed post hoc by 4 operators, and the intraclass correlation coefficient for MBF among these 4 lines was 0.94 (95% confidence interval [CI], 0.88–0.98), indicating excellent reproducibility.

Assessment of Outcomes
The primary outcome was death resulting from any cardiac cause. Patients who died of noncardiac causes were censored. Vital status of all patients was ascertained by integrating data from the Social Security Death Index, the National Death Index, and the Partners Healthcare Research Patient Data Registry. Cause of death was determined by blinded adjudication of hospital records and death certificates. Early revascularization (within 90 days) was ascertained from the Partners Healthcare Research Patient Data Registry and hospital records. Mortality resulting from any cause was used as a secondary end point.

Statistical Analysis
Statistical significance was assessed with Wilcoxon tests, Fisher exact, and χ² tests for continuous, dichotomous, and categorical variables, respectively. Two-sided values of P<0.05 were considered significant. All statistical analyses were performed with SAS 9.3 (SAS Institute Inc, Cary, NC).

Multivariable Modeling
The Cox proportional hazards model12 was used to assess the impact of CFR on cardiac mortality after controlling for the effects of critical covariates. A series of models were developed starting with the Duke Clinical Score, an index of coronary artery disease (CAD) likelihood and prognosis based on clinical covariates.20 Rest LVEF, combined extent and severity of scar and ischemia, stress-induced LVEF augmentation (LVEF reserve), and CFR (dichotomized separately at the median values for diabetics, 1.6, and nondiabetics, 1.9) were then sequentially incorporated into the model. To investigate the effects of absolute peak stress MBF, we generated additional models containing absolute stress MBF instead of CFR. The models were examined for the validity of the proportional hazards assumption (using time-dependent covariates, standardized score process plots, and the Kolmogorov-type supremum test) and for additive value, taking care to avoid overfitting. Survival was plotted using direct adjusted survival probabilities21 from the Cox survival model. To assess for biases introduced by early revascularization, analyses were repeated, censoring all patients who underwent early revascularization.22 In an exploratory analysis, we considered the effect of any revascularization, including those >90 days after the PET scan, as a time-dependent covariate.

Assessment of Incremental Value
Incremental prognostic value of CFR was assessed with the likelihood ratio test to determine the improvement in prediction power of each sequential Cox model. The Harrell c index23 and D’Agostino-Nam12 calibration statistic were calculated for each model. The potential impact of CFR on risk stratification was assessed by net reclassification improvement23 at 2 years with the use of threshold annual rates of cardiac mortality of 1% and 3%, derived from the American College of Cardiology/American Heart Association guidelines for the management of chronic stable angina.26

Quantitative MBF and Flow Reserve
Absolute MBF (in mL·g⁻¹·min⁻¹) was computed from the dynamic rest and stress imaging series with commercially available software (Corridor4DM; INVIA Medical Imaging Solution, Ann Arbor, MI) and previously validated methods.12,17 Automated factor analysis was used to generate blood pool (arterial input function) and tissue time–activity curves.18 Regional and global rest and peak stress MBFs were calculated by fitting the rubidium-82 time-activity curves to a 2-compartment tracer kinetic model as described previously.19 Per-patient coronary flow reserve (CFR) was calculated as the ratio of absolute MBF at stress over rest for the entire LV. Quantification of MBF was performed post hoc by 4 operators in randomly allocated blocks of 50 patients. Before flow quantification, the intraclass correlation coefficient for CFR among these 4 readers on a training set was 0.94 (95% confidence interval [CI], 0.88–0.98), indicating excellent reproducibility.

Image Analysis
Semi-quantitative Analysis of Myocardial Perfusion
Semi-quantitative 17-segment visual interpretation of the gated myocardial perfusion images was performed by experienced observers using a standard 5-point scoring system.13,14 Summed rest and stress scores were calculated as the sum of individual segmental scores on the respective images, and their difference was recorded as summed difference score. These were converted to percentages of left ventricular (LV) myocardium by dividing by the maximum score, ie, 68. For each of these variables, higher scores reflect larger areas of myocardial ischemia and/or scar.

