OBJECTIVES
We sought to evaluate the incidence of silent ischemia versus symptomatic ischemia six months after percutaneous coronary intervention (PCI) and its impact on prognosis and to test the utility of myocardial perfusion single-photon emission computed tomography (SPECT), or MPS, for risk stratification in these patients.

BACKGROUND
Silent ischemia is frequent after PCI. However, little is known about silent ischemia and long-term outcome after PCI and stenting.

METHODS
In 356 consecutive patients with successful PCI and stenting and follow-up MPS after six months, long-term follow-up (4.1 ± 0.3 years) was performed. The MPS images were interpreted by defining summed stress, rest, and difference scores (summed difference score [SDS] = extent of ischemia) and related to symptoms and outcome. Critical events included cardiac death, myocardial infarction, and target vessel revascularization.

RESULTS
Eighty-one patients (23%) had evidence of target vessel ischemia, which was silent in 62%. The only independent predictor of silent ischemia was SDS (odds ratio 0.64, p = 0.001). During follow-up, 67 critical events occurred. For patients with an SDS of 0, 1–4, and >4, the critical event rates were 17%, 29%, and 69%, respectively. Similarly, patients without ischemia, silent ischemia, and symptomatic ischemia had 17%, 32%, and 52% of critical events, respectively. Diabetes (relative risk 1.98, p = 0.03) and SDS (relative risk 1.2, p < 0.001) were independent predictors of critical events. The MPS image added incremental information for the prediction of critical events.

CONCLUSIONS
Six months after PCI and stenting, 23% of patients had target vessel ischemia, which was silent in 62%. Silent ischemia predicted a worse outcome than did no ischemia and tended to have a better outcome than symptomatic ischemia. This was closely related to the extent of ischemia. The SDS added incremental value to pre-scan findings with respect to diagnosis and prognosis, indicating the utility of MPS for risk stratification after PCI and stenting. (J Am Coll Cardiol 2003;42:33–40) © 2003 by the American College of Cardiology Foundation

Restenosis is the main problem in patients who have had a percutaneous coronary intervention (PCI). Restenosis rates have been reduced by the frequent use of stents (1,2), from between 20% and 65% before stenting (1–3) to a level of 15% to 32% (average 20%) with stenting (4,5), depending on the method of follow-up and the criteria used to define restenosis. It has been reported that 14% to 60% of patients with restenosis do not complain about recurrent symptoms (6,7). Still, restenosis has been shown to be prognostically relevant. This seems to be related to the myocardium at risk behind the restenotic lesion (6). However, there are almost no data available on objective measures of ischemia after PCI and stenting (8) and of its prognostic importance.

Based on its ability to assess and quantify myocardial ischemia and scar, myocardial perfusion single-photon emission computed tomography (SPECT), or MPS, has been shown to provide prognostic information in multiple coronary artery disease (CAD) settings (9–15).

Therefore, the goals of the present study were fourfold: 1) to evaluate the incidence of silent ischemia versus symptomatic ischemia after PCI and stenting; 2) to identify predictors of silent ischemia versus symptomatic ischemia in these patients; 3) to define predictors of long-term outcome in patients with respect to their symptomatic status; and 4) to determine the incremental value of nuclear testing over clinical and stress testing variables.

METHODS
Study population. All 369 consecutive patients who underwent successful PCI and stenting at our institution in 1997 and who were followed up after six months by routine

See page 41
MPS form the basis of this study. They were prospectively followed up after a minimum of three years (range 3.2 to 4.9 years; average 4.1 ± 0.3 years). Only 13 patients (3.5%) were lost to follow-up, leaving a study population of 356 patients (diagnostic patients) (Fig. 1). Seventeen patients in whom the results of MPS resulted in early revascularization (PCI or coronary artery bypass grafting (CABG) < 60 days after nuclear testing [16,17]) and 32 patients with evidence of ischemia in areas other than the target vessel were excluded from the prognostic analysis of this study, resulting in a prognostic population of 307 patients (Fig. 1).

