Clinical and Angiographic Predictors of Restenosis After Percutaneous Coronary Intervention
Insights From the Prevention of Restenosis With Tranilast and Its Outcomes (PRESTO) Trial

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Background—Restenosis prediction from published studies is hampered by inadequate sample size and incomplete angiographic follow-up. The prediction of restenosis with the existing variables is poor. The aim of the present study was to include the clinical and angiographic variables commonly associated with angiographic restenosis and develop a prediction model for restenosis from the PRESTO database.

Methods and Results—This study included 1312 patients with a single lesion enrolled in the angiographic substudy of the PRESTO trial. We constructed 2 risk scores. The first used preprocedural variables (female gender, vessel size \[\leq 2.5 \text{ mm}, 2.5 \text{ to } 3 \text{ mm}, 3 \text{ to } 3.5 \text{ mm}, 3.5 \text{ to } 4 \text{ mm}, > 4 \text{ mm}]$, lesion length $>20 \text{ mm}$, diabetes, smoking status, type C lesion, any previous percutaneous coronary intervention [PCI], and unstable angina) derived from previous studies. Estimated restenosis rates and corresponding variability for each possible level of the resultant risk score were obtained via bootstrapping techniques. The area under the receiver-operator characteristic (ROC) curve was 0.63, indicating modest discriminatory ability to predict restenosis. The second approach constructed a multiple logistic regression model considering significant univariate clinical and angiographic predictors of restenosis identified from the PRESTO database (treated diabetes mellitus, nonsmoker, vessel size, lesion length, American College of Cardiology/American Heart Association type C lesion, ostial location, and previous PCI). The area under the ROC curve for this risk score was also 0.63.

Conclusions—The preprocedural clinical and angiographic variables from available studies and from the PRESTO trial have only modest predictive ability for restenosis after PCI. (Circulation. 2004;109:2727-2731.)

Key Words: restenosis ■ angioplasty ■ coronary artery disease
after PCI. The primary end point was the first occurrence of MACE within 9 months, defined as death, myocardial infarction (MI), and/or ischemia-driven target vessel revascularization (TVR). Restenosis was defined as ≥50% stenosis in the treated segment at follow-up or at least 50% loss of the original gain in the minimal luminal diameter (MLD). The type of intervention performed was at the investigator’s discretion, with the exclusion of intracoronary radiation.

The present study included all patients with a single lesion enrolled in the prespecified angiographic substudy of the PRESTO trial. Restriction to a single lesion was necessary to associate restenosis with a particular target lesion and hence use lesion-specific characteristics in the analysis. Patients enrolled in the angiographic substudy were required to undergo follow-up angiography at 9 months, or sooner if clinically warranted. Quantitative and qualitative angiography assessments were performed by the core laboratories. Angiograms for quantitative coronary angiography (QCA) were done with the cardiovascular measurement system (Medis Medical Imaging Systems). Each patient received 100 to 200 μg of intracoronary nitroglycerin before all required films. Qualitative assessment for all patients was performed by the investigators as well.

### Statistical Analyses

Summary data are expressed as the mean value ± SD or as a percentage. Unadjusted comparisons between those who developed restenosis within 9 months and those who did not were performed with χ2 tests for categorical patient or lesion characteristics and 2-sample t tests for continuous variables.

In the first approach, we included variables that are simple to assess and have frequently been reported to be strong predictors of restenosis risk. The goal of this approach was to construct a simple scoring system that could be used to assess preprocedural risk of restenosis. On the basis of a review of the literature, the following scoring system that could be used to assess preprocedural risk of restenosis risk. The goal of this approach was to construct a simple score out of this model. The area under the ROC curve was calculated on the basis of the estimated risks from the final model.

#### Results

A total of 11 484 patients were enrolled in the PRESTO trial. Informed consent for repeat angiograms was obtained from 2682 patients, and follow-up was terminated when 2018 patient follow-up angiograms were submitted to the core laboratory. We analyzed 1312 single-lesion patients (82% [n=1070] received stents) with complete baseline, procedural, and follow-up angiographic information.

