Interventional Cardiology

Late Loss in Lumen Diameter and Binary Restenosis for Drug-Eluting Stent Comparison

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**Background**—Published rates of coronary restenosis have fallen below 10% in drug-eluting stent trials. Early evaluations of new stents have used continuous end points that are presumed surrogates for restenosis, but the generalizability and power of such end points have not been examined systematically.

**Methods and Results**—We examined the relationship between incremental changes in observed late loss in lumen diameter and the probability of restenosis using reported late loss from 22 published trials of various types of stents (bare-metal, drug-eluting, and small-vessel stents). Next, the power of late loss differences was compared with that of corresponding binary restenosis rates. The relationship between mean late loss and its SD was linear and did not vary with stent type (drug-eluting or bare-metal) or vessel diameter. At all levels of late loss examined (0 to 1 mm), incremental changes were associated with increasing restenosis risk (with an increasing magnitude of effect at higher levels of late loss). The power to detect a treatment effect was greater for late loss than for binary angiographic restenosis (≥32% relative increase in power, ≥24% absolute increase for late loss between 0.2 and 0.6 mm).

**Conclusions**—Late loss is monotonically related to restenosis risk in published stent trials. It is a generalizable and powerful angiographic end point in early or small trials of new drug-eluting stents. *(Circulation. 2005;111:3435-3442.)*

Key Words: angioplasty ■ coronary disease ■ restenosis ■ stents ■ trials

Coronary restenosis after successful stent implantation is measured by a variety of methods that seek to quantify either the magnitude of renarrowing or the incidence of late-term clinical failure. The assessment of coronary restenosis as a renarrowing process is performed ≈6 to 9 months after stenting with the use of quantitative angiographic and intravascular ultrasound metrics such as percent diameter stenosis or percent volume obstruction. The assessment of coronary restenosis as a failure event utilizes dichotomous end points, such as the occurrence of a 50% diameter stenosis or clinically driven repeated target lesion intervention at follow-up, that signify a critical amount of renarrowing associated with resting flow or flow reserve obstruction.

Successful drug-eluting stents have reduced angiographic restenosis rates by ≥75% compared with bare-metal stents, resulting in binary angiographic and clinical restenosis rates of only 5% to 10%. Because low binary event rates result in decreased statistical power in randomized trials, the number of patients needed to make comparisons between new and proven drug-eluting stents has increased substantially. Continuous end points such as follow-up minimum lumen diameter (MLD), percent diameter stenosis, and late loss have been used to test new stent technologies, particularly in early-phase, small–sample size trials, because of their inherent greater statistical power.

Whereas relative measures of restenosis, such as percent diameter stenosis, depend on vessel diameter for their calculation and interpretation, absolute measures of restenosis magnitude can be more easily compared across trials of varying vessel size. Late loss, defined as the difference between immediate postprocedure MLD and MLD 6 to 9 months after percutaneous coronary intervention, is an angiographic measure of the absolute amount of renarrowing. Specifically, it measures the change in MLD of the treated coronary segment due to vascular contraction and neointimal hyperplasia. A general model adjusted for acute gain was developed in 1993 that directly related late loss to the incidence of binary restenosis. For coronary stents, which by design resist vascular contraction and generally achieve a uniform lumen diameter within the stented segment, late loss is an angiographic surrogate for neointimal hyperplasia, the target of drug-eluting stents.

Within the sirolimus-eluting stent trials, mean late loss is correlated with the probability of angiographic and clinical restenosis. We sought to determine (1) whether this correlation between mean late loss and restenosis rates was generalizable to other stent studies and (2) whether the use of late loss as an end point in modest-sized clinical trials would be more powerful than the traditional binary restenosis end points. Specifically, we hypothesized that late loss in drug-eluting stent trials is a monotonic measure of restenosis risk, and we developed a model of late loss for evaluating contemporary drug-eluting stents.
Methods

Literature Selection and Data Evaluation
A comprehensive MEDLINE literature search produced original reports of 22 clinical trials testing drug-eluting or bare-metal stents for the treatment of de novo coronary lesions that included late loss as an end point.5,6,8,14–33 To evaluate the effect of variation in reference vessel diameter across trials, trials of small-vessel stenting were also included. Reports of stenting for total occlusion, ostial or left main lesions, saphenous vein grafts, and in-stent restenosis were excluded.