**Angioplasty and stenting.** Angioplasty and stenting were performed according to published guidelines (18,19). All patients received heparin to a target activated thrombin time level of 200 to 300 s, and all patients were taking aspirin (100 mg/day). In addition, all patients received ticlopidine or clopidogrel in standard doses for four weeks, as well as routine statin therapy.

**Rest/stress myocardial perfusion protocol.** After six months, all patients underwent a routine rest/ergometry stress technetium-99m (Tc-99m) sestamibi MPS protocol. Whenever possible, beta-blockers as well as negative chro-
notropic calcium antagonists were withheld for 48 h and long-acting nitrates for 24 h before exercise testing. A rest-SPECT scan was obtained after administration of 400 MBq Tc-99m sestamibi. A symptom-limited exercise test was performed, using routine protocols with a 12-lead electrocardiographic (ECG) recording each minute of exercise and 12-lead ECG monitoring throughout the test. End points of exercise testing were physical exhaustion, severe angina, sustained ventricular arrhythmia, or exertional hypotension. At near-maximal exercise, an 800-MBq dose of Tc-99m sestamibi was injected, and exercise was continued for an additional minute after injection. Blood pressure was measured and recorded at rest, at the end of each stress stage, and at peak stress. The maximal degree of ST-segment change at 60 ms after the J point of the ECG was measured and assessed as horizontal, downsloping, or upsloping. The ECG response was categorized as either nonischemic (no significant ECG changes), ischemic (>1-mm horizontal, downsloping or 1.5-mm upsloping ST-segment elevation or depression), or nondiagnostic (exercise-induced changes not interpretable).

**Imaging by SPECT.** Imaging by SPECT was performed following standard protocols. No attenuation or scatter correction was used. **Image interpretation.** Semiquantitative visual interpretation was performed using a 20-segment model, as previously described (10). Each segment was scored using a 5-point scoring system: 0 = normal, 1 = equivocal, 2 = moderate, 3 = severe reduction of radioisotope uptake, and 4 = apparent absence of detectable tracer uptake in a segment. A summed stress score (SSS) was obtained by adding the scores of the 20 segments of the stress images (20), and a summed rest score (SRS) by adding the scores of the 20 segments on the rest images. To assess defect reversibility, a summed difference score (SDS) was calculated by subtract-

| MPS form the basis of this study. They were prospectively followed up after a minimum of three years (range 3.2 to 4.9 years; average 4.1 ± 0.3 years). Only 13 patients (3.5%) were lost to follow-up, leaving a study population of 356 patients (diagnostic patients) (Fig. 1). Seventeen patients in whom the results of MPS resulted in early revascularization (PCI or coronary artery bypass grafting (CABG) < 60 days after nuclear testing [16,17]) and 32 patients with evidence of ischemia in areas other than the target vessel were excluded from the prognostic analysis of this study, resulting in a prognostic population of 307 patients (Fig. 1).

**Angioplasty and stenting.** Angioplasty and stenting were performed according to published guidelines (18,19). All patients received heparin to a target activated thrombin time level of 200 to 300 s, and all patients were taking aspirin (100 mg/day). In addition, all patients received ticlopidine or clopidogrel in standard doses for four weeks, as well as routine statin therapy.

**Rest/stress myocardial perfusion protocol.** After six months, all patients underwent a routine rest/ergometry stress technetium-99m (Tc-99m) sestamibi MPS protocol. Whenever possible, beta-blockers as well as negative chro-
notropic calcium antagonists were withheld for 48 h and long-acting nitrates for 24 h before exercise testing. A rest-SPECT scan was obtained after administration of 400 MBq Tc-99m sestamibi. A symptom-limited exercise test was performed, using routine protocols with a 12-lead electrocardiographic (ECG) recording each minute of exercise and 12-lead ECG monitoring throughout the test. End points of exercise testing were physical exhaustion, severe angina, sustained ventricular arrhythmia, or exertional hypotension. At near-maximal exercise, an 800-MBq dose of Tc-99m sestamibi was injected, and exercise was continued for an additional minute after injection. Blood pressure was measured and recorded at rest, at the end of each stress stage, and at peak stress. The maximal degree of ST-segment change at 60 ms after the J point of the ECG was measured and assessed as horizontal, downsloping, or upsloping. The ECG response was categorized as either nonischemic (no significant ECG changes), ischemic (>1-mm horizontal, downsloping or 1.5-mm upsloping ST-segment elevation or depression), or nondiagnostic (exercise-induced changes not interpretable).

