Clinical and Angiographic Predictors of Restenosis After Stent Deployment in Diabetic Patients

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Background—Restenosis and consequent adverse cardiac events are increased in diabetics undergoing percutaneous coronary intervention. Use of intracoronary stents may ameliorate such risks; however, factors influencing the likelihood of restenosis after stent deployment in this high-risk patient subgroup are unknown.

Methods and Results—We retrospectively analyzed all stented diabetic patients in 16 studies of percutaneous coronary intervention, all of which underwent core angiographic analysis at Cardialysis, Rotterdam. Univariate and multivariate analyses, with 37 clinical and angiographic variables, compared those with and without restenosis and predicted restenosis rates calculated through the use of reference charts derived from angiographic data. Within the studies, 418 of 3090 (14%) stented patients with 6-month angiographic follow-up had diabetes. Restenosis (≥50% diameter stenosis at follow-up) occurred in 550 of 2672 (20.6%) nondiabetic and 130 of 418 (31.1%) diabetic patients (P<0.001). Univariate predictors of restenosis in diabetics were smaller vessel reference diameter (RD) (P<0.001), smaller minimal luminal diameter before stenting (P=0.01), smaller minimal luminal diameter and percent diameter stenosis after stenting (P<0.001, P=0.04), greater stented length of vessel (P<0.001), and reduced body mass index (BMI) (P=0.04). With the use of multivariate analysis, only smaller RD (P=0.003), greater stented length of vessel (P=0.04), and reduced BMI (P=0.04) were associated with restenosis. Reference charts demonstrated an incremental risk of restenosis that appears solely dependent on vessel RD.

Conclusions—Restenosis after stent deployment is significantly increased in diabetic patients. Vessel caliber, stented length of vessel, and lower BMI are predictors of in-stent restenosis in patients with diabetes. Furthermore, vessel caliber affected the predicted risk of restenosis incrementally. (Circulation. 2004;109:867-873.)

Key Words: diabetes mellitus ■ restenosis ■ stents

Patients with diabetes mellitus have substantially higher cardiovascular mortality rates than the general population, even after adjustment for confounding factors. Coronary angiographic studies have demonstrated higher incidences of multivessel and left mainstem disease in diabetics as well as more distal disease with a higher plaque burden, smaller vessel reference diameter, and poorer collateral formation. Such propensity for coronary disease may be related to an underlying atherosclerosis-prone state involving such factors as endothelial dysfunction, dyslipidemia, hyperglycemia, insulin resistance, and the presence of advanced glycosylation end products. The increasing incidence of diabetes (reaching epidemic proportions) has important implications for the treatment of coronary artery disease in this patient subset.

Diabetes has been shown to be a predictor of poor outcomes in all modes of coronary revascularization, and therefore the optimal treatment strategy for these patients remains unclear. Randomized trials of percutaneous coronary intervention (PCI) versus CABG for multivessel disease in diabetics (BARI, EAST, ARTS) have consistently demonstrated a benefit for CABG in terms of symptomatic relief of angina, freedom from subsequent cardiac events, and absolute survival. Factors influencing this observed benefit include the increased rates of occlusive-type restenosis and of new lesion formation in diabetic patients after PCI. Procedural success rates for single-vessel PCI have been demonstrated to be similar for diabetic and nondiabetic individuals, and currently available data suggest that stent deployment decreases restenosis and cardiac event rates in diabetic patients.

However, there are few data on the differences between those diabetics who have development of restenosis after stent deployment and those who do not; whether diabetics are at higher risk owing to longer lesions, smaller vessel caliber, and therefore higher restenosis rates or whether simply being
diabetic adds a constant increment to restenosis risk to all patients is unclear.

The present study evaluates patients from 16 interventional trials through the use of multivariate analysis to determine clinical and angiographic factors that might be associated with diabetic in-stent restenosis.

Methods

Patient Population

All patients from 16 PCI studies including stent deployment were considered for analysis. Of these studies, 3 were randomized trials of stent deployment versus balloon angioplasty (ADVANCE, BENESTENT II, DUET), 10 were registries of newer stent designs (BENESTENT II pilot, DUET, EASI, FINESS 2, MAGIC 5L, ROSE, SOPHOS, WEST 1, WELLESTENT), and 2 assessed the efficacy of intravascular ultrasound–guided stent implantation (MUSIC, WEST 2), and 2 assessed the efficacy of novel oral treatments to prevent restenosis after PCI (EXCITE, TRAPIST) (see abbreviations and acronyms in Table 1).