Definitions

Late loss was defined as the difference between the MLD immediately after the procedure and the MLD at 6- to 8-month follow-up. Percent diameter stenosis was defined as \((1-(\text{MLD/reference vessel diameter})) \times 100\). Binary angiographic restenosis was defined as a >50% diameter stenosis at follow-up. To evaluate the relationship of mean late loss to both binary angiographic restenosis and its standard deviation (SD), the in-stent rather than in-segment (including the 5-mm margins proximal and distal to the stent) late loss was used because in-segment measurement was not available in most studies (Tables 1 and 2).

Statistical Analysis
Baseline clinical and angiographic variables were recorded as mean and SD for continuous variables and percentage for binary variables.

Evaluation of Monotonicity of Relationship Between Mean and SD of Late Loss
We performed regression analysis on the SD of in-stent late loss for each trial with mean late loss as the predictor variable. We tested linear, nonlinear (using polynomial terms), and interaction effects (for drug-eluting versus bare-metal and for small-vessel versus non–small-vessel stenting). A 2-sided \(P\) value \(\leq 0.05\) was considered significant.

Power Transformation for Late Loss Distribution
In drug-eluting stent trials, distributions with low late loss (in which the mean late loss value is a fraction of the SD) require transformation to account for right-skewed data, whereas higher late loss distributions (as in bare-metal stents with mean late loss values \(\sim 1\) mm and relatively smaller SDs) do not require transformation for normality.13 We estimated the power transformation necessary to overcome the magnitude of rightward skew by interpolating the optimum power between those of the drug-eluting and control arms of the SIRIUS trial, anchored at mean late losses of 0.17 and 1.0 mm, respectively.13

Prediction of Binary Restenosis Rate From Mean In-Stent Late Loss
The power transformation model was used to predict the binary angiographic restenosis rate from late loss. Essentially, the transformed mean and SD were used to estimate the probability of exceeding the transformed late loss threshold for binary restenosis by integrating the area under the cumulative distribution function. The predicted probability of restenosis, assuming a given mean MLD and reference diameter, was calculated for varying mean late loss from 0 to 1.0 mm, in 0.1-mm increments.

Power Comparison (Late Loss Versus Binary Angiographic Restenosis)
The powers of the end points late loss and binary angiographic restenosis were compared with the example of a hypothetical trial designed to detect a 35% treatment effect between 2 stents using 200 subjects per arm. In the range of late loss values from 0 to 1.0 mm, power was estimated for a 35% treatment effect on the end point of late loss and compared with the power of the corresponding predicted restenosis rates and treatment effect from the model.

Results

Study Characteristics
Summary statistics for late loss and binary angiographic restenosis rates are listed in Tables 1 and 2 for 22 stent trials.5,6,8,14–33 In-stent late loss was widely reported for all studies of bare-metal stents and ranged from 0.65 to 1.21 mm, whereas in-stent late loss for drug-eluting stents ranged from \(-0.01\) to 0.81 mm. In-segment late loss was rarely reported in the bare-metal stent studies. The range of residual stenosis after stenting was wide (1.7% to 19.8%), with a trend toward low residual stenosis in the recent pivotal drug-eluting stent trials TAXUS IV and SIRIUS (4.2% to 6%\(^{34}\) compared with the early stent studies STRESS and BENESTENT (19% to 22%).16,27 The prevalence of diabetes mellitus varied from 0% to 31%. Mean reference vessel diameter ranged from 2.50 to 3.07 mm for the standard stent studies and from 2.23 to 2.55 mm for the small-vessel studies.

Late Loss Is Positively Correlated With Restenosis Rate
A generalizable correlation across bare-metal stent and drug-eluting stent trials would be required for late loss to serve as a valid surrogate for binary restenosis. Two analyses were performed to establish the nature of this relationship: (1) an analysis of the relationship between observed mean late loss from each trial and the corresponding observed restenosis rates and (2) an analysis of the relationship between the mean late loss and the corresponding SDs.

Late Loss Is Related Monotonically to Binary Restenosis
The relationship between mean in-stent late loss and restenosis rate for all study samples was found to be curvilinear and monotonic (Figure 1), that is, higher mean late losses were associated with higher reported rates of binary angiographic restenosis. Interaction terms for bare-metal versus drug-eluting and small-vessel versus non–small-vessel stenting were nonsignificant, with no apparent heterogeneity of the relationship across these categories.