### Patient Characteristics

Table 1 compares the baseline characteristics of patients who subsequently developed restenosis (n=601) with those who did not (n=711). Restenosis rates were higher in patients with hypertension, treated diabetes mellitus, previous revascularization or CHF, and current unstable angina. Patients on nonsteroidal analogues, abciximab, or angiotensin receptor blockers also had higher rates of restenosis. Current smokers had lower restenosis rates. Among the angiographic characteristics (Table 2), lesion length (>20 mm), restenotic lesions, lesions with in-stent restenosis, ostial lesions, and

### Table 1. Baseline Clinical Characteristics for Single-Lesion Patients

<table>
<thead>
<tr>
<th></th>
<th>Restenosis (n=601)</th>
<th>No Restenosis (n=711)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>59.7±10.3</td>
<td>59.1±10.2</td>
<td>0.24</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>458 (76)</td>
<td>560 (79)</td>
<td>0.27</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.2±4.6</td>
<td>28.2±4.4</td>
<td>0.86</td>
</tr>
<tr>
<td>Medical history, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>119 (20)</td>
<td>188 (26)</td>
<td>0.005</td>
</tr>
<tr>
<td>Hypertension</td>
<td>371 (62)</td>
<td>387 (54)</td>
<td>0.008</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>398 (66)</td>
<td>497 (70)</td>
<td>0.15</td>
</tr>
<tr>
<td>Previous MI</td>
<td>229 (38)</td>
<td>279 (39)</td>
<td>0.67</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>75 (12)</td>
<td>64 (9)</td>
<td>0.041</td>
</tr>
<tr>
<td>Previous PCI(s)</td>
<td>224 (37)</td>
<td>178 (25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of CHF</td>
<td>36 (6)</td>
<td>17 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>35 (6)</td>
<td>29 (4)</td>
<td>0.14</td>
</tr>
<tr>
<td>Unilateral or bilateral carotid endarterectomy</td>
<td>13 (2)</td>
<td>6 (1)</td>
<td>0.046</td>
</tr>
<tr>
<td>Current unstable angina</td>
<td>332 (55)</td>
<td>339 (48)</td>
<td>0.007</td>
</tr>
<tr>
<td>Cardiovascular medications, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>422 (70)</td>
<td>489 (69)</td>
<td>0.57</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>482 (80)</td>
<td>579 (81)</td>
<td>0.57</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>249 (41)</td>
<td>270 (38)</td>
<td>0.20</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>299 (50)</td>
<td>309 (43)</td>
<td>0.023</td>
</tr>
<tr>
<td>Ticlopidine/clopidogrel</td>
<td>558 (93)</td>
<td>655 (92)</td>
<td>0.62</td>
</tr>
<tr>
<td>Abciximab and/or GP ib/illa</td>
<td>185 (31)</td>
<td>180 (25)</td>
<td>0.028</td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
<td>416 (69)</td>
<td>456 (64)</td>
<td>0.05</td>
</tr>
<tr>
<td>Baseline high (3.0+) CRP</td>
<td>27 (5)</td>
<td>29 (4)</td>
<td>0.19</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td></td>
<td></td>
<td>0.014</td>
</tr>
<tr>
<td>Diabetes, diet controlled only</td>
<td>29 (5)</td>
<td>45 (6)</td>
<td></td>
</tr>
<tr>
<td>Diabetes, insulin or oral agent</td>
<td>118 (20)</td>
<td>99 (14)</td>
<td></td>
</tr>
<tr>
<td>Ejection fraction percent</td>
<td>60.5±12.7</td>
<td>62.8±13.0</td>
<td>0.018</td>
</tr>
</tbody>
</table>