**Imaging by SPECT.** Imaging by SPECT was performed following standard protocols. No attenuation or scatter correction was used. **Image interpretation.** Semiquantitative visual interpretation was performed using a 20-segment model, as previously described (10). Each segment was scored using a 5-point scoring system: 0 = normal, 1 = equivocal, 2 = moderate, 3 = severe reduction of radioisotope uptake, and 4 = apparent absence of detectable tracer uptake in a segment. A summed stress score (SSS) was obtained by adding the scores of the 20 segments of the stress images (20), and a summed rest score (SRS) by adding the scores of the 20 segments on the rest images. To assess defect reversibility, a summed difference score (SDS) was calculated by subtract-

| MPS form the basis of this study. They were prospectively followed up after a minimum of three years (range 3.2 to 4.9 years; average 4.1 ± 0.3 years). Only 13 patients (3.5%) were lost to follow-up, leaving a study population of 356 patients (diagnostic patients) (Fig. 1). Seventeen patients in whom the results of MPS resulted in early revascularization (PCI or coronary artery bypass grafting (CABG) < 60 days after nuclear testing [16,17]) and 32 patients with evidence of ischemia in areas other than the target vessel were excluded from the prognostic analysis of this study, resulting in a prognostic population of 307 patients (Fig. 1).

**Angioplasty and stenting.** Angioplasty and stenting were performed according to published guidelines (18,19). All patients received heparin to a target activated thrombin time level of 200 to 300 s, and all patients were taking aspirin (100 mg/day). In addition, all patients received ticlopidine or clopidogrel in standard doses for four weeks, as well as routine statin therapy.

**Rest/stress myocardial perfusion protocol.** After six months, all patients underwent a routine rest/ergometry stress technetium-99m (Tc-99m) sestamibi MPS protocol. Whenever possible, beta-blockers as well as negative chro-
ing SRS from SSS, reflecting the severity and extent of ischemia. An SSS <4 was considered normal, 4 to 8 mildly abnormal, 9 to 13 moderately abnormal, and >13 severely abnormal. For the degree of ischemia, an SDS of 0 was considered nonischemic, 1 to 4 mildly ischemic, and >4 moderately to severely ischemic (13). Peri-infarction ischemia was defined as ischemia that was adjacent to an infarcted area and was located in the same vessel territory. Anteroseptal, lateral, and inferior/inferoseptal defects in MPS were consistent with left anterior descending, left circumflex, and right coronary artery restenosis, respectively.

**Statistical analysis.** A comparison between patient groups was performed using the Student t test for continuous variables and the Fisher exact test for categorical variables. All continuous variables were described as the mean value ± SD. A p value <0.05 was considered statistically significant. A logistic regression model was used to identify variables that were associated with silent ischemia. Hypertension, diabetes, number of risk factors, history of myocardial infarction, history of revascularization, rate-pressure product during stress testing, ischemia on the stress ECG, left ventricular ejection fraction, and SDS were incorporated into this model. Furthermore, receiver-operating characteristic curves were used to identify an SDS that best separated silent from symptomatic ischemia.

