Clinical Restenosis After Coronary Stenting: Perspectives From Multicenter Clinical Trials

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OBJECTIVES
We sought to evaluate clinical restenosis in a large population of patients who had undergone coronary stent placement.

BACKGROUND
One-year success after coronary stenting is limited mainly by restenosis of and requirement for repeat revascularization of the treated lesion.

METHODS
We studied 6,186 patients (6,219 lesions) pooled from several recently completed coronary stent trials. Clinical restenosis was defined using three different definitions: target lesion revascularization (TLR) beyond 30 days, target vessel revascularization (TVR) beyond 30 days, and target vessel failure (TVF), defined as TVR, any death, or myocardial infarction (MI) of the target vessel territory after hospital discharge.

RESULTS
By one year, 638 (12.2%) patients had TLR, 748 (14.3%) had TVR, and 848 (16.0%) had TVF, more than two-thirds higher than the rate of these end points at six months. The severity of angiographic restenosis (≥50% follow-up diameter stenosis [DS]) in 419 of 1,437 (29%) patients undergoing routine angiographic follow-up correlated directly with the likelihood of TLR (73% vs. 26% for >70% DS compared with <60% DS). Smaller pretreatment minimum lumen diameter (MLD), smaller final MLD, longer stent length, diabetes mellitus, unstable angina, and hypertension were independent predictors of TLR. Prior MI and current smoking were negative predictors.

CONCLUSIONS
At one year after stenting, most clinical restenosis reflected TLR, which was predicted by the same variables previously associated with an increased risk of angiographic restenosis. The lower absolute rate of clinical restenosis relative to angiographic restenosis was due to infrequent TLR in lesions with less severe (<60% DS) angiographic renarrowing. (J Am Coll Cardiol 2002;40:2082–9) © 2002 by the American College of Cardiology Foundation

Long-term clinical success after coronary stent implantation is limited by restenosis of the index coronary lesion as well as progression of nonstented disease at other sites. Accurate assessment of these outcomes is critical for the evaluation of current and future interventional devices and other therapies designed to prevent or limit restenosis.

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Restenosis is most commonly defined by angiographic criteria utilizing a dichotomous distinction based on ≥50% diameter stenosis (DS) at the site of a previously successful intervention. After successful coronary stent implantation, this loss of lumen is almost entirely due to neointimal hyperplasia, rather than elastic recoil or negative remodeling that is operative after conventional balloon angioplasty, and is essentially complete by six months after the stent procedure (1,2).

While the study of angiographic or intravascular ultrasound parameters of restenosis has been useful for understanding biologic mechanisms of restenosis (3,4), clinical outcomes must be regarded as the true measure of treatment success (5). Such assessment has been limited by the difficulty in defining clinical restenosis measures, which correlate with the biologic response as defined by a variety of angiographic parameters (6–8). Several potential clinical correlates of angiographic restenosis have been studied, ranging from a narrowly defined end point of clinically driven repeat revascularization of the original target lesion to the more broadly inclusive end point of target vessel failure, which includes clinically driven revascularization of any lesion within the target vessel, as well as any death or myocardial infarction (MI) potentially involving the target vessel territory. Previous studies of coronary stenting including both angiographic and clinical restenosis outcomes have consistently observed a significant disparity between the two rates, with the rate of clinical restenosis about one-half of the angiographic restenosis rate (9–11).

The aim of this study was to evaluate clinical restenosis in a large population of coronary stent patients. We compared the frequency of clinical restenosis during the course of one-year follow-up and determined incremental risk as a function of follow-up duration. Furthermore, we studied various lesion and clinical characteristics as correlates of clinical restenosis and examined potential explanations for the disparity in clinical and angiographic restenosis rates in a subset of patients assigned to routine angiographic follow-up.

METHODS

Study design. Data from six major clinical trials of native coronary artery stenting with relatively homogenous inclusion criteria and study protocols were pooled for this
analysis. The details of the study protocols and justification for pooling have been previously reported (12). Briefly, the population included 6,186 patients who underwent stenting of 6,219 target vessels using the Palmaz-Schatz coronary stent or one of six second-generation designs. The stenting protocol for each study included routine high-pressure postdilation with recommended balloon:artery ratios of 1.1 to 1.2:1, and aspirin plus four weeks of ticlopidine 250 mg twice daily as the standard postprocedure antithrombotic regimen. All of the studies utilized the same angiographic core laboratory, and the same Clinical Events Committee (CEC) adjudicated all clinical events.