SD of Late Loss Is Related Monotonically to Its Mean
If the relationship of the mean and SD of late loss does not follow a monotonic relationship, identification of a population with a higher mean but lower SD than an existing reference could occur, creating the theoretical possibility that a higher mean would be associated with a lower restenosis rate. Such a paradoxical situation would make interpretation of mean late loss values complex. In contrast, we found that the relationship between the late loss mean and SD was monotonic across the 22 trials with reported in-stent late loss (Figure 2), suggesting that conditions for such a paradoxical relationship did not exist. Linear regression revealed that the relationship between mean and SD was best described with the following function: \(SD \text{ of late loss} = 0.33 + 0.31 \times \text{mean late loss in millimeters.}\

Comparative Efficiency of Late Loss and Binary Angiographic Restenosis
Power calculations for the restenosis end points late loss and binary angiographic restenosis were compared for a hypothetical stent study of modest sample size (200 subjects per arm). As
generally expected with the comparison of continuous and binary variables measuring similar processes, late loss was consistently found to be a more efficient end point than binary angiographic restenosis across mean late loss, ranging from 0 to 1.0 mm (Figure 3). The largest difference in power between the 2 end points occurred at mean late loss levels of 0.1 to 0.7 mm.

**TABLE 1. Baseline and Procedure Characteristics Across Drug-Eluting and Bare-Metal Stent Trials**

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>First Author</th>
<th>Stent</th>
<th>Mean Vessel Diameter, mm</th>
<th>MLD After Stent, mm</th>
<th>Mean Residual Stenosis, %</th>
<th>Diabetes Prevalence, %</th>
<th>Mean Lesion Length, mm</th>
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</thead>
<tbody>
<tr>
<td>ASCENT</td>
<td>Baim</td>
<td>Palmaz-Schatz Multi-Link</td>
<td>2.95</td>
<td>...</td>
<td>10</td>
<td>20</td>
<td>11</td>
</tr>
<tr>
<td>BENESTENT</td>
<td>Serrys</td>
<td>Palmaz-Schatz</td>
<td>2.99</td>
<td>...</td>
<td>22</td>
<td>7</td>
<td>7.1</td>
</tr>
<tr>
<td>BENESTENT II</td>
<td>Serrys</td>
<td>Palmaz-Schatz (heparin-coated)</td>
<td>2.96</td>
<td>...</td>
<td>16</td>
<td>13</td>
<td>8.2</td>
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<tr>
<td>C-SIRIUS*</td>
<td>Schampaert</td>
<td>Bx Velocity Cypher (sirolimus-eluting)</td>
<td>2.62</td>
<td>2.5</td>
<td>5.2</td>
<td>24</td>
<td>12.6</td>
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<tr>
<td>DELIVER</td>
<td>Lansky</td>
<td>RX ML Penta RC ACHIEVE (paclitaxel-eluting)</td>
<td>2.77</td>
<td>2.82</td>
<td>19.8</td>
<td>27</td>
<td>11.1</td>
</tr>
<tr>
<td>ELUTES*</td>
<td>Gershlick</td>
<td>V-Flex Plus V-Flex Plus (paclitaxel-eluting 0.2 μg/mm²)</td>
<td>3.03</td>
<td>2.78</td>
<td>9.6</td>
<td>22</td>
<td>11.3</td>
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<td>V-Flex Plus (paclitaxel-eluting 0.7 μg/mm²)</td>
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<td>2.63</td>
<td>10.6</td>
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<tr>
<td></td>
<td></td>
<td>V-Flex Plus (paclitaxel-eluting 1.4 μg/mm²)</td>
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<td>2.72</td>
<td>8.1</td>
<td>21</td>
<td>10.2</td>
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<tr>
<td></td>
<td></td>
<td>V-Flex Plus (paclitaxel-eluting 2.7 μg/mm²)</td>
<td>2.95</td>
<td>2.66</td>
<td>10.1</td>
<td>11</td>
<td>11.1</td>
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<td>Schofer</td>
<td>Bx Velocity Cypher (sirolimus-eluting)</td>
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<td>FUTURE I*</td>
<td>Grube</td>
<td>S-Stent S-Stent (everolimus-eluting)</td>
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<td>3.07</td>
<td>1.8</td>
<td>4</td>
<td>9.2</td>
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<td>Lansky</td>
<td>GR-II Palmaz-Schatz</td>
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<td>...</td>
<td>15.6</td>
<td>23</td>
<td>14.3</td>
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<tr>
<td>ISAR STEREO</td>
<td>Kastrati</td>
<td>ACS RX Multi-Link Duet ACS RX Multi-Link</td>
<td>3.1</td>
<td>...</td>
<td>2.7</td>
<td>17</td>
<td>13.9</td>
</tr>
<tr>
<td>NIRVANA</td>
<td>Baim</td>
<td>NIR Palmaz-Schatz</td>