GP ib/illa indicates glycoprotein ib/illa; CRP, C-reactive protein.
TABLE 2. Lesion Characteristics for Single-Lesion Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Restenosis (n=601)</th>
<th>No Restenosis (n=711)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion length, n (%)</td>
<td></td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>&lt;10 mm</td>
<td>159 (27)</td>
<td>218 (31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>10–20 mm</td>
<td>344 (58)</td>
<td>428 (61)</td>
<td>0.08</td>
</tr>
<tr>
<td>&gt;20 mm</td>
<td>94 (16)</td>
<td>58 (8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Pre-PCI stenosis</td>
<td>85.2±11.9</td>
<td>86.1±10.8</td>
<td>0.15</td>
</tr>
<tr>
<td>Post-PCI stenosis</td>
<td>5.2±8.3</td>
<td>5.4±8.3</td>
<td>0.76</td>
</tr>
<tr>
<td>PCI procedure, n (%)</td>
<td>597 (99)</td>
<td>707 (99)</td>
<td>0.81</td>
</tr>
<tr>
<td>Balloon dilation</td>
<td>482 (80)</td>
<td>588 (83)</td>
<td>0.24</td>
</tr>
<tr>
<td>Stent</td>
<td></td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>De novo</td>
<td>457 (76)</td>
<td>614 (86)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diffuse disease</td>
<td>149 (25)</td>
<td>91 (13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>In-stent restenosis</td>
<td>114 (19)</td>
<td>77 (11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ostial</td>
<td>56 (9)</td>
<td>32 (5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Restenotic</td>
<td>144 (24)</td>
<td>97 (14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Totally occlusive</td>
<td>50 (8)</td>
<td>50 (7)</td>
<td>0.38</td>
</tr>
<tr>
<td>ACC/AHA lesion type, n (%)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type A, B1, B2</td>
<td>486 (81)</td>
<td>636 (90)</td>
<td>0.39</td>
</tr>
<tr>
<td>Type C</td>
<td>114 (19)</td>
<td>74 (10)</td>
<td></td>
</tr>
<tr>
<td>Thrombus, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite</td>
<td>35 (6)</td>
<td>49 (7)</td>
<td></td>
</tr>
<tr>
<td>Possible</td>
<td>169 (28)</td>
<td>218 (31)</td>
<td></td>
</tr>
<tr>
<td>Vessel, left anterior descending, n (%)</td>
<td>267 (44)</td>
<td>267 (38)</td>
<td>0.08</td>
</tr>
<tr>
<td>Lesion characteristics, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ACC/AHA type C lesions were associated with higher frequency of restenosis. The QCA data demonstrated that smaller reference vessel diameter was associated with higher rates of restenosis (Table 3).

Table 4 shows the variables found to be predictors of significant restenosis from previous studies. The integer score (points) assigned to a variable were approximately proportional to the estimated continuous coefficient from the logistic model. Using this risk score, 4 subgroups were constructed with risk score of 0 to 2, 3 to 7, 8 to 14, and ≥15 (Table 5). The risk score of 0 to 2 (n=57) was associated with 28% (95% CI, 16% to 40%) restenosis, 3 to 7 (n=807) with 40% (95% CI, 37% to 43%), 8 to 14 (n=349) with 63% (95% CI, 58% to 68%), and risk score of ≥15 (n=11) was associated with 91% (95% CI, 74% to 100%) risk of restenosis. The area under the ROC curve was 0.63, indicating only a modest discriminatory ability of the model. The data did not deviate significantly from the logistic model, as indicated by the nonsignificant Hosmer-Lemeshow goodness-of-fit test (P=0.18). Likewise, the Figure plots observed and predicted risks as assessed by the risk scores, and the graph indicates that the model fitted the data well and correctly ranked patient risks.