Baseline characteristics of patients enrolled in these studies have already been published but are summarized in Table 2. Body mass index (BMI) was calculated by dividing an individual’s weight in kilograms by the height in meters squared. According to the World Health Organization classification, BMI between 18.5 and 24.9 was considered normal; between 25 and 30, overweight; and >30, obese. All clinical information was monitored and forwarded to the core laboratory (Cardialysis, Rotterdam, the Netherlands) and entered into the study databases. Studies were approved by institutional ethics committees, and written informed consent was obtained from all patients.

All patients who received intracoronary stents, underwent 6-month angiographic follow-up, and had complete clinical and angiographic data were included in the final analysis. Angiographic restenosis, defined as ≥50% diameter stenosis (DS) at the treated site, was determined for diabetic and nondiabetic cohorts within each of the included studies. Univariate analyses were performed with 37 clinical and angiographic factors to establish whether any were predictive of restenosis in the overall diabetic cohort; significant findings were then entered into a multivariate analysis to remove confounding factors.

Reference charts to predict 6-month in-stent restenosis were constructed, with reference diameter (RD) before the procedure and stent length after the procedure used as variables, as previously described. On the basis of the available data, a statistical model was constructed to predict the probability of restenosis for given parameters. In general, the probability of restenosis increases continuously for smaller RD and longer stented lengths. To visually demonstrate this, ranges were defined to examine the data categorically rather than continuously. As an estimate of the probability of restenosis in each category, the midpoint of the intervals was used, on the assumption that within each interval, the probability of restenosis is constant. A reference chart with a probability for restenosis in each interval/range was thereby generated, providing probabilities rather than actual/measured rates in the input data set.

Angiographic Analysis

All procedural and follow-up angiograms were sent to the core laboratory (Cardialysis, Rotterdam, the Netherlands) and analyzed by the Cardiovascular Angiography Analysis System, which has previously been validated. For each patient, multiple matched angiographic views were obtained after intracoronary administration of nitrate. Patients with an unsuccessful procedure or without angiographic follow-up were excluded from the analysis. For patients who had undergone multileision coronary angioplasty, the most severe restenotic lesion at follow-up was entered into the analysis. The minimal lumen diameter (MLD) and RD obtained by an interpolated method were determined on an end-diastolic frame. The proportion of patients in the individual trials undergoing angiographic follow-up varied according to the trial-specific protocol.

<table>
<thead>
<tr>
<th>TABLE 1. Abbreviations and Acronyms for Trials Included in This Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADVANCE</td>
</tr>
<tr>
<td>BENESTENT</td>
</tr>
<tr>
<td>DUET</td>
</tr>
<tr>
<td>EASI</td>
</tr>
<tr>
<td>MUSIC</td>
</tr>
<tr>
<td>ROSE</td>
</tr>
<tr>
<td>SOPHOS</td>
</tr>
<tr>
<td>TRAPIST</td>
</tr>
<tr>
<td>WEST 1.2</td>
</tr>
<tr>
<td>WELLESTENT</td>
</tr>
</tbody>
</table>

Statistical Analysis

Statistical analysis was performed with the use of the SAS software package (SAS Institute, Cary, NC). Continuous variables were compared by means of Student’s t test and the categoric variables by Fisher’s exact test. We performed a logistic regression on the dependent variable Y, where Y=1 for diabetic patients with restenosis and Y=0 for patients without restenosis. As explanatory variables, we considered 37 clinical and angiographic variables. We executed a univariate logistic regression defined by the formula Log (P[1]/P[0])=A+B*Y, with X as the explanatory variable, A the intercept, and B the regression parameter. Preprocedural and postprocedural measures of vessel caliber were entered as continuous variables into the univariate logistic regression. The calculated odds ratios indicate how the risk for restenosis changed when the value of the exploratory variable changed. When the exploratory variable had no influence on restenosis, the odds ratio is 1. A value for the odds ratio <1 indicates risk reduction, whereas, in contrast, a value >1 indicates an increased risk. Multivariate logistic regression, defined by the formula Log ((P[1]–1)/(P[0]–1))=A+B1*X1+...+Bn*Xn, where Xi is the explanatory variable, A the intercept, and B(1),... B(n) the regression parameters, was then performed. With the stepwise procedure, a group of explanatory variables was selected that as a group were multivariately significant. A P value of <0.05 was considered significant.