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<td>7</td>
<td>23</td>
<td>13.3</td>
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<td>Morice</td>
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<td>SIRIUS</td>
<td>Moses</td>
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<td>Fischman</td>
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<td>13.3</td>
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<tr>
<td>TAXUS II</td>
<td>Colombo</td>
<td>NIR TAXUS (paclitaxel-eluting, slow release)</td>
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<td>2.58</td>
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<td>10.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NIR TAXUS (paclitaxel-eluting, moderate release)</td>
<td>2.73</td>
<td>2.52</td>
<td>12</td>
<td>14</td>
<td>10.7</td>
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<td>TAXUS IV</td>
<td>Stone</td>
<td>Express TAXUS (paclitaxel-eluting)</td>
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<td>2.67</td>
<td>4.9</td>
<td>25</td>
<td>13.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TAXUS (paclitaxel-eluting)</td>
<td>2.75</td>
<td>2.66</td>
<td>4.2</td>
<td>23</td>
<td>13.4</td>
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<td>VISION</td>
<td>Kereiakes</td>
<td>Multi-Link Vision</td>
<td>2.92</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>10.6</td>
</tr>
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<td>Small-vessel trials</td>
<td>Park</td>
<td>Multi-Link</td>
<td>2.55</td>
<td>2.44</td>
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<td>13.1</td>
<td>...</td>
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<td>ISAR-SMART</td>
<td>Kastrati</td>
<td>Multi-Link</td>
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<td>2.35</td>
<td>7</td>
<td>25</td>
<td>12.5</td>
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<td>Koning</td>
<td>beStent Small</td>
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<td>2.06</td>
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<td>SISCA</td>
<td>Doucet</td>
<td>beStent Artist</td>
<td>2.5</td>
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<td>12.4</td>
<td>17.8</td>
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<tr>
<td></td>
<td>Moer</td>
<td>beStent (heparin-coated)</td>
<td>2.44</td>
<td>2.22</td>
<td>11.3</td>
<td>12.2</td>
<td>...</td>
</tr>
</tbody>
</table>

*Trials with <50 subjects per arm.

Relationship of Late Loss to Binary Restenosis Rate

Using the relationship between the mean in-stent late loss and its SD defined above, one can predict the SD for a given hypothetical mean. We previously described a statistical method to overcome the greater degree of right skew in the late loss distribution at lower means by using a power
transformation varying with the mean late loss. Combination of these 2 methods yields a model to predict binary angiographic restenosis rates from late loss for a study population of any given reference vessel diameter and residual stenosis (Table 3). This model describes a monotonic and curvilinear relationship between mean late loss and restenosis rate (Figure 4). The expected incremental restenosis rate between 2 mean late losses of 0.2 and 0.4 mm is 3.1%, whereas the incremental restenosis rate between 2 mean late losses of 0.4 and 0.6 mm is 6.4% in a reference population.
with mean reference vessel diameter of 2.79 mm and residual stenosis of 6% (Table 3).

**Discussion**

The success of drug-eluting stents has changed expectations of coronary stent performance. Standard clinical binary end points have become difficult to use as the only measures of restenosis in the clinical studies necessary for the evaluation of new drug-eluting stents. Binary angiographic restenosis and clinical revascularization of the target lesion or vessel now occur too infrequently to provide stable estimates for either single-arm studies or adequate contrast of restenosis rates between competing drug-eluting stent systems for randomized trials. Small- to moderate-sized trials of new drug-stent combinations or new drug-dose formulations cannot be performed with efficiency with the use of traditional binary outcomes that require a minimum of 1000 evaluable patients per arm to enclose a restenosis rate of 6% within a 3% 95% CI. To prevent unnecessary exposure to ineffective therapies, a need for more powerful end points of restenosis has emerged.