On the basis of the significant univariate clinical and angiographic variables from the PRESTO trial, we constructed a multivariate model for predictors associated with significant restenosis. We identified treated diabetes mellitus (OR=1.45 [1.06 to 1.98], P=0.02), nonsmoker (OR=1.34 [1.01 to 1.76], P=0.04), vessel size ≤3 mm versus >3 mm (OR=1.32 [1.04 to 1.68], P=0.02), length of the lesion (≥20 mm versus <10 mm, OR=2.36 [1.49 to 3.75], P=0.0003; 10 to 20 versus <10, OR=1.17 [0.91 to 1.50], P=0.22), ostial lesion (OR=1.82 [1.13 to 2.9], P=0.013), and previous PCI (OR=1.41 [1.09 to 1.81], P=0.008) as significant predictors of restenosis. The assigned treatment to tranilast had no effect on angiographic restenosis. The area under the ROC curve was 0.63, indicating only a modest ability of the model to discriminate between patients who developed restenosis and those who did not.

### Discussion

In the PRESTO study, the largest study designed to prevent restenosis, several clinical and angiographic predictors of coronary restenosis were identified, namely, treated diabetes mellitus, previous PCI, ACC/AHA type C lesion, ostial lesion, and lesion length ≥20 mm. The prediction model, including clinical and angiographic variables derived from

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**TABLE 3. Lesion Characteristics for Single-Lesion Patients (QCA Data)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Restenosis (n=601)</th>
<th>No Restenosis (n=711)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-PCI MLD</td>
<td>0.8±0.5</td>
<td>0.8±0.4</td>
<td>0.07</td>
</tr>
<tr>
<td>Pre-PCI reference diameter</td>
<td>2.9±0.5</td>
<td>3.0±0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Complex lesion, n (%)</td>
<td>113 (19)</td>
<td>191 (27)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**TABLE 4. Risk Score Model Derived From Variables Chosen From Previously Published Studies**

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>Integer Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion length &gt;20 mm</td>
<td>2.07 (1.34, 3.21)</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>ACC/AHA type C lesion</td>
<td>1.81 (1.26, 2.59)</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>1.46 (1.14, 1.88)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Treated diabetes mellitus</td>
<td>1.41 (1.03, 1.92)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>1.39 (1.05, 1.83)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Vessel size &gt;4 mm</td>
<td>1.00 (reference)</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>3.5–4 mm</td>
<td>1.18 (0.55, 2.53)</td>
<td>0.680</td>
<td>1</td>
</tr>
<tr>
<td>3–3.5 mm</td>
<td>1.44 (0.71, 2.94)</td>
<td>0.317</td>
<td>2</td>
</tr>
<tr>
<td>≤3 mm</td>
<td>1.76 (0.87, 3.54)</td>
<td>0.115</td>
<td>3</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>1.19 (0.94, 1.51)</td>
<td>0.147</td>
<td>1</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.15 (0.87, 1.52)</td>
<td>0.317</td>
<td>1</td>
</tr>
</tbody>
</table>

**TABLE 5. Summary Lookup Table For Risk**

<table>
<thead>
<tr>
<th>Risk Score Range</th>
<th>No. of Patients</th>
<th>Estimated Risk of Restenosis, %</th>
<th>95% CI Based on Bootstrapped SE, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–2</td>
<td>57</td>
<td>28</td>
<td>16–40</td>
</tr>
<tr>
<td>3–7</td>
<td>807</td>
<td>40</td>
<td>37–43</td>
</tr>
<tr>
<td>8–14</td>
<td>349</td>
<td>63</td>
<td>58–68</td>
</tr>
<tr>
<td>15+</td>
<td>11</td>
<td>91</td>
<td>74–100</td>
</tr>
</tbody>
</table>

In 88 patients, risk score was not calculated for one or more missing values needed to compute the score.
Clinical and Angiographic Predictors of Restenosis