For prognostic purposes, a composite end point was defined, including all-cause mortality, nonfatal myocardial infarction, and "late" (not test-induced) revascularization. A Cox proportional hazards model was used to evaluate variables that were independently predictive of this composite end point. Age, hypertension, smoking, hypercholesterolemia, diabetes, family history of CAD, number of diseased vessels at the time of PCI, anginal status during stress testing, maximal heart rate reached, ischemic ECG changes during exercise testing, left ventricular ejection fraction, and SDS were incorporated into the analysis. The incremental value of nuclear testing was determined by calculating the change in global chi-square after having added the nuclear variables to the pre-scan information with respect to the detection of silent ischemia (logistic regression model) and with respect to prognosis (Cox model). The analyses were done using the SPSS statistical package.

**RESULTS**

Of the 356 diagnostic patients (Fig. 1), 291 were male and 65 female, with an age range between 33 and 92 years (average 64.7 ± 10.1). A previous myocardial infarction was reported in 56% and previous revascularization in 26% of patients. At coronary angiography, 34% had single-vessel disease and 66% had multivessel disease. Single “culprit” vessel stenting was performed in 74% and multivessel stenting in 26%. Usually, coronary stenoses with <70% obstruction were not treated, leaving a patient population for MPS testing at risk of both restenosis (ischemia in the target vessel area) and progression of disease/ischemia in a remote area with initially only mild stenoses.

**Incidence of ischemia.** Six months after PCI, 68 of tested patients (19%) complained about angina, 45 (13%) had ischemic stress-ECG changes (nondiagnostic ECG in 48 patients [13%]), and 113 (32%) had MPS evidence of ischemia. Of note, only 43 (63%) of the 68 patients who reported angina had MPS evidence of ischemia. Scintigraphic ischemia was located in the target vessel in 23% and in remote areas in 9%. Thus, 81 patients had evidence of target vessel ischemia, 32 had evidence of remote ischemia, and 243 had no ischemia.

**Target vessel ischemia and symptomatic status.** In 81 patients with target vessel ischemia, angina was reported in 31 (38%), whereas ischemia was silent in 50 (62%). Therefore, 14% of the overall diagnostic patient population (n = 356) had evidence of silent target vessel ischemia six months after PCI and stenting. In Table 1, baseline characteristics and stress test variables of patients with versus without scintigraphic target vessel ischemia are compared; in addition, patients with ischemia are subclassified into those with angina and those with silent ischemia.

Patients with evidence of ischemia differed from those without ischemia in that they had more vessels dilated than patients without ischemia, reached a lower heart rate during stress testing, and more often had ischemic ECG changes. Summed stress, rest, and difference scores were significantly higher in patients with ischemia than in patients without evidence of ischemia. Of note, anti-anginal drug withdrawal was not different between the two groups.

When patients with silent versus symptomatic ischemia were compared, patients with silent ischemia had less cardiovascular risk factors, less frequently a history of hypertension or previous cardiac surgery, and fewer vessels with significant stenosis at the time of intervention than patients with symptomatic ischemia (Table 1). Regarding stress testing and nuclear variables, patients with silent ischemia had less ischemic ECG changes and lower summed stress and difference but not rest scores than patients with symptomatic ischemia. Furthermore, patients with silent ischemia more often had evidence of peri-infarction ischemia. Of note, there was a tendency of patients with silent ischemia to stop their anti-anginal drugs more often before stress testing, as compared with their symptomatic counterparts. However, the difference did not reach statistical significance (p = 0.08).

Of 31 patients with symptomatic ischemia after PCI, 81% presented with angina at baseline, whereas angina occurred in 66% of 50 patients with silent ischemia after PCI (p = 0.15).

**Predictors of silent ischemia and incremental value of nuclear testing.** Factors that influenced the occurrence of silent ischemia were the number of risk factors, hypertension, history of CABG, number of vessels with significant stenosis at the time of PCI, ischemic ECG changes, and, with respect to nuclear variables, SSS and SDS (Table 1).