**Clinical follow-up and definitions.** Clinical follow-up was obtained at hospital discharge, and one month, six months, and one year after the procedure. Target lesion revascularization (TLR) was defined as any repeat percutaneous revascularization or surgical bypass of the original target lesion site that occurred 30 or more days after the index procedure and was driven by clinical findings (presence of ischemic symptoms and/or a positive functional ischemia study), in the presence of a DS ≥50% as determined by the angiographic core laboratory. Even if ischemic symptoms or a positive functional ischemia study were absent, revascularization for a DS ≥70% was also considered to be clinically driven. If quantitative angiographic data were not available or were deemed unreliable due to the presence of diffuse disease or other technical issues, then the presence of ischemia was considered adequate evidence for a clinically driven indication. The target lesion was considered to be the area covered by the stent plus a 5-mm margin proximal and distal to the stent edges. Target lesion revascularization performed earlier than 30 days after the procedure was defined as related to an early procedural complication or failure and not included as clinical restenosis. Target vessel revascularization (TVR) was defined as percutaneous revascularization or bypass of the target lesion or any segment of the epicardial coronary artery containing the target lesion or more proximal vessels that may have been traversed by the angioplasty guidewire during the index procedure. Criteria for clinically driven indication and clinical restenosis were the same as for TLR. Target vessel failure was defined as any TVR, any death, or MI of the target vessel territory other than that attributed to a complication of the index procedure.

**Angiographic follow-up.** A prespecified subset of patients from these studies was designated for routine angiographic follow-up analysis. This subset consisted of 1,959 (31.7%) patients with single lesion treatment, who were further analyzed to evaluate the potential bias that routine angiographic follow-up exerts on clinical decisions for repeat revascularization as well as possible explanations for the disparity between angiographic and clinical restenosis rates. Angiographic restenosis was defined according to the binary distinction of ≥50% DS at the time of angiographic follow-up.

**Statistical analysis.** Continuous variables are presented as medians and interquartile range. Binary variables are presented as counts and percentages. Survival estimates were computed using Kaplan-Meier methods and compared using the log-rank test. Predictors of TLR were analyzed using stepwise logistic regression analysis for the population assigned to only clinical follow-up. Patients who died or sustained Q-wave MI before one year without prior TLR were excluded from the models. Variables for stent model and individual study were included in the model to assess for association with the TLR end point. A two-sided value of p < 0.05 was required for statistical significance. The discriminatory strength of multivariable associations was assessed by the c statistic. All statistical analyses were performed using SAS for Windows Version 6.12 (SAS Institute, Cary, North Carolina).

### RESULTS

Baseline clinical and angiographic characteristics for the study cohort are depicted in Table 1.

**Effect of follow-up duration.** The effect of follow-up duration is depicted in Figure 1, demonstrating approximately a 70% increase in each of the clinical restenosis end points for 12-month compared with six-month follow-up intervals.

**Predictors of TLR.** The significant independent predictors of TLR in the cohort with only clinical follow-up are shown in Table 2. There was no independent effect of stent

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**Table 1. Baseline Clinical and Lesion Characteristics**

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>N = 6,186</th>
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<tbody>
<tr>
<td>Age (yrs), median (quartiles)</td>
<td>63 (54, 71)</td>
</tr>
<tr>
<td>Female (n, %)</td>
<td>2,101 (34.0)</td>
</tr>
<tr>
<td>Diabetes mellitus (n, %)</td>
<td>1,296 (21.0)</td>
</tr>
<tr>
<td>Hypertension (n, %)</td>
<td>3,569 (57.7)</td>
</tr>
<tr>
<td>Prior MI (n, %)</td>
<td>2,054 (33.2)</td>
</tr>
<tr>
<td>Unstable angina (n, %)</td>
<td>2,629 (42.5)</td>
</tr>
<tr>
<td>Cigarette smoking in past year (n, %)</td>
<td>1,332 (21.5)</td>
</tr>
<tr>
<td>Prior restenosis lesion (n, %)</td>
<td>691 (11.2)</td>
</tr>
<tr>
<td>Left anterior descending lesion (n, %)</td>
<td>2,549 (41.2)</td>
</tr>
<tr>
<td>Glycoprotein IIb/IIIa inhibitor (n, %)</td>
<td>470 (7.6)</td>
</tr>
</tbody>
</table>

**Quantitative Angiography**

<table>
<thead>
<tr>
<th>N = 6,219</th>
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<tbody>
<tr>
<td>Reference diameter, median (quartiles)</td>
</tr>
<tr>
<td>Diameter &lt; 2.50 mm (n, %)</td>
</tr>
<tr>
<td>Pretreatment MLD, median (quartiles)</td>
</tr>
<tr>
<td>Lesion length, median (quartiles)</td>
</tr>
<tr>
<td>Lesion length, &gt; 20 mm (n, %)</td>
</tr>
<tr>
<td>Final MLD (median [quartiles])</td>
</tr>
</tbody>
</table>

MI = myocardial infarction; MLD = minimum lumen diameter.
design or individual study. Of note, left anterior descending artery lesion treatment and prior restenosis were not significantly associated with TLR after adjustment for these covariates. The c statistic for the model was 0.68.