Results

In the 16 studies analyzed, 3090 patients received intracoronary stents and completed planned 6-month follow-up angiography. The proportion of diabetics and individual restenosis rates for the included trials are summarized in Table 3. Of the overall population, 418 were diabetic, in whom a total of 467 lesions were treated by PCI. Restenosis, defined as
<table>
<thead>
<tr>
<th>Demographics</th>
<th>No Restenosis (n=288)</th>
<th>Restenosis (n=130)</th>
<th>P</th>
<th>Univariate Analysis</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range), y</td>
<td>61.6 (40.0–82.9)</td>
<td>63.2 (38.4–81.1)</td>
<td>0.11</td>
<td>...</td>
<td>...</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>221 (76.7)</td>
<td>93 (71.5)</td>
<td>0.27</td>
<td>...</td>
<td>...</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>BMI, mean (range)</td>
<td>28.9 (17.7–41.7)</td>
<td>27.9 (20.3–37.3)</td>
<td>0.03</td>
<td>0.94</td>
<td>0.89–1.00</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>111 (48.7)</td>
<td>49 (49.5)</td>
<td>0.90</td>
<td>...</td>
<td>...</td>
<td>0.89</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>125 (54.8)</td>
<td>53 (53.5)</td>
<td>0.90</td>
<td>...</td>
<td>...</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>81 (28.1)</td>
<td>35 (26.9)</td>
<td>0.91</td>
<td>...</td>
<td>...</td>
<td>0.80</td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>138 (47.9)</td>
<td>70 (53.8)</td>
<td>0.29</td>
<td>...</td>
<td>...</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>69 (24.0)</td>
<td>25 (19.2)</td>
<td>0.31</td>
<td>...</td>
<td>...</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>Family history</td>
<td>71 (34.8)</td>
<td>33 (36.3)</td>
<td>0.90</td>
<td>...</td>
<td>...</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>Anginal status at screening</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silent ischemia</td>
<td>8 (3.5)</td>
<td>3 (3.1)</td>
<td>1.00</td>
<td>...</td>
<td>...</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>Stable angina</td>
<td>128 (56.4)</td>
<td>57 (58.8)</td>
<td>0.71</td>
<td>...</td>
<td>...</td>
<td>0.69</td>
<td></td>
</tr>
<tr>
<td>Unstable angina</td>
<td>91 (40.1)</td>
<td>37 (38.1)</td>
<td>0.80</td>
<td>...</td>
<td>...</td>
<td>0.80</td>
<td></td>
</tr>
<tr>
<td>Vascular disease at screening</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>80 (35.1)</td>
<td>39 (39.4)</td>
<td>0.46</td>
<td>...</td>
<td>...</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>Q waves on ECG</td>
<td>26 (17.9)</td>
<td>10 (21.3)</td>
<td>0.67</td>
<td>...</td>
<td>...</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>Previous CABG</td>
<td>8 (3.5)</td>
<td>5 (5.1)</td>
<td>0.54</td>
<td>...</td>
<td>...</td>
<td>0.51</td>
<td></td>
</tr>
<tr>
<td>Previous PCI</td>
<td>33 (14.5)</td>
<td>14 (14.1)</td>
<td>1.00</td>
<td>...</td>
<td>...</td>
<td>0.94</td>
<td></td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>16 (7.6)</td>
<td>12 (12.1)</td>
<td>0.21</td>
<td>...</td>
<td>...</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>Medications at screening</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blocker</td>
<td>79 (59.4)</td>
<td>26 (60.5)</td>
<td>1.00</td>
<td>...</td>