LV Systolic Function
Rest and stress LV ejection fractions (LVEFs) were calculated from gated myocardial perfusion images with commercially available software. LVEF reserve was considered present when LVEF increased from rest to stress.
Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nondiabetics (n=1611)</th>
<th>Diabetics (n=1172)</th>
<th>All Patients (n=2783)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>64.3 (55.3–76)</td>
<td>65.4 (57.3–74.1)</td>
<td>64.8 (56.1–75.2)</td>
<td>0.63</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>747 (46.4)</td>
<td>586 (50)</td>
<td>1333 (47.9)</td>
<td>0.06</td>
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<td>Hispanic, n (%)</td>
<td>134 (8.3)</td>
<td>169 (14.4)</td>
<td>303 (10.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>White</td>
<td>1134 (70.4)</td>
<td>628 (53.6)</td>
<td>1762 (63.3)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>208 (12.9)</td>
<td>245 (20.9)</td>
<td>453 (16.3)</td>
<td></td>
</tr>
<tr>
<td>Other/unknown</td>
<td>269 (16.7)</td>
<td>299 (25.5)</td>
<td>568 (20.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Risk factors</strong></td>
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<td></td>
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<tr>
<td>BMI, kg/m²</td>
<td>27.5 (24.4–32.3)</td>
<td>30.9 (26.5–37.6)</td>
<td>28.8 (25.1–34.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI ≥30 kg/m², n (%)</td>
<td>548 (34)</td>
<td>656 (56)</td>
<td>1204 (43.3)</td>
<td>&lt;0.0001</td>
</tr>
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<td>Hypertension, n (%)</td>
<td>1207 (74.9)</td>
<td>1064 (90.8)</td>
<td>2271 (81.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>966 (60)</td>
<td>887 (75.7)</td>
<td>1853 (66.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Family history of CAD, n (%)</td>
<td>471 (29.2)</td>
<td>285 (24.3)</td>
<td>756 (27.2)</td>
<td>0.004</td>
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<tr>
<td>Tobacco use, n (%)</td>
<td>175 (10.9)</td>
<td>119 (10.2)</td>
<td>294 (10.6)</td>
<td>0.57</td>
</tr>
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<td>Duke clinical risk, %</td>
<td>37.8 (14–74.4)</td>
<td>61.7 (28–86.7)</td>
<td>47.9 (18.7–81.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Diabetes complications, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Retinopathy</td>
<td>0 (0)</td>
<td>85 (7.3)</td>
<td>85 (3.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>0 (0)</td>
<td>178 (15.2)</td>
<td>178 (6.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>53 (3.3)</td>
<td>206 (17.6)</td>
<td>259 (9.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>0 (0)</td>
<td>157 (13.4)</td>
<td>157 (5.6)</td>
<td>&lt;0.0001</td>
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<tr>
<td><strong>Diabetes control</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA₁c unknown, n (%)</td>
<td>1356 (84.2)</td>
<td>577 (49.2)</td>
<td>1933 (69.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HbA₁c, %</td>
<td>5.8 (5.6–6.1)</td>
<td>7.1 (6.4–8.4)</td>
<td>6.5 (5.9–7.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Medications, n (%)</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>911 (58.5)</td>
<td>794 (67.7)</td>
<td>1705 (61.3)</td>
<td>&lt;0.0001</td>
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<tr>
<td>β-adrenergic blockers</td>
<td>940 (58.3)</td>
<td>822 (70.1)</td>
<td>1762 (63.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cholesterol agents</td>
<td>880 (54.6)</td>
<td>843 (71.9)</td>
<td>1723 (61.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Insulin</td>
<td>0 (0)</td>
<td>443 (37.8)</td>
<td>443 (15.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Oral hypoglycemic agents</td>
<td>3 (0.2)</td>
<td>281 (24)</td>
<td>284 (10.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>303 (18.8)</td>
<td>318 (27.1)</td>
<td>621 (22.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>514 (31.9)</td>
<td>590 (50.3)</td>
<td>1104 (39.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nitrates</td>
<td>160 (9.9)</td>
<td>196 (16.7)</td>
<td>356 (12.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diuretics</td>
<td>476 (29.5)</td>
<td>549 (46.8)</td>
<td>1025 (36.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Indications, n (%)</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Chest pain</td>
<td>753 (46.7)</td>
<td>553 (47.2)</td>
<td>1306 (46.9)</td>
<td>0.82</td>
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<tr>
<td>Dyspnea</td>
<td>457 (28.4)</td>
<td>395 (33.7)</td>
<td>852 (30.6)</td>
<td>0.003</td>
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<tr>
<td>Post-MI</td>
<td>136 (8.4)</td>
<td>115 (9.8)</td>
<td>251 (9)</td>
<td>0.23</td>
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<tr>
<td>Preoperative</td>
<td>251 (15.6)</td>
<td>157 (13.4)</td>
<td>408 (14.7)</td>
<td>0.12</td>
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<tr>
<td><strong>Cardiovascular history, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Any prior CAD</td>
<td>569 (35.3)</td>
<td>606 (51.7)</td>
<td>1175 (42.2)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Recent MI (≤30 d)</td>
<td>156 (9.7)</td>
<td>160 (13.7)</td>
<td>316 (11.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Remote MI (&gt;30 d)</td>
<td>248 (15.4)</td>
<td>263 (22.4)</td>
<td>511 (18.4)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Prior PCI</td>
<td>286 (17.8)</td>
<td>326 (27.8)</td>
<td>612 (22)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>160 (9.9)</td>
<td>209 (17.8)</td>
<td>369 (13.3)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Cerebrovascular disease</td>
<td>82 (5.1)</td>
<td>88 (7.5)</td>
<td>170 (6.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>83 (5.2)</td>
<td>98 (8.4)</td>
<td>181 (6.5)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Early revascularization (≤90 d post-PET)</td>
<td>120 (7.4)</td>
<td>115 (9.8)</td>
<td>235 (8.4)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

