Relationship of Late Loss in Lumen Diameter to Coronary Restenosis in Sirolimus-Eluting Stents

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Background—Observed rates of restenosis after drug-eluting stenting are low (<10%). Identification of a reliable and powerful angiographic end point will be useful in future trials.

Methods and Results—Late loss (postprocedural minimum lumen diameter minus 8-month minimum lumen diameter) was measured in the angiographic cohorts of the SIRIUS (n=703) and E-SIRIUS (n=308) trials. Two techniques, the standard normal approximation and an optimized power transformation, were used to predict binary angiographic restenosis rates and compare them with observed restenosis rates. The mean in-stent late loss observed in the SIRIUS trial was 0.17±0.45 mm (sirolimus) versus 1.00±0.70 mm (control). If a normal distribution was assumed, late loss accurately estimated in-stent binary angiographic restenosis for the control arm (predicted 35.4% versus observed 35.4%) but underestimated it in the sirolimus arm (predicted 0.6% versus observed 3.2%). Power transformation improved the reliability of the estimate in the sirolimus arm (predicted 3.2% [CI 1.0% to 6.7%]) with similar improvements in the E-SIRIUS trial (predicted 4.0% [CI 1.2% to 7.0%] versus observed 3.9%). In the sirolimus-eluting stent arm, in-stent late loss correlated better with target-lesion revascularization than in-segment late loss (c-statistic=0.915 versus 0.665).

Conclusions—Because distributions of late loss with a low mean are right-skewed, the use of a transformation improves the accuracy of predicting low binary restenosis rates. Late loss is monotonically correlated with the probability of restenosis and yields a more efficient estimate of the restenosis process in the era of lower binary restenosis rates.

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Key Words: angioplasty ■ stents ■ restenosis
restenosis metrics as discriminators between competing DES therapies is necessary, especially for underpowered pilot (50 to 150 subjects) and pivotal (≈1000 subjects) trials. The traditional angiographic variables, late MLD and percent diameter stenosis, are powerful continuous measures, but late loss (postprocedural MLD minus 8-month MLD) has the unique ability to distinguish the magnitude of late intimal renarrowing from baseline and procedural variables (reference vessel diameter and residual stenosis). We sought to evaluate the reliability of late loss in providing a monotonic (nondecreasing) metric of antirestenosis effect and its ability to predict relative measures of restenosis in the DES era.

Methods

Study Population
Primary data were analyzed from the SIRIUS (Sirolimus-Eluting Bx VELOCITY Balloon-Expandable Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesions) and E-SIRIUS (European Sirolimus-Eluting Bx VELOCITY Balloon-Expandable Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesions) randomized trials.10,19 The SIRIUS trial was