<td>...</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>Nitrate</td>
<td>87 (65.4)</td>
<td>29 (67.4)</td>
<td>0.86</td>
<td>...</td>
<td>...</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>62 (46.6)</td>
<td>14 (32.6)</td>
<td>0.11</td>
<td>...</td>
<td>...</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>112 (91.8)</td>
<td>35 (87.5)</td>
<td>0.53</td>
<td>...</td>
<td>...</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>25 (21.6)</td>
<td>14 (32.6)</td>
<td>0.21</td>
<td>...</td>
<td>...</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>Diuretic</td>
<td>14 (12.1)</td>
<td>4 (9.3)</td>
<td>0.78</td>
<td>...</td>
<td>...</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>Heparin</td>
<td>13 (12.4)</td>
<td>3 (7.5)</td>
<td>0.56</td>
<td>...</td>
<td>...</td>
<td>0.41</td>
<td></td>
</tr>
<tr>
<td>Warfarin/coumarin</td>
<td>3 (2.9)</td>
<td>2 (5.0)</td>
<td>0.62</td>
<td>...</td>
<td>...</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>Coronary angiography</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>69 (30.3)</td>
<td>29 (29.3)</td>
<td>0.90</td>
<td>...</td>
<td>...</td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td>Left mainstem lesion</td>
<td>0 (0.0)</td>
<td>2 (1.6)</td>
<td>1.00</td>
<td>...</td>
<td>...</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>Left anterior descending lesion</td>
<td>130 (48.1)</td>
<td>56 (43.4)</td>
<td>0.39</td>
<td>...</td>
<td>...</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>Circumflex lesion</td>
<td>79 (29.3)</td>
<td>32 (24.8)</td>
<td>0.40</td>
<td>...</td>
<td>...</td>
<td>0.35</td>
<td></td>
</tr>
<tr>
<td>Right coronary lesion</td>
<td>102 (37.8)</td>
<td>52 (40.3)</td>
<td>0.66</td>
<td>...</td>
<td>...</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>RD pre-PCI, mean (range), mm</td>
<td>2.9 (1.6–5.5)</td>
<td>2.7 (1.6–4.0)</td>
<td>&lt;0.001</td>
<td>0.40</td>
<td>0.25–0.63</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>% DS pre-PCI, mean (range)</td>
<td>64.7 (39.0–100.0)</td>
<td>65.6 (31.0–100.0)</td>
<td>0.48</td>
<td>...</td>
<td>...</td>
<td>0.44</td>
<td></td>
</tr>
<tr>
<td>MLD pre-PCI, mean (range), mm</td>
<td>1.0 (0.0–2.1)</td>
<td>0.9 (0.0–2.4)</td>
<td>0.02</td>
<td>0.46</td>
<td>0.25–0.83</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Stented length, mean (range), mm</td>
<td>12.1 (2.2–47.6)</td>
<td>15.3 (2.8–53.6)</td>
<td>0.003</td>
<td>1.04</td>
<td>1.02–1.07</td>
<td>0.0008</td>
<td></td>
</tr>
<tr>
<td>RD post-PCI, mean (range), mm</td>
<td>3.2 (1.8–4.4)</td>
<td>3.0 (2.0–4.7)</td>
<td>&lt;0.001</td>
<td>0.45</td>
<td>0.28–0.71</td>
<td>0.0008</td>
<td></td>
</tr>
<tr>
<td>% DS post-PCI, mean (range)</td>
<td>15.7 (2.0–42.9)</td>
<td>17.4 (0.5–52.0)</td>
<td>0.05</td>
<td>1.03</td>
<td>1.00–1.06</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>MLD post-PCI, mean (range), mm</td>
<td>2.7 (1.2–3.9)</td>
<td>2.5 (1.1–4.1)</td>
<td>&lt;0.001</td>
<td>0.37</td>
<td>0.23–0.60</td>
<td>0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Values are n (%) or n (range).
was significantly increased in the diabetic population (130 of 418 [31.1%] diabetics compared with 550 of 2672 [20.6%] nondiabetic patients, \(P<0.001\)) (Table 2).