(Continued)
Table 1. Continued

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nondiabetics (n=1611)</th>
<th>Diabetics (n=1172)</th>
<th>All Patients (n=2783)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imaging parameters</td>
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<tr>
<td>Rest LVEF, n (%)</td>
<td>60 (50–67)</td>
<td>56 (45–64)</td>
<td>58 (48–66)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Stress-induced LVEF, n (%)</td>
<td>1283 (79.6)</td>
<td>864 (73.7)</td>
<td>2147 (77.1)</td>
<td>0.0003</td>
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<td>Ischemia+scar, %</td>
<td>0 (0–6.8)</td>
<td>2.9 (0–14.7)</td>
<td>0 (0–10.3)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Ischemia, %</td>
<td>0 (0–2.9)</td>
<td>0 (0–7.4)</td>
<td>0 (0–5.9)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Scar, %</td>
<td>0 (0–1.5)</td>
<td>0 (0–4.4)</td>
<td>0 (0–2.9)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Global CFR, n (%)</td>
<td>1.87 (1.43–2.35)</td>
<td>1.58 (1.24–2)</td>
<td>1.73 (1.34–2.22)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Global MBF, mL·g⁻¹·min⁻¹</td>
<td>1.97 (1.37–2.73)</td>
<td>1.6 (1.12–2.19)</td>
<td>1.8 (1.23–2.52)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Impaired CFR, n (%)</td>
<td>852 (52.9)</td>
<td>600 (51.2)</td>
<td>1452 (52.2)</td>
<td>0.4</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; CAD, coronary artery disease; HbA1c, hemoglobin A1c; ACE, angiotensin-converting enzyme; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; PET, positron emission tomography; LVEF, left ventricular ejection fraction; CFR, coronary flow reserve; and MBF, myocardial blood flow. Continuous variables are presented as median (quartiles 1–3). Dichotomous variables are presented as number (percent). Patients whose LVEF at stress was greater than that at rest were considered to have positive stress-induced increase in LVEF.

Analysis of Annualized Event Rates

To assess the relative prognostic impact of diabetes mellitus and that of prior CAD, 4 groups were constructed: (1) patients with known prior CAD (history of revascularization or myocardial infarction) but free of diabetes mellitus, (2) patients with diabetes mellitus without history of CAD with impaired CFR, (3) patients with diabetes mellitus without a history of CAD with preserved CFR, and (4) patients without diabetes mellitus or CAD with normal scans (no perfusion abnormality at stress and rest LVEF ≥50%). Poisson regression was performed to compute annualized cardiac mortality rates adjusted for Duke clinical risk score, combined extent and severity of scar and ischemia, rest LVEF, and early revascularization. The hypothesis that diabetes mellitus carries CAD-equivalent risk only among patients with decreased CFR was evaluated by comparing annualized cardiac mortality for group 1 versus 2, group 1 versus 3, and group 3 versus 4.

Results

Patient Characteristics

A total of 2783 consecutive patients (1172 with and 1611 without diabetes mellitus) met inclusion and exclusion criteria during the study period and were followed up for a median of 1.4 years (first and third quartiles, 0.7 and 3.2 years). Baseline characteristics are given in Table 1. The most common indications for testing were evaluation for chest pain, dyspnea, or their combination. Approximately half of all studies were normal by semiquantitative visual analysis.

Table 2. Causes of Death

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Impaired CFR</th>
<th>Preserved CFR</th>
<th>All Patients</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetics</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>600</td>
<td>572</td>
<td>1172</td>
<td></td>
</tr>
<tr>
<td>Cardiac, n (%)</td>
<td>66 (7.6)</td>
<td>12 (1.3)</td>
<td>78 (4.3)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Any cause, n (%)</td>
<td>104 (11.9)</td>
<td>34 (3.5)</td>
<td>138 (7.5)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Nondiabetics</td>
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<tr>
<td>n</td>
<td>852</td>
<td>759</td>
<td>1611</td>
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</tr>
<tr>
<td>Cardiac, n (%)</td>
<td>53 (4.2)</td>
<td>6 (0.4)</td>
<td>59 (3.3)</td>
<td>&lt;0.0001</td>
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<td>Any cause, n (%)</td>
<td>117 (9.3)</td>
<td>24 (1.8)</td>
<td>141 (5.4)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

CFR indicates coronary flow reserve.