We sought to evaluate the generalizability and power of the angiographic end point late loss as a summary statistic for study samples. We demonstrated that across the published stent trials, a strong positive association exists between the mean in-stent late loss estimates and binary angiographic restenosis rates. Specifically, over the range of trials observing late loss from 0 to 1.3 mm, higher sample mean late losses were associated with higher sample restenosis rates. Consequently, the conditions for a paradoxical result in which an increasing increment of late loss might correspond to a decreasing increment of binary restenosis risk did not exist.

Further statistical support for this positive monotonic (non-decreasing) correlation was the association of late loss sample mean and SD. The theoretical possibility that an increasing per arm to enclose a restenosis rate of 6% within a 3% 95% CI. To prevent unnecessary exposure to ineffective therapies, a need for more powerful end points of restenosis has emerged.

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**TABLE 3. Prediction of Binary Angiographic Restenosis Rate From Mean In-Stent Late Loss**

<table>
<thead>
<tr>
<th>Mean Late Loss, mm</th>
<th>Predicted SD, mm</th>
<th>BAR (Normal)</th>
<th>Optimum Power</th>
<th>BAR (Transformed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.33</td>
<td>0.0</td>
<td>0.0</td>
<td>0.4</td>
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<tr>
<td>0.1</td>
<td>0.36</td>
<td>0.1</td>
<td>0.1</td>
<td>0.8</td>
</tr>
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<td>0.2</td>
<td>0.39</td>
<td>0.3</td>
<td>0.2</td>
<td>1.5</td>
</tr>
<tr>
<td>0.3</td>
<td>0.42</td>
<td>1.0</td>
<td>0.3</td>
<td>2.7</td>
</tr>
<tr>
<td>0.4</td>
<td>0.45</td>
<td>2.6</td>
<td>0.4</td>
<td>4.6</td>
</tr>
<tr>
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<td>0.48</td>
<td>5.4</td>
<td>0.5</td>
<td>7.3</td>
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<tr>
<td>0.6</td>
<td>0.51</td>
<td>9.4</td>
<td>0.6</td>
<td>11.0</td>
</tr>
<tr>
<td>0.7</td>
<td>0.55</td>
<td>14.6</td>
<td>0.7</td>
<td>15.6</td>
</tr>
<tr>
<td>0.8</td>
<td>0.58</td>
<td>20.5</td>
<td>0.8</td>
<td>21.0</td>
</tr>
<tr>
<td>0.9</td>
<td>0.61</td>
<td>26.9</td>
<td>0.9</td>
<td>27.0</td>
</tr>
<tr>
<td>1</td>
<td>0.64</td>
<td>33.3</td>
<td>1.0</td>
<td>33.3</td>
</tr>
</tbody>
</table>

BAR indicates binary angiographic restenosis. Predicted SD is based on regression ($SD=0.33+0.31 \times$late loss); predicted restenosis rate is based on normality of power-transformed late loss and delta method approximation of variance. In this example mean reference vessel diameter was assumed to be 2.79 mm, and mean poststent MLD was assumed to be 2.67 mm.
increment of mean late loss could correspond to a decreasing increment of SD, and thus paradoxically lower restenosis risk, was also not demonstrated in the empirical observations of trials reporting late loss to date.

The utility of late loss as a measure of restenosis in clinical trials is supported by the following observations. First, if a uniform stent diameter at deployment is assumed, late loss is a consistent measure of the magnitude of the renarrowing process. Although it is estimated from 2 angiograms, usually separated over a 6- to 9-month period, the estimates have shown a consistency of correlation between its value and restenosis rate (Figure 1). Because the renarrowing process within a stent is due solely to the hyperplastic component, with no contribution from the vascular contraction component seen in nonstent procedures, late loss is an intuitive measure of neointimal hyperplasia, the pathological target of drug-eluting stents.11

Second, late loss is a powerful measure of binary restenosis proclivity. The predictable monotonic relationship of late loss to restenosis allows estimation of restenosis probability in a given study population with known reference vessel diameter and poststent MLD. Observed results (Figure 1) and our model (Figure 4) both show substantial increased risk of binary angiographic restenosis when observed mean late loss increases over the range of 0.1- to 0.7-mm mean in-stent late loss. This generalized model of late loss is not a regression of late loss on binary restenosis but rather an empirical model relating mean values of late loss to their predictable distributions. Thus, the curvilinear predictive model, based on expected late loss probability densities, is similar in shape to the observed data.