Repeat TLR and follow-up DS. The mean DS at the time the CEC adjudicated TLR was 69.1 ± 11.9%. Figure 2 shows the cumulative frequency distribution of follow-up DS for patients undergoing TLR. The DS was <60% for only 22% of patients with adjudicated TLR, while 46% of these patients had >70% DS. Un adjudicated TLR included 66 (14%) patients with <50% follow-up DS, of whom 49 had reported symptoms (27 with symptoms referable to other disease who had incidental TLR, seven with TLR during protocol follow-up angiogram, and 15 without documented ischemia involving the target vessel and with clearly documented DS <50% after review of quantitative angiography).

Clinical restenosis relative to angiographic restenosis. Angiographic follow-up was available for 1,437 (74%) of the 1,959 lesions assigned to routine angiographic follow-up and was performed at 202 ± 44 days after the index procedure. Angiographic restenosis was present in 419 (29.2%) lesions. Clinical restenosis rates (using adjudicated or any reported event) for the patients with binary angiographic restenosis are reported in Table 3, showing that only about one-half of patients with angiographic restenosis manifested clinical restenosis. Figure 3A displays the cumulative distribution frequency of follow-up DS, and Figure 3B shows clinical restenosis rates relative to the severity of angiographic restenosis for all patients with angiographic binary restenosis. Nearly one-half of lesions that met criteria for angiographic restenosis had follow-up DS <60%, and only 22% had DS >70%. The likelihood for TLR correlated directly with severity of angiographic restenosis, being performed in only 26% of lesions with <60% DS.

Receiver operator characteristic curves of TLR relative to...
follow-up DS are shown in Figures 4A and 4B for any TLR and adjudicated TLR, respectively.

Effect of routine angiographic follow-up. Assignment to routine angiographic follow-up significantly increased the rate of any TLR compared with assignment to only clinical follow-up (17.4% vs. 12.1%, \( p = 0.001 \)). Adjudication by the CEC partially corrected for this difference (13.9% vs. 11.0%, \( p = 0.03 \)).

DISCUSSION

Of 6,186 patients undergoing stenting of 6,219 de novo or restenotic native coronary lesions using a variety of stent designs, one-year clinical outcome was determined mainly by the requirement for repeat revascularization of the original target lesion. While definitions of clinical restenosis that include revascularization of the entire target vessel or attribute any death or recurrent MI in the target vessel territory to clinical failure of the percutaneous revascularization provide a more complete clinical assessment, these events were far less frequent than TLR and increased the absolute one-year end point rate only 2.1% and 3.8%, respectively. While these other late events are critical to the safety evaluation of a new device or treatment strategy, they probably do not contribute significantly to assessments of clinical outcomes due to restenosis per se.

Table 3. Clinical Restenosis Rates in Patients With Binary Angiographic Restenosis

<table>
<thead>
<tr>
<th>Clinical Restenosis End Point</th>
<th>Any Event  N = 419</th>
<th>Adjudicated Event N = 419</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target lesion revascularization</td>
<td>213 (52%)</td>
<td>187 (45%)</td>
</tr>
<tr>
<td>Target vessel revascularization</td>
<td>219 (52%)</td>
<td>193 (46%)</td>
</tr>
<tr>
<td>Target vessel failure</td>
<td>224 (53%)</td>
<td>198 (47%)</td>
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</table>

Effect of follow-up duration on clinical restenosis rates. An important finding of our study is the demonstration of how the duration of follow-up influences the perceived rate of clinical restenosis. Had follow-up been limited to six months, the reported rate of TLR would have been only 7%. While the pathologic process of restenosis occurs mostly during the first few months and is essentially complete by six months, our results indicate a significant delay between those processes and clinical manifestation of restenosis as a revascularization procedure. Longer (9 to 12 month) follow-up for clinical restenosis end points should, thus, be required to maximize the capture of these events. While this lag may represent a delay in the development of symptoms beyond the time required for completion of the biologic restenosis process or ongoing changes in the pathophysiology of the restenosis lesion, it more likely represents an inherent delay caused by the time required for recognition of symptoms and appropriate evaluation and management. Regardless, any assessment of new devices or treatment strategies designed to limit restenosis must consider the time point at which clinical restenosis end points are reported.