Figure 1. Effect of diabetes mellitus and perfusion abnormalities on cardiac mortality. Unadjusted annualized cardiac mortality in categories of total extent of myocardial ischemia and scar for patients with and without diabetes mellitus. Even after the extent and severity of ischemia and scar were accounted for, patients with diabetes mellitus experienced higher rates of cardiac mortality than those without diabetes mellitus.
Unadjusted Correlates of Cardiac Mortality Among Diabetics

Impaired CFR was associated with 6.0-fold (95% CI, 3.2–11.0; \(P<0.0001\)) and 8.9-fold (95% CI, 3.8–20.8; \(P<0.0001\)) increased rates of cardiac death among diabetics and nondiabetics, respectively. Other significant correlates of increased rate of cardiac death included age, male sex, body mass index, and prior CAD. Chest pain as a reason for testing and obesity were associated with a decreased cardiac mortality, possibly reflecting confounding, although other explanations have also been proposed. Dyspnea was associated with increased cardiac mortality among diabetics, perhaps in part because of a slightly lower LVEF among diabetics with dyspnea, 54% (quartile 1–3, 40% to 65%), compared with those without, 56% (quartile 1–3, 47% to 64%; \(P=0.053\)). Dyspnea was not associated with increased cardiac mortality among nondiabetics. In addition, a decrease in rest LVEF and increasing burden of scar, ischemia, or their combination on semiquantitative visual analysis were significantly associated with increased cardiac mortality in both patient cohorts.

Multivariable Survival Analysis and Incremental Prognostic Value

A series of multivariable models were then constructed to assess the incremental value of CFR after adjustment for
critical covariates known to be associated with increased risk of cardiac mortality for diabetics and nondiabetics (Tables 3 and 4). Among diabetics, adding CFR to a model including the clinical risk, early revascularization, rest LVEF, history of nephropathy and retinopathy, LVEF reserve, and combined extent of ischemia and scar was associated with a significant increase in global $\chi^2$ and decrease in Akaika information criterion, indicating improved model fit and a significant increase in the $c$ index from 0.77 to 0.79 ($P=0.04$). Compared with those with preserved CFR, the fully adjusted hazard ratio of impaired for cardiac death was 3.2 (95% CI, 1.7–6.2; $P=0.0004$; Figure 3). Although the inclusion of peak stress MBF alone added incremental prognostic information, the use of CFR resulted in a significantly better model fit (global $\chi^2=97.3$ versus 110.6, respectively).

Similarly, for nondiabetics, adding CFR to a model containing the clinical risk, early revascularization, rest LVEF, LVEF reserve, and combined extent of ischemia and scar improved model fit and $c$ statistic (95% CI, 0.82–0.85; $P=0.03$). The fully adjusted hazard ratio for cardiac death of impaired CFR was 4.9 (95% CI, 2.0–11.5; $P=0.0004$).

### Risk Reclassification

For both diabetics and nondiabetics, adding CFR to the model resulted in the reclassification of $\approx 1$ in 3 patients across clinically relevant categories of risk (net reclassification improvement, 0.171 and 0.214, respectively; Tables 5 and 6). More than half of patients at intermediate risk, between 1% and 3% annual cardiac mortality, were reclassified (net reclassification improvement, 0.657 and 0.897 for diabetics and nondiabetics, respectively). Importantly, diabetic and nondiabetic patients who were reclassified downward from intermediate risk experienced 0.2% and 0.0% annualized cardiac mortality, respectively (Figures I and II in the online-only Data Supplement). Improvements in risk reclassification were also noted after the addition of CFR among patients considered low and high risk on the basis of clinical risk and traditional stress imaging findings.

### All-Cause Mortality

Analyses were repeated using mortality from any cause as a secondary outcome, and the results were similar. After adjustment for clinical risk and traditional stress imaging findings, impaired CFR remained a significant correlate of mortality for both diabetics and nondiabetics and was associated with 2.0- and 3.4-fold increased rates of death, respectively ($P<0.001$). Addition of CFR improved c indexes for both diabetics ($P=0.008$) and nondiabetics ($P=0.03$) with favorable risk reclassification (Table I in the online-only Data Supplement).

### Comparison of Patients With and Without Diabetes Mellitus

We sought to determine whether the presence of preserved CFR could separate diabetic patients without known CAD
with favorable prognosis (ie, comparable to patients without CAD or diabetes mellitus and with normal myocardial perfusion and systolic function) from those with unfavorable prognosis (ie, comparable to patients with known CAD with or without diabetes mellitus). Adjusted annualized cardiac mortality was highest in patients with known CAD and diabetes mellitus and lowest among patients with neither diabetes mellitus nor known CAD (Figure 4). Diabetic patients without known CAD showed different annual cardiac mortality rates, depending on their CFR. Those with preserved CFR had a very low annual cardiac mortality that was comparable to those in patients without diabetes mellitus or CAD with normal stress perfusion and systolic function (0.3%/y versus 0.5%/y, respectively; \( P = 0.65 \)) and markedly lower than in patients with known CAD (0.3%/y versus 2.0%/y, respectively; \( P = 0.015 \)). In contrast, adjusted annualized cardiac mortality in diabetics without known CAD who exhibited impaired CFR was comparable to that for nondiabetic patients with known CAD (2.8%/y versus 2.0%/y; \( P = 0.33 \)).