Additionally, when late loss is expected to range from 0.1 to 0.7 mm, as in trials designed to compare new drug-eluting stents, late loss has greater power than binary angiographic restenosis to discriminate restenosis tendency for moderate-sized (≈200 subjects) trials (Figure 3) and even more so for smaller sample sizes. Although larger pivotal trials (of ≥1500 subjects) would be required to power dichotomous end points such as target vessel failure, the confidence bounds of the late loss estimate are narrower than those of the binary angiographic restenosis end points at any sample size.

If there is substantial tapering of a vessel over the length of the analysis segment, then the true magnitude of neointimal hyperplasia may be underestimated by late loss. This is a particular problem for the “in-segment” measurement of late loss in which subtraction of the MLD obtained from the 5-mm “step-up” and “step-down” shoulders may systematically underestimate the amount of neointimal hyperplasia compared with the in-stent measurement. If there were significant poststent variability of MLD along the length of the stent, then the same limitation would be true for the in-stent measurement. In the present stenting trials with an average residual stenosis of 5%, however, the residual diameter is relatively uniform throughout the stent (ie, with little tapering of the stent itself); therefore, most variability in the in-stent late loss measurement is created by variations in the MLD at late follow-up, not after the procedure.

**Late Loss and Clinical Trials of Drug-Eluting Stents**

New drug-eluting stents are best evaluated by execution of 1 or 2 large “pivotal” randomized trials in which comparison is made to an accepted standard. Pivotal trials seek to estimate efficacy (freedom from restenosis) and detect important rare serious adverse events, such as coronary thrombosis or aneurysm formation. End points that combine safety and efficacy measures, such as target vessel failure or major adverse cardiac events (both of which include death, myocardial infarction, and clinically driven repeated coronary revascularization), have been deemed to be the most inclusive and remain important for pivotal stent trials. Large sample sizes (generally >1000 to 2000 subjects) are required for contrasting target vessel failure rates between the competing randomized arms, expected to range from 5% to 15%. In smaller pilot, nonpivotal, or follow-up trials, these end points lose power. The strong positive correlation and generalized monotonic relationship between late loss and restenosis, combined with its high statistical power, make late loss an attractive end point for nonpivotal drug-eluting stent trials.

We have estimated that even small differences in mean in-stent late loss can translate to important differences in binary restenosis (Table 3, Figure 4). Small differences in clinical restenosis are important for several reasons. First, cost-effectiveness analysis suggests that small differences in restenosis rates can translate to meaningful differences in cost.33 Second, the small differences in restenosis risk seen in pivotal study populations are likely amplified in practice, where the magnitude of clinical benefit is expected to increase with the risk profile of the target patient population.34,35 Regardless of the actual (and currently unknown) threshold of late loss difference that is clinically relevant, increasing values of late loss are associated with increasing risk of binary restenosis. These findings support the notion that late loss performance can reliably predict the restenosis propensity for new drug-eluting stents.
Limitations
We chose binary angiographic restenosis as the outcome variable used to validate late loss. Our choice of angiographic binary restenosis was based on the wide availability of this standard variable in the literature and the lack of a consistently reported clinical restenosis end point. Although the 50% diameter stenosis cutoff definition of binary angiographic restenosis may not define all patients with physiological coronary flow obstruction, it is a robust measure of clinical restenosis, with high correlation between binary angiographic restenosis and target lesion or target vessel revascularization. Finally, the end point percent diameter stenosis is an excellent measure of the final follow-up result in a given patient. However, percent diameter stenosis has a wide range (eg, 15% to 35% for percent diameter stenosis versus 0 to 1.0 for late loss), and its calculation and interpretation are dependent on reference vessel size, making its use in nonrandomized comparisons more problematic than that of late loss.

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References


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