Disparity between angiographic restenosis and clinical restenosis rates. The large database of coronary stent patients including those with routine angiographic as well as only clinical follow-up allowed for detailed evaluation of the well-described discordance between angiographic and clinical restenosis rates. The finding of clinically relevant restenosis in only about 50% of patients with angiographic restenosis is similar to several earlier reports (9,10,13). Despite these numerical differences between angiographic and clinical restenosis, however, there is compelling evidence that they represent the same process through different filters: 1) there is a clear correlation between the severity of
angiographic restenosis and the likelihood of TLR and 2) the same important predictors of angiographic restenosis also predict TLR. In contrast with a dissociation of follow-up angiographic findings and late clinical outcomes, our results indicate that the frequent milder degrees of angiographic restenosis do not cause sufficient limitation of coronary blood flow to produce symptomatic ischemia and drive the patient towards a repeat procedure. Our group has previously reported that angiographic parameters of restenosis represent a continuous process for any given lesion or treatment device and that this process is largely dependent on the final lumen diameter achieved (3). It is, therefore, not
surprising that the uniform excellent results after coronary stenting are associated with frequent less severe angiographic renarrowing.

Based on this finding, other potential cutoff values for the dichotomous angiographic restenosis definition were tested. Receiver operator characteristic curves demonstrate that, for both clinically driven as well as any reported TLR, the slight gain in specificity for cutoffs of >60% or >70% DS was

**Figure 4.** Receiver operator characteristic curves for target lesion revascularization (TLR) as a function of severity of angiographic restenosis (A = any reported TLR; B = adjudicated TLR). An area under the curve approaching 1.0 represents optimal discrimination for the measure of interest (follow-up diameter stenosis [DS]). A result in the upper left hand corner of the graph would indicate a perfect cutoff value with maximum sensitivity and specificity. As shown in A and B, the cutoff value of 50% DS best represents this position.
offset by much greater reductions in sensitivity. The curves further suggest that the currently accepted definition of >50% DS provides excellent balance of sensitivity and specificity.

Independent correlates of TLR. This pooled analysis confirms earlier reports from BENESTENT II (11) and adds additional power to our previous reports from ACS Multilink Stent Clinical Equivalence Trial (ASCENT) (14) and NIR Vascular Advanced North American Trial (NIRVANA) (15) (patients from ASCENT and NIRVANA are included in the pooled analysis) that routine angiographic follow-up significantly inflates reported rates of TLR. Of particular note, the present study shows that this effect remains significant even after adjudication of TLR events by the CEC.

To avoid this potential bias, the independent correlates of TLR were further evaluated in the patients having only clinical follow-up. The clinical, lesion, and procedural variables that were significantly associated with TLR were similar to those previously reported for angiographic restenosis after stent implantation, including vessel size, final lumen diameter, lesion length, stent length, unstable angina presentation, and the presence of diabetes mellitus (16–18). In contrast with previous reports, we did not find that stent design was significantly associated with TLR after adjustment for these significant variables (18,19). This discrepancy may be due to different assortments of available stents between the two studies. Our finding of an association of prior MI with lower risk for TLR more than likely represents the presence of a clinically silent, collateralized, or nonviable territory rather than a true difference in the severity of restenosis in these patients. We have previously discussed the apparent paradox of a lower risk for TLR in smokers (20).

Similar to previous studies of angiographic restenosis (18), despite the inclusion of all clinical, lesion, and procedural variables known to influence restenosis rates, the discriminatory ability of the multivariable model is only fair with a c statistic of 0.68. It is likely that other unmeasured patient-specific variables account for most of this difference. Genetic variations in platelet function (21), angiotensin-converting enzyme activity (22,23), inflammatory response (24,25), or alteration of one or more signal transduction pathways (26) may be among these factors.

Study limitations. There are two important limitations of our study. First, the patients are pooled from several randomized clinical trials and nonrandomized registries rather than a single clinical trial or unselected series. Even though similar inclusion and exclusion criteria existed and results are partially standardized by the use of the same angiographic core laboratory and CEC, we cannot exclude unmeasured differences in the populations or outcomes across these studies. Secondly, because the patients and lesions treated were highly selected as clinical trial participants and with median reference diameter approaching 3.0, the results are not generalizable to the overall population of patients undergoing coronary stenting. Likewise, the analysis is constrained by treatment strategies in effect at the time of these trials and cannot assess the effect of current strategies, such as routine use of glycoprotein IIb/IIIa inhibitors.

Conclusions. In this selected group of patients with generally large vessel size, clinical restenosis, defined as clinically indicated TLR, occurs in approximately 12% of patients by one year after the procedure, more than 70% higher than the rate when assessed at six months. Clinical restenosis occurs in only about one-half of patients with angiographic restenosis and correlates directly with the severity of angiographic renarrowing. Moreover, the clinical, lesion, and procedural correlates of clinical restenosis are similar to those of angiographic restenosis but, as in the models for angiographic restenosis, serve as only fair predictors for individual patients. These results indicate that evaluation of targeted antirestenosis therapies should include at least one-year follow-up for assessment of clinical restenosis. Meanwhile, efforts should be made to optimize modifiable procedural risk factors, while continuing to address other potential risks that may be related to interpatient differences.

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