In the logistic regression model, a low SDS (extent and severity of ischemia) turned out to be the only independent
predictor of silent ischemia, indicating that patients with a lower SDS were more likely to be asymptomatic, whereas patients with a higher SDS were more likely to be symptomatic. The odds ratio for the occurrence of silent ischemia by SDS (decrease of SDS by 1) was 0.64 (95% confidence interval 0.5 to 0.8; \( p = 0.001 \)). In addition, SDS added significant incremental information to pre-scan information with respect to the detection of silent ischemia, as determined by the increase of global chi-square (from 18 to 41; \( p < 0.001 \)).

The receiver-operating characteristic curve revealed an SDS of 4 to be the best separator of patients with silent versus symptomatic ischemia (Fig. 2).

### Outcome and predictors of prognosis

During the four-year follow-up, 67 composite end points were reported in the 307 patients (event rate of 22%, which is consistent with

**Table 1. Baseline Patient Characteristics (n = 324)**

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Ischemia* (n = 81)</th>
<th>No Ischemia* (n = 243)</th>
<th>( p ) Value</th>
<th>Symptomatic Ischemia (n = 31)</th>
<th>Silent Ischemia (n = 50)</th>
<th>( p ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (% female)</td>
<td>17</td>
<td>19</td>
<td>NS</td>
<td>19</td>
<td>16</td>
<td>NS</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>64.7 ± 9.6</td>
<td>64.7 ± 10.2</td>
<td>NS</td>
<td>64.9 ± 10.2</td>
<td>64.5 ± 9.4</td>
<td>NS</td>
</tr>
<tr>
<td>No. of risk factors</td>
<td>2.2 ± 1.2</td>
<td>2.1 ± 1.0</td>
<td>NS</td>
<td>2.5 ± 1.2</td>
<td>2.0 ± 1.2</td>
<td>0.04</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>49</td>
<td>44</td>
<td>NS</td>
<td>68</td>
<td>38</td>
<td>0.01</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>62</td>
<td>57</td>
<td>NS</td>
<td>71</td>
<td>58</td>
<td>NS</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>63</td>
<td>67</td>
<td>NS</td>
<td>71</td>
<td>58</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>15</td>
<td>14</td>
<td>NS</td>
<td>19</td>
<td>12</td>
<td>NS</td>
</tr>
<tr>
<td>Previous myocardial infarction (%)</td>
<td>53</td>
<td>57</td>
<td>NS</td>
<td>48</td>
<td>56</td>
<td>NS</td>
</tr>
<tr>
<td>Previous revascularizations (%)</td>
<td>26</td>
<td>26</td>
<td>NS</td>
<td>32</td>
<td>22</td>
<td>NS</td>
</tr>
<tr>
<td>PCI (%)</td>
<td>17</td>
<td>17</td>
<td>NS</td>
<td>16</td>
<td>18</td>
<td>NS</td>
</tr>
<tr>
<td>CABG (%)</td>
<td>10</td>
<td>10</td>
<td>NS</td>
<td>19</td>
<td>4</td>
<td>0.04</td>
</tr>
<tr>
<td>No. of vessels with stenosis &gt;75%</td>
<td>2.0 ± 0.7</td>
<td>1.9 ± 0.8</td>
<td>NS</td>
<td>2.2 ± 0.8</td>
<td>1.8 ± 0.7</td>
<td>0.02</td>
</tr>
<tr>
<td>No. of dilated vessels at baseline</td>
<td>1.4 ± 0.6</td>
<td>1.2 ± 0.5</td>
<td>0.02</td>
<td>1.3 ± 0.5</td>
<td>1.5 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>61 ± 10</td>
<td>61 ± 14</td>
<td>NS</td>
<td>61 ± 9</td>
<td>61 ± 11</td>
<td>NS</td>
</tr>
<tr>
<td>Exercise and MPS variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiinal drugs withdrawn (%)</td>
<td>67</td>
<td>60</td>
<td>NS</td>
<td>55</td>
<td>73</td>
<td>NS</td>
</tr>
<tr>
<td>Maximum heart rate (beats/min)</td>
<td>140 ± 18</td>
<td>148 ± 19</td>
<td>0.001</td>
<td>137 ± 19</td>
<td>142 ± 17</td>
<td>NS</td>
</tr>
<tr>
<td>Rate–pressure product†</td>
<td>25,369 ± 5,538</td>
<td>25,472 ± 7,699</td>
<td>NS</td>
<td>25,019 ± 5,487</td>
<td>25,578 ± 5,617</td>
<td>NS</td>
</tr>
<tr>
<td>Ischemic stress ECG (%)</td>
<td>31</td>
<td>5</td>
<td>&lt; 0.001</td>
<td>48</td>
<td>20</td>
<td>0.01</td>
</tr>
<tr>
<td>SSS</td>
<td>9.2 ± 5.9</td>
<td>2.6 ± 4.9</td>
<td>&lt; 0.001</td>
<td>11.5 ± 5.6</td>
<td>7.7 ± 5.7</td>
<td>0.005</td>
</tr>
<tr>
<td>SRS</td>
<td>5.2 ± 4.4</td>
<td>2.6 ± 4.9</td>
<td>&lt; 0.001</td>
<td>5.5 ± 4.4</td>
<td>5.0 ± 4.4</td>
<td>NS</td>
</tr>
<tr>
<td>SDS</td>
<td>4.0 ± 3.0</td>
<td>0</td>
<td>&lt; 0.001</td>
<td>5.9 ± 3.0</td>
<td>2.8 ± 2.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Peri-infarction ischemia (%)</td>
<td>27</td>
<td>—</td>
<td>—</td>
<td>13</td>
<td>36</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*In target vessel. †Heart rate × blood pressure at peak exercise. Data are presented as the percentage of patients or mean value ± SD.