By univariate analysis, predictors of reduced in-stent restenosis in diabetics were larger RD (OR = 0.40 [95% CI 0.25 to 0.63]; \(P<0.0001\)) and MLD (OR = 0.46 [0.25 to 0.83]; \(P=0.01\)) before stenting, larger MLD (OR = 0.37 [0.23 to 0.60]; \(P<0.0001\)) and RD (OR = 0.45 [0.28 to 0.71]; \(P=0.0008\)) after stenting, and higher BMI (OR = 0.94 [0.89 to 1.00]; \(P=0.04\)). Predictors of increased in-stent restenosis were higher percent DS after stenting (OR = 1.03 [1.00 to 1.06]; \(P=0.04\)) and longer stented length of vessel (OR = 1.04 [1.02 to 1.06]; \(P=0.0008\)) (Table 3). By stepwise multivariate logistic regression analysis, only larger RD before stenting (OR = 0.38 [0.20 to 0.70]; \(P=0.003\)), longer stented length of vessel (OR = 1.03 [1.00 to 1.06]; \(P=0.04\)), and reduced BMI (OR = 0.92 [0.85 to 0.99]; \(P=0.04\)) predicted increased restenosis in diabetics.

Cumulative frequency curves for MLD and percent DS at 6-month follow-up angiography were similar for diabetic and nondiabetic patients (Figure 1).

Reference charts to predict 6-month rates of in-stent restenosis were constructed with preprocedure RD and stented length after the procedure used as variables (Figure 2). Diabetic patients, as expected, had an increased frequency of restenosis for all vessel RDs and stented lengths. When nondiabetic values were subtracted from diabetic predicted restenosis rates, a “subtraction” graph was constructed, removing the baseline effect of nondiabetic restenosis to investigate the effect of diabetes alone. The striking finding was that vessel RD rather than stented vessel length appeared to govern the increased rate of restenosis, with rates being constant across the range of RD (Figure 3). There was a standard 6% increase in predicted restenosis rate for all diabetics, with further increments of an additional 3% for

### Table 3. Numbers and In-Stent Restenosis Rates for Nondiabetic and Diabetic Patients Within the Study Population

<table>
<thead>
<tr>
<th>Study</th>
<th>No. With QCA Follow-Up</th>
<th>Restenosis Rates, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nondiabetic, n Diabetic, n (%)</td>
<td>Nondiabetic</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>76 13 (14.6)</td>
<td>26.3 46.2</td>
</tr>
<tr>
<td>BENESTENT I</td>
<td>221 16 (6.8)</td>
<td>21.3 25.0</td>
</tr>
<tr>
<td>BENESTENT II pilot</td>
<td>178 14 (7.3)</td>
<td>11.2 21.4</td>
</tr>
<tr>
<td>BENESTENT II</td>
<td>161 33 (17)</td>
<td>15.5 27.3</td>
</tr>
<tr>
<td>DUET</td>
<td>161 24 (13)</td>
<td>16.1 20.8</td>
</tr>
<tr>
<td>EASI</td>
<td>220 29 (11.6)</td>
<td>15.5 31.0</td>
</tr>
<tr>
<td>EXCITE</td>
<td>435 91 (17.3)</td>
<td>26.4 34.1</td>
</tr>
<tr>
<td>FINESS 2</td>
<td>109 29 (21)</td>
<td>18.3 24.1</td>
</tr>
<tr>
<td>MAGIC 5L</td>
<td>217 32 (12.9)</td>
<td>39.6 34.4</td>
</tr>
<tr>
<td>MUSIC</td>
<td>127 17 (11.8)</td>
<td>11.0 0.0</td>
</tr>
<tr>
<td>ROSE</td>
<td>92 16 (14.8)</td>
<td>18.5 37.5</td>
</tr>
<tr>
<td>SOPHOS</td>
<td>157 22 (12.3)</td>
<td>16.6 27.3</td>
</tr>
<tr>
<td>TRAPIST</td>
<td>231 35 (13.2)</td>
<td>24.2 48.6</td>
</tr>
<tr>
<td>WEST 1</td>
<td>87 8 (8.4)</td>
<td>11.5 12.5</td>
</tr>
<tr>
<td>WEST 2</td>
<td>129 21 (14)</td>
<td>9.3 33.3</td>
</tr>
<tr>
<td>WELLSTENT NATIVE</td>
<td>71 18 (20.2)</td>
<td>31.0 44.4</td>
</tr>
<tr>
<td>Total</td>
<td>2672 418 (15.3)</td>
<td>20.6 31.1</td>
</tr>
</tbody>
</table>

\(≥50\%\) DS at follow-up, was significantly increased in the diabetic population (130 of 418 [31.1%] diabetics compared with 550 of 2672 [20.6%] nondiabetic patients, \(P<0.001\)) (Table 2).

Figure 1. Cumulative frequency curves for percent DS (top) and vessel RD (bottom) comparing diabetic and nondiabetic patients at 6-month angiographic follow-up.
vessel RD between 2.65 and 3 mm and a further 4% for RD <2.65 mm. This gives overall additional absolute restenosis rates over and above the risk for nondiabetic individuals of 6% for larger vessels, 9% for intermediate-sized vessels, and 13% for small vessels.