**Discussion**

This study demonstrates that the presence of coronary vascular dysfunction, as assessed by PET, is an independent correlate of cardiac and all-cause mortality among diabetics and nondiabetics. We observed that inability to appropriately augment MBF in response to stress identified diabetics and nondiabetics with substantially higher cardiac mortality (7.6%/y versus 1.3%/y and 4.2%/y versus 0.4%/y, respectively; both \( P < 0.0001 \)). Furthermore, identification of coronary vasodilatory dysfunction improved risk stratification beyond comprehensive clinical assessment, LV systolic function, and semiquantitative measures of myocardial ischemia and scar. Indeed, quantitative estimation of coronary vasodilator reserve in this cohort was able to improve risk stratification in more than half of both diabetic and nondiabetic patients with intermediate risk based on clinical risk factors and traditional stress imaging findings. Importantly, diabetic patients without known CAD with impaired coronary vascular function experienced a rate of cardiac death comparable to and possibly higher than that for nondiabetic patients with known CAD. Conversely, the rate of cardiac death in diabetic patients without known CAD was very low in the presence of relatively preserved coronary vascular function. These findings may account in part for the inconsistent relationship between diabetes mellitus and cardiac risk reported in the literature.30–33

Noninvasive measures of coronary vasodilator reserve integrate the hemodynamic effects of focal epicardial coronary stenosis, the fluid dynamic effects of diffuse atherosclerosis, and the presence of coronary microvascular dysfunction. As a result, the observed relationship between impaired CFR and prognosis may be due to any or all of these factors combined. Patients with diabetes mellitus may be more likely

**Table 4. Multivariable Survival Analysis in Nondiabetics**

<table>
<thead>
<tr>
<th>covariate</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
<th>Model 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>fit statistic</td>
<td>( P = 0.0001 )</td>
<td>( P = 0.0007 )</td>
<td>( P = 0.0006 )</td>
<td>( P = 0.0001 )</td>
<td>( P = 0.0001 )</td>
</tr>
<tr>
<td>AIC</td>
<td>781.22</td>
<td>744.86</td>
<td>739.31</td>
<td>741.31</td>
<td>N/S</td>
</tr>
<tr>
<td>adjusted calibration ( \chi^2 )</td>
<td>9.90</td>
<td>0.36</td>
<td>5.61</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td>c-index</td>
<td>0.75</td>
<td>Referent</td>
<td>0.80</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>0.69–0.82</td>
<td>0.73–0.86</td>
<td>0.75–0.88</td>
<td>0.75–0.88</td>
<td>0.80–0.90</td>
</tr>
<tr>
<td>HR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duke clinical risk, %</td>
<td>1.02</td>
<td>1.02</td>
<td>1.01</td>
<td>1.01</td>
<td>1.01</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.02–1.03</td>
<td>1.01–1.03</td>
<td>1.00–1.02</td>
<td>1.00–1.02</td>
<td>1.00–1.02</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>0.93</td>
<td>0.95</td>
<td>0.95</td>
<td>0.95</td>
<td>0.95</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.88–0.98</td>
<td>0.91–1.00</td>
<td>0.90–1.00</td>
<td>0.90–1.00</td>
<td>0.90–1.00</td>
</tr>
<tr>
<td>early revascularization</td>
<td>0.96</td>
<td>0.92</td>
<td>0.71</td>
<td>0.4</td>
<td>0.50</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.96</td>
<td>0.92</td>
<td>0.71</td>
<td>0.4</td>
<td>0.50</td>
</tr>
<tr>
<td>rest LVEF, %</td>
<td>0.95</td>
<td>0.94–0.97</td>
<td>0.94–0.98</td>
<td>0.94–0.98</td>
<td>0.94–0.98</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.03</td>
<td>0.006</td>
<td>1.03</td>
<td>0.008</td>
<td>1.02</td>
</tr>
<tr>
<td>scar + ischemia, %</td>
<td>1.01</td>
<td>1.01–1.04</td>
<td>1.01–1.04</td>
<td>1.00–1.04</td>
<td></td>
</tr>
<tr>
<td>LVEF reserve</td>
<td>0.99</td>
<td>0.96</td>
<td>1.06</td>
<td>0.85</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>0.55–1.77</td>
<td>0.59–1.88</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>impaired CFR</td>
<td>4.85</td>
<td></td>
<td>0.0004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>2.04–11.54</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AIC indicates Akaike information criterion; HR, hazard ratio; BMI, body mass index; LVEF, left ventricular ejection fraction; and CFR, coronary flow reserve. Summary of characteristics of nested models. \( P \) values for fit statistics are for comparison of each model to the next simpler model (eg, model 5 vs 4). C Indexes and calibration statistics are calculated for 2-year event data. Global \( \chi^2 \) is the likelihood ratio \( \chi^2 \) statistic for the entire model.
to have advanced multivessel epicardial coronary disease. Additionally, diffuse, albeit nonobstructive, atherosclerosis seen in diabetics is known to be associated with vascular dysfunction. Finally, microvascular dysfunction is more prevalent among those with diabetes mellitus. The increased prevalence of all 3 factors, namely multivessel epicardial disease, diffuse disease, and microvascular dysfunction, among diabetics may account in part for the relatively worse