CABG = coronary artery bypass grafting; ECG = electrocardiogram; MPS = myocardial perfusion SPECT; NS = not significant; PCI = percutaneous coronary intervention; SDS = summed difference score; SRS = summed rest score; SSS = summed stress score.

---

**Figure 2.** Receiver-operating characteristic curve for the discrimination between silent and symptomatic ischemia. Note that the best discrimination of silent versus symptomatic ischemia was found with a summed difference score (SDS) of 4.
a 5% overall event rate per year) (Table 2): 16 deaths, 8 nonfatal myocardial infarctions, and 50 late revascularizations (36 PCI, 14 CABG). End points were observed more frequently in patients with evidence of ischemia than in patients without ischemia (p = 0.001) (Table 2). This difference was mostly driven by more frequent revascularization procedures in the former (p < 0.001).

Among all possible prognostic factors tested, the Cox model identified a history of hypertension to be a borderline predictor and diabetes mellitus as well as extent of ischemia (SDS) to be independent predictors of the composite end point (Table 3). Among these, SDS was the most powerful predictor of events. This resulted in significantly different event-free survival curves for patients with no (SDS = 0), mild (SDS = 1 to 3), and moderate/severe ischemia (SDS = >4), with 17%, 29%, and 69% event rates (annual event rates of 4%, 7%, and 17%), respectively (Fig. 3). Event-free survival curves for patients without ischemia, with silent ischemia, and symptomatic ischemia (Fig. 4) paralleled the event-free survival curves in Figure 3, with 17%, 32%, and 52% (annual event rates of 4%, 8%, and 13%), respectively. Patients with silent ischemia tended to have better event-free survival than patients with symptomatic ischemia (p = 0.12). However, patients with silent and symptomatic ischemia had a worse prognosis than patients without evidence of ischemia (p = 0.006 and p < 0.0001, respectively). If patients without ischemia were subclassified into those with (n = 25) and those without symptoms (n = 217), then the former group had an event-free survival that was significantly worse than that of the latter group (p < 0.01) and very similar to that of patients with silent ischemia (data not shown).

Prognostic information contained in clinical, ECG, and scintigraphic findings are compared in Figure 5. It shows the incremental prognostic information (significant increase in global chi-square) after adding ECG variables to clinical findings and, in a second step, after adding nuclear information (SDS) to all pre-scan information (Fig. 5).