**Discussion**

Large studies of patients undergoing PCI with planned 6-month angiographic follow-up have identified the clinical and angiographic predictors of restenosis.3 These studies have also demonstrated that angiographic restenosis is more frequent than clinically driven repeat target lesion revascularization.32 Our analysis demonstrates that diabetic patients have development of in-stent restenosis significantly more frequently than nondiabetics 6 months after intervention. Our finding that 31.1% of diabetic patients have restenosis at 6 months concurs broadly with the studies of Van Belle et al,14 in which restenosis in stented diabetics was 27% at 6 months, and that of Elezi et al,13 in which the restenosis rate was 37.5%. Furthermore, the occurrence of in-stent restenosis in diabetics signifies a worse prognosis in terms of both cardiac morbidity and overall mortality.10 Clinical outcomes were not specifically investigated in this study; given increased restenosis in diabetics compared with nondiabetics and the known correlation of restenosis with coronary events, it would be expected that diabetics should fare less well than their nondiabetic counterparts after intracoronary stenting in terms of event-free survival and death, as has been borne out in previous clinical studies.12,13

In this series of patients enrolled in 16 PCI studies, univariate predictors of in-stent restenosis in diabetics were smaller indexes of vessel caliber (RD before and after PCI, MLD before and after PCI), higher percent DS after stenting, greater stented length of vessel, and reduced BMI. By multivariate analysis, only smaller RD before the procedure, greater stented length of the vessel, and reduced BMI were predictors of restenosis in diabetics. Both vessel caliber and stent length are determinants of restenosis in nondiabetic patients also, but, hitherto, BMI has not been described as influencing restenosis. It is also interesting that lower BMI was associated with increased restenosis, although by World Health Organization criteria, both groups were, on average,
overweight but not obese, and the absolute difference in BMI between the two groups was small (mean BMI without restenosis, 28.9; mean with restenosis, 27.9). It is interesting to speculate on the interpretation of such a result; whether the lower BMI in the restenosis group might reflect a smaller body habitus with consequent smaller coronary vessel caliber is unclear, as height was not recorded. Further studies might seek to elucidate the reason for this finding and explore the relation between BMI, vessel caliber, and restenosis risk.

Vessel caliber was a predictor of restenosis in this study; previous authors have described increased risk of restenosis for percutaneous intervention in small vessels, a risk that may not be offset by coronary stent placement in diabetics. Our data suggest that vessel caliber is the principal determinant of in-stent restenosis in diabetic patients, with an escalating risk not affected by stented vessel length. This finding concurs with previous findings describing the lack of effect of stented vessel length on risk of restenosis, including after deployment of long (25 to 35 mm) stents.

Diabetes and its atherogenic vascular milieu are not the only factors that influence the risk of restenosis after vascular injury such as stent deployment; the risk of restenosis may also be dictated by the antidiabetic drugs used. Novel thiazolidinedione agents demonstrate greater inhibition of arterial smooth muscle cell proliferation than biguanides and sulfonylureas and have been shown in preliminary trials to be effective in preventing restenosis. Because we do not have data on the split within our study population between diet-controlled, insulin-dependent, or non–insulin-dependent diabetics and in the latter case on the type of oral antidiabetic therapy used, we are unable to comment on how these variables may have affected our findings.

**Study Limitations**

Although there was some standardization of clinical and angiographic data collection, only data common to all 16 study databases were included in the analysis. Furthermore, in these studies, diabetes was recorded as a binary (yes/no) variable, and therefore, we cannot accurately define whether these results apply strictly to insulin-dependent or non–insulin-dependent diabetes mellitus or to the mode of treatment used. In addition, exclusion criteria for PCI studies mean that this study population was carefully selected and probably at lower risk of restenosis than an unselected “everyday” PCI population. Finally, it should be noted that the different trials that make up this study population used different stent types, including both balloon-expandable and self-expanding designs. All stents used in these populations were bare-metal stents, and it is possible that these results may not be applicable to evolving practice, including in particular the use of drug-eluting stents.

**Conclusions**

Coronary in-stent restenosis after PCI occurs more frequently in diabetic individuals than in nondiabetics. Predictors of in-stent restenosis at 6 months after the procedure by multivariate analysis are vessel caliber, stented vessel length, and low BMI. The rate of restenosis calculated by constructed reference charts demonstrated that vessel RD was the principal determinant of restenosis, with rates of 6%, 9%, and 13% over nondiabetic restenosis rates for large-, medium-, and small-sized vessels, respectively. These data may help target resource allocation for costly drug-eluting stents to those diabetics who might have the most to gain.

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**References**


Clinical and Angiographic Predictors of Restenosis After Stent Deployment in Diabetic Patients

Nick E.J. West, Peter N. Ruygrok, Clemens M.C. Disco, Mark W.I. Webster, Wietze K. Lindeboom, William W. O'Neill, Nestor F. Mercado and Patrick W. Serruys

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