Figure 3. Cardiac mortality incidence of cardiac mortality for patients with (A and B) and without (C and D) diabetes mellitus and with impaired (red) or preserved (blue) coronary flow reserve (CFR) presented in Kaplan-Meier form (A and C) showing significantly increased cardiac mortality with impaired CFR \(P<0.0001\), which continued after adjustment\(^{21}\) for Duke clinical risk score, body mass index, nephropathy/retinopathy, early revascularization, rest left ventricular ejection fraction (LVEF), extent of myocardial ischemia and scar, and LVEF reserve (B; \(P=0.0004\)). HR indicates hazard ratio.

### Table 5. Risk Reclassification

<table>
<thead>
<tr>
<th></th>
<th>Model Without CFR</th>
<th>Model With CFR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;1% Annual Risk</td>
<td>&gt;3% Annual Risk</td>
</tr>
<tr>
<td>Diabetics</td>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>Patients with cardiac death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1% Annual risk</td>
<td>1 (23.2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>1%–3% Annual risk</td>
<td>1 (5.4)</td>
<td>9 (48.1)</td>
</tr>
<tr>
<td>&gt;3% Annual risk</td>
<td>0 (0)</td>
<td>64 (91.2)</td>
</tr>
<tr>
<td>Total</td>
<td>2</td>
<td>73</td>
</tr>
<tr>
<td>Patients without cardiac death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1% Annual risk</td>
<td>197 (75.9)</td>
<td>62.7 (24.1)</td>
</tr>
<tr>
<td>1%–3% Annual risk</td>
<td>177 (39.3)</td>
<td>191.3 (42.5)</td>
</tr>
<tr>
<td>&gt;3% Annual risk</td>
<td>0 (0)</td>
<td>82 (18.2)</td>
</tr>
<tr>
<td>Total</td>
<td>374</td>
<td>364</td>
</tr>
<tr>
<td>Non-diabetics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with cardiac death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1% Annual risk</td>
<td>7.4 (32.2)</td>
<td>15.5 (67.8)</td>
</tr>
<tr>
<td>1%–3% Annual risk</td>
<td>2.4 (8.8)</td>
<td>17.2 (62.7)</td>
</tr>
<tr>
<td>&gt;3% Annual risk</td>
<td>0 (0)</td>
<td>24.9 (91.4)</td>
</tr>
<tr>
<td>Total</td>
<td>9.8</td>
<td>35.1</td>
</tr>
<tr>
<td>Patients without cardiac death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1% Annual risk</td>
<td>890.6 (78.3)</td>
<td>246.5 (21.7)</td>
</tr>
<tr>
<td>1%–3% Annual risk</td>
<td>106.6 (34.2)</td>
<td>149.8 (48.1)</td>
</tr>
<tr>
<td>&gt;3% Annual risk</td>
<td>1.0 (1.2)</td>
<td>69.1 (81.5)</td>
</tr>
<tr>
<td>Total</td>
<td>998.2</td>
<td>410.9</td>
</tr>
</tbody>
</table>

CFR indicates coronary flow reserve. Reclassification table for censored data using the method of Steyerberg and Pencina\(^{29}\) from 2-year event data. Values in parentheses indicate percentages of each pretest category reclassified to each poststress category.
Thus, the excess cardiac mortality seen in diabetic patients with visually normal stress testing is due to a relatively small subgroup of these patients who also have severely impaired coronary vasodilator function. Conversely, the extremely high cardiac mortality rate (3.5%/y) seen in those diabetics despite the absence of overt ischemia or scar suggests that patients with diffuse epicardial atherosclerosis and/or microvascular dysfunction carry a prognosis comparable to the prognosis for those with obstructive epicardial stenosis. This observation was confirmed by comparing adjusted annualized cardiac mortality among all diabetics without a history of CAD who had preserved CFR, including those with abnormal scans, with nondiabetics without CAD, myocardial scar, ischemia, or systolic dysfunction, showing that diabetes mellitus itself in the absence of vasodilator dysfunction is not associated with excess cardiac mortality. This finding has implications for the classification of diabetes mellitus as a coronary disease risk equivalent.3 Specifically, only among diabetics with impaired vascular function is prognosis comparable to that of nondiabetic patients with known CAD. Differing levels of vascular health among previously studied cohorts may account for inconsistencies in the relative mortality rates of diabetics without CAD and nondiabetes with CAD.30–33 The therapeutic implications of the observation that diabetics with impaired CFR have CAD-equivalent rates of cardiac death whereas those diabetics with preserved CFR have extremely favorable prognosis are uncertain and deserve further investigation. Specifically, whether impaired CFR can identify diabetics who will benefit from aspirin or other medical interventions with conflicting evidence among diabetics may warrant further exploration.