Seventeen patients had been excluded from this prognostic evaluation because of MPS-induced early revascularization. Eleven of them (65%) were symptomatic and 41% had significant ST-segment depression during the test. In addition, SDS was somewhat higher than in the other patients with target vessel ischemia (4.9 ± 3.2 vs. 3.7 ± 3.0; p = NS). During follow-up, one of these patients died (after 3 years), one had CABG (after 4.5 years), and three had PCI (one in the target vessel, two in other coronary vessels, which is consistent with an event rate of 29%, or 7% per year).

In 32 patients without target vessel ischemia but evidence of ischemia in another coronary vessel territory, 19 (59%) had silent ischemia and 8 (25%) had ischemic ECG changes. During follow-up in these patients, one patient died and eight needed revascularization procedures (2 CABG, 6 PCI), which is consistent with an event rate of 28%, or an annual event rate of 7%.

**DISCUSSION**

The present analysis of a large patient population prospectively tested six months after PCI and stenting revealed important findings regarding the incidence and long-term outcome of patients with silent versus symptomatic ischemia after PCI and stenting. Twenty three percent of patients developed recurrent ischemia in the target vessel, as shown by MPS. In patients with target vessel ischemia, angina was present in only 38% and ischemic ECG changes in 31%. The extent and severity of ischemia, as described by SDS, was the only independent predictor of silent ischemia. In addition, MPS allowed us to differentiate between ischemia related to restenosis (target vessel area) and that related to progression of disease in remote areas. Nuclear testing added incremental value to clinical and ECG findings to detect silent ischemia. Patients with silent ischemia had a smaller extent of ischemia than patients with symptomatic ischemia.

Among several prognostic factors tested, the severity and extent of ischemia (SDS) was the most powerful predictor of outcome. Patients without evidence of ischemia, with a small, moderate, or large extent of ischemia after six months, had long-term annual event rates of 4%, 7%, and
17%, respectively. In addition, the information contained in the SDS added significant incremental prognostic information to the evaluation of patients after PCI and stenting. Survival curves paralleled those of no, silent, and symptomatic ischemia, indicating that silent ischemia, associated with less severe ischemia, carries a certain distinct risk which lies in the middle between no and symptomatic ischemia.

**Incidence of silent ischemia and restenosis after PCI.** In a pooled analysis (n = 3,774) of angiographic data by Ruygrok et al. (21), a restenosis rate of 23% was found after PCI and PCI and stenting. Of these patients, 55% had silent restenosis. This finding is in accordance with the present analysis and a previously published report from our group of patients with PTCA only (6). In contrast to that study, where an overall ischemia rate of 28% was found six months after balloon angioplasty (no stents) in a group of 490 consecutive patients, the incidence of target vessel ischemia was now 23% with stents, most likely reflecting the

---

**Figure 3.** Kaplan-Meier event-free survival curves by summed difference score (SDS) categories. Patients with an SDS of 0 (n = 242) had significantly lower event rates than patients with an SDS of 1 to 4 (n = 49; p = 0.03); these patients had significantly lower event rates than patients with SDS > 4 (n = 16; p = 0.005). Note the significant differences in outcome between patients with no, mild, and moderate to severe ischemia, as defined by SDS. MPS = myocardial perfusion SPECT.

**Figure 4.** Kaplan-Meier event-free survival curves by symptomatic status. Patients without ischemia (n = 242) had significantly lower event rates than patients with silent (n = 44) or symptomatic ischemia (n = 21; p = 0.006 and p < 0.0001, respectively); patients with silent ischemia tended to have lower event rates than patients with symptomatic ischemia (p = 0.12). MPS = myocardial perfusion SPECT.
reduction of restenosis by stents. This finding has been extended by the present analysis, which determined SDS to be the only independent predictor of silent ischemia. In the study by Ruygrok et al. (21), only male gender, the reference vessel diameter at follow-up, and a lesser lesion severity after six months were associated with asymptomatic restenosis.