Coronary interventions continue to evolve, and it remains important to stratify patients who would derive the most short- and long-term benefit. Although most of the studies on prediction of restenosis antedate the use of stents, there has been no change in the clinical variables predicting restenosis.3,5,7,11 Diabetes mellitus continues to be a strong clinical predictor of restenosis.4,12 In the present study, patients with treated diabetes mellitus had a 45% higher risk of restenosis compared with nondiabetics. Conversely, current smokers have less restenosis. This smoker’s paradox has been well described.9,10,13 The correlation of small vessel size, complex type C lesions, longer length of the lesion, ostial location, and previous angioplasty with risk of restenosis also has been documented.14–16

Prediction of Restenosis

A primary aim of a study in the present era would be to identify patients at the highest risk for restenosis. This would help in the optimal use of costly drug-eluting stents. The predictive accuracy for restenosis of the previous published studies was poor to modest.2,4,7 In an analysis of 9120 treated lesions in 8156 patients chosen from a pooled 19 different studies, there was poor correlation of preprocedural variables with restenosis. However, we cannot totally exclude withdrawal bias.20

Conclusions

The present study demonstrates the clinical and angiographic variables associated with risk of restenosis after PCI in a large data set representing recent practice. The predictive accuracy of the model from the commonly identified variables, and also chosen from the trial, is only modest. The relatively low follow-up and used different poststent antithrombotic regimens.

The present study is the largest in the current era with restenosis as one of the major end points. The predictive accuracy for restenosis was modest, with an area under the ROC curve of 0.63. We initially chose a model that was simple and could be used to assess the patient’s risk of restenosis. The risk score derived from variables chosen from previous published studies could not differentiate low from intermediate risk for restenosis. Moreover, even with almost no risk factors for restenosis, the restenosis rates were 28% (95% CI, 16% to 40%). Conversely, patients with multiple adverse clinical and angiographic variables placed the patient at a very high risk of restenosis, which may be helpful in risk stratifying very-high-risk patients for subsequent restenosis.

The inclusion of patients with previous PCI and patients with in-stent restenosis may increase the restenosis rates even in patients without any clinical and angiographic predictors of restenosis. We did not include any post-PCI angiographic variables that are known to influence the prediction of restenosis. In a study by Mercado et al.,7 there was only modest gain after inclusion of angiographic and post-PCI variables. In the other 2 studies antedating the present era, there was poor correlation of preprocedural variables with risk of subsequent restenosis.4,17 The aim of the present study, however, was to predict restenosis solely on the basis of preprocedural clinical and angiographic variables. The low predictive accuracy of the 2 models constructed in the present study is most likely because of noninclusion of postprocedural variables, stent design, and various other genetic, infection, inflammatory, and some unknown factors that can influence restenosis.14,18,19

Study Limitations

This large prospective study lacked the predictive accuracy to differentiate patients who did and who did not develop restenosis. Solely on the basis of clinical and angiographic variables, we are not able to predetermine the risk of angiographic restenosis. We cannot extrapolate the results of this study to multiple lesions, because we by necessity confined our analysis to single lesions. Although this study is one of the largest and is representative of recent practice, many important subsets, namely, vein grafts, bifurcation, and left main disease, which are known to have higher restenosis, were underrepresented. Also, other features believed to be associated with higher risk of restenosis, eg, chronic total occlusion, and patients with chronic renal failure were under-represented. Thus, these features could not be evaluated in the present study. The PRESTO trial did not include patients who received intracoronary brachytherapy or drug-eluting stents, and therefore, our analysis cannot be extrapolated to this subset. The angiographic study was prespecified in the trial; however, we cannot totally exclude withdrawal bias.20
predictive accuracy of the models in this analysis is at first disappointing, given the multiple variables used and the large sample size of the study. Conversely, the results perhaps should not come as a surprise in light of the complexity of the phenomenon of restenosis. Restenosis is a multifactorial biological process involving not only patient and lesion characteristics but also vessel-wall features, blood-borne components, systemic risk factors, and probably a genetic susceptibility. From the perspective of an individual patient, for the present, the prediction of restenosis can be made only in general terms.

References
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