The present study is a single-center, nonrandomized, observational study and has all of the inherent limitations of that study design. Thus, it is likely that some amount of residual confounding remains despite careful adjustment for clinically relevant covariates. On the other hand, compared with data derived from patients selectively enrolled in a randomized trial, these data, with very limited exclusion criteria, may be more representative of patients seen in routine clinical prac-

### Table 6. Comparison of Performance of Coronary Flow Reserve in Diabetics and Nondiabetics

<table>
<thead>
<tr>
<th>Cardiac Mortality</th>
<th>Diabetics (n=1172)</th>
<th>Nondiabetics (n=1611)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annualized cardiac mortality, %</td>
<td>4.3</td>
<td>2.3</td>
</tr>
<tr>
<td>HR for CFR</td>
<td>3.23 (1.68–6.20)</td>
<td>4.85 (2.04–11.54)</td>
</tr>
<tr>
<td>c Index</td>
<td>0.794 (0.740–0.849)</td>
<td>0.852 (0.804–0.900)</td>
</tr>
<tr>
<td>Continuous NRI</td>
<td>0.611 (0.367–0.830)</td>
<td>0.822 (0.637–0.992)</td>
</tr>
<tr>
<td>NRI (1%/y and 3%/y)</td>
<td>0.171 (0.034–0.312)</td>
<td>0.214 (0.050–0.375)</td>
</tr>
<tr>
<td>NRI (1%/y and 3%/y), intermediate-risk stratum</td>
<td>0.657 (0.293–1.029)</td>
<td>0.897 (0.561–1.222)</td>
</tr>
<tr>
<td>IDI</td>
<td>0.016 (0.005–0.027)</td>
<td>0.019 (0.005–0.034)</td>
</tr>
<tr>
<td>Relative IDI</td>
<td>0.130 (0.039–0.217)</td>
<td>0.154 (0.043–0.268)</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio; CFR, coronary flow reserve; NRI, net reclassification improvement; and IDI, integrated discrimination improvement. Similar data for all-cause mortality are available in Table I in the online-only Data Supplement. Comparison of prognostic performance of CFR. Estimates for HR, c-index, NRI, and IDI are adjusted for Duke clinical risk score, body mass index, nephropathy/retinopathy (diabetics only), rest left ventricular ejection fraction, combined extent and severity of scar, and ischemia and left ventricular ejection fraction reserve. Values in parentheses are 95% confidence interval.

Figure 4. Annualized cardiac mortality among patients with diabetes mellitus (DM) or coronary artery disease (CAD). Adjusted cardiac mortality among patients with CAD (ie, history of coronary revascularization or myocardial infarction) without DM (orange), DM patients without CAD who have impaired coronary flow reserve (CFR; red), DM patients without CAD who have preserved CFR (blue), and patients without DM or CAD with normal scans (no scar, ischemia, or left ventricular dysfunction; green) presented as survival curves (A) and annualized cardiac mortality rates (B). Data for patients with CAD and DM are also presented for comparison (purple). MPI indicates myocardial perfusion imaging; EF, ejection fraction; NI MPI, normal myocardial perfusion imaging; and CD, cardiac death.
Conclusions
Among both patients with and without diabetes mellitus, assessment of coronary vasodilator function provides incremental risk stratification beyond routine measures of clinical risk, including estimates of LV systolic function and the extent and severity of myocardial ischemia and scar, and results in a meaningful risk reclassification of 1 in 3 patients with known or suspected CAD. Furthermore, nearly two thirds of diabetic patients without overt myocardial ischemia or scar who also have relatively preserved coronary vasodilator capacity have an extremely low rate of cardiac mortality (0.4%/y). The presence of abnormal CFR identified diabetic patients without overt CAD who experience a rate of cardiac death at least as high as (and possibly higher than) that for nondiabetics with known CAD. These findings may provide a pathophysiological explanation for the inconsistencies in studies comparing mortality rates of diabetes without CAD and nondiabetics with CAD.

Source of Funding
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Disclosures
Dr Di Carli receives research grant support from Toshiba. Dr Murthy has a minor equity position in General Electric. The other authors report no conflicts.

References
11. Di Carli MF, Murthy VL. Cardiac PET/CT for the evaluation of known or suspected coronary artery disease. Radiographics. 2011;31:1239–1254.
Patients with diabetes mellitus are at increased risk of adverse cardiac events even in the absence of overt myocardial ischemia or scar compared with patients without diabetes mellitus. Coronary flow reserve (CFR) is a quantitative measure of coronary vascular dysfunction, which is an early manifestation of coronary artery disease. CFR can be measured noninvasively with positron emission tomography. The present study establishes that CFR is associated with increased rates of cardiac mortality among both diabetics and nondiabetics and results in similar improvement in risk discrimination and recategorization for both cohorts. In both cases, ≈1 in 3 patients has a clinically relevant change in assessed risk based on CFR, even after accounting for clinical risk factors and traditional stress imaging findings. Intriguingly, diabetic patients without known coronary artery disease with visually normal stress tests but impaired CFR experience a 2.8%/y cardiac mortality rate, comparable to that for patients with known coronary artery disease (2.0%/y). Conversely, diabetic patients without known coronary artery disease and visually normal stress tests who have preserved CFR experience cardiac mortality rates comparable to those of nondiabetic patients free of coronary artery disease with normal stress imaging findings (0.3%/y versus 0.5%/y, respectively). These findings offer important insights into the mechanism of increased cardiac risk among diabetics and the classification of diabetes mellitus as a cardiac risk equivalent.
Association Between Coronary Vascular Dysfunction and Cardiac Mortality in Patients With and Without Diabetes Mellitus
Venkatesh L. Murthy, Masanao Naya, Courtney R. Foster, Mariya Gaber, Jon Hainer, Josh Klein, Sharmila Dorbala, Ron Blankstein and Marcelo F. Di Carli

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SUPPLEMENTAL MATERIAL

ASSOCIATION BETWEEN CORONARY VASCULAR DYSFUNCTION AND CARDIAC MORTALITY IN PATIENTS WITH AND WITHOUT DIABETES MELLITUS

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Short Title: Murthy, et al. Coronary vascular function in diabetes

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Fax: (617) 582-6056
## Supplemental Table 1. Multivariable Survival Analysis (Non-Diabetics)

<table>
<thead>
<tr>
<th></th>
<th>Diabetics (N=1172)</th>
<th>Non-Diabetics (N=1611)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Annualized Mortality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-Cause Mortality</td>
<td>7.5%</td>
<td>5.4%</td>
</tr>
<tr>
<td>HR for CFR</td>
<td>2.03 (1.34-3.08)</td>
<td>3.42 (2.17-5.38)</td>
</tr>
<tr>
<td>C-Index</td>
<td>0.778 (0.736-0.819)</td>
<td>0.775 (0.736-0.814)</td>
</tr>
<tr>
<td>Continuous NRI</td>
<td>0.503 (0.312-0.701)</td>
<td>0.678 (0.519-0.826)</td>
</tr>
<tr>
<td>NRI (2 and 6%/yr)</td>
<td>0.126 (0.052-0.207)</td>
<td>0.197 (0.110-0.288)</td>
</tr>
<tr>
<td>NRI (2 and 6%/yr), Intermediate Risk Stratum</td>
<td>0.535 (0.263-0.822)</td>
<td>0.406 (0.185-0.628)</td>
</tr>
<tr>
<td>IDI</td>
<td>0.012 (0.004-0.020)</td>
<td>0.029 (0.021-0.038)</td>
</tr>
<tr>
<td>Relative IDI</td>
<td>0.089 (0.028-0.146)</td>
<td>0.286 (0.197-0.387)</td>
</tr>
</tbody>
</table>

Comparison of prognostic performance of CFR. Estimates for HR, c-index, NRI and IDI are adjusted for Duke clinical risk score, BMI, nephropathy/retinopathy (diabetics only), rest LVEF, combined extent and severity of scar and ischemia and LVEF reserve. CFR=coronary flow reserve. HR=hazard ratio. NRI=net reclassification improvement. IDI=integrated discrimination improvement.
**Supplement Figure 1. Risk Reclassification for Diabetics**

Illustration of risk reclassification by addition of coronary flow reserve (CFR) to a model containing clinical risk factors, left ventricular ejection fraction (LVEF), LVEF reserve and combined extent of myocardial ischemia and scar. The height of each bar is proportional to the number of patients in each pre-CFR risk category (<1, 1-3 and >3% per year risk of cardiac death) as estimated by a model containing clinical risk factors, rest LVEF, LVEF reserve and extent of myocardial ischemia and scar (Model 5, Table 3A, Main Text). Each of these bars is subdivided proportionate to the number of patients reclassified as <1 (green), 1-3 (blue) and >3% (red) per year risk of cardiac death categories after the addition of CFR to the risk model (Model 6, Table 3A, Main Text). The horizontal bar charts at right represent the observed annualized rates of cardiac mortality in each of the post-CFR risk categories.
SUPPLEMENT FIGURE 2. RISK RECLASSIFICATION FOR NON-DIABETICS

Illustration of risk reclassification by addition of coronary flow reserve (CFR) to a model containing clinical risk factors, left ventricular ejection fraction (LVEF), LVEF reserve and combined extent of myocardial ischemia and scar. The height of each bar is proportional to the number of patients in each pre-CFR risk category (<1, 1-3 and >3% per year risk of cardiac death) as estimated by a model containing clinical risk factors, rest LVEF, LVEF reserve and extent of myocardial ischemia and scar (Model 4, Table 3B, Main Text). Each of these bars is subdivided proportionate to the number of patients reclassified as <1 (green), 1-3 (blue) and >3% (red) per year risk of cardiac death categories after the addition of CFR to the risk model (Model 5, Table 3B, Main Text). The horizontal bar charts at right represent the observed annualized rates of cardiac mortality in each of the post-CFR risk categories.