Chest pain during an exercise stress test has been shown to be a poor marker of restenosis, with reported sensitivities of only 24% to 63% (22,23). Electrocardiographic changes are not very accurate for detecting restenosis, too, with reported sensitivities ranging from 15% to 79% (mean 56%) and specificities from 33% to 88% (mean 73%) (6,22–26). In contrast, a number of reports have indicated that nuclear imaging is more accurate for restenosis detection, with a sensitivity of 87% and a specificity of 78% in a pooled analysis (26).

Outcome and prognostic predictors. Routine six-month follow-up angiography, followed by high rates of repeat intervention of restenotic lesions, could be related to reduced 10-year mortality rates (27,28). This was independent of whether restenosis was symptomatic or silent. In addition, Pancholy et al. (29) showed that the extent of perfusion abnormality and a history of diabetes mellitus were the most important predictors of events in patients with chronic CAD and that silent ischemia had similar prognostic power as compared with symptomatic ischemia (30–32). These prognostic observations are in accordance with the findings of the present analysis, which demonstrated that the extent of ischemia (SDS) and diabetes were independent predictors of events during long-term follow-up after PCI and stenting.

In addition, the present analysis suggests that the extent of ischemia, as defined by SDS, is well suited for risk stratification: patients with a large ischemic region and/or symptomatic ischemia have the highest rate of subsequent events, whereas a smaller ischemic area, as found in silent ischemia, was associated with a lower event rate. Importantly, however, the event rate of silent ischemia was significantly higher than that of patients without ischemia, although somewhat lower than that of patients with symptomatic ischemia.

Patients with early (six-month) induced revascularization tended to have a higher SDS than the other patients with evidence of target vessel ischemia, but after repeat intervention, they had a favorable long-term outcome (although the number is too small to draw definitive conclusions). In contrast, patients with remote ischemia indicating progression of CAD had similar event rates as patients with target vessel ischemia. Thus, nuclear testing had significant incremental value for risk prediction, in addition to clinical and ECG parameters.

Study limitations. No systematic follow-up angiography was performed in this clinical study; therefore, the accuracy of MPS to detect angiographic restenosis cannot be described. However, this was done previously (26) and was not the aim of the present study. Death and myocardial infarction rates were low, as could be expected for such a patient population; therefore, event rates were mainly driven by late revascularizations. To exclude revascularizations indicated by the index MPS in this study, all patients who had revascularization within 60 days of this test were excluded. Still, the prognostic power of the test described relates mainly to nonfatal events and not to mortality. Of note, patients who died tended to have a higher SSS and SRS than patients with late revascularization (SSS 7.7 ± 10.5 vs. 5.2 ± 7.4, p = 0.28 and SRS 6.2 ± 9.6 vs. 3.1 ± 4.6, p = 0.09), reflecting the impact of a higher SRS as a surrogate marker of left ventricular ejection fraction as a major predictor of survival.

Conclusions. Based on these observations, 23% of patients had target vessel ischemia six months after PCI and stenting, which was silent in 62%, representing 14% of the total patient population. Patients with silent ischemia had a smaller extent of ischemia than did symptomatic patients. However, the prognosis of patients with silent ischemia

Figure 5. Incremental value of nuclear testing in the evaluation of long-term prognosis. *#Significant increase in global chi-square (*p = 0.001, #p = 0.002).

ECG = electrocardiogram; SDS = summed difference score.
tended to be better than that of patients with angina but was distinctively worse than that of patients without ischemia.

The extent of ischemia, as represented by SDS, added incremental information to clinical and ECG variables with respect to the detection of silent ischemia and with respect to prognosis. The modality of MPS allowed separation into low, medium, and high risk for adverse events and is therefore suitable for risk stratification several months after PCI and stenting.

Reprint requests and correspondence: Dr. Michael J. Zellweger, Department of Cardiology, University Hospital, Petersgraben 4, CH-4031, Basel, Switzerland. E-mail: mzellweger@uhbs.ch.

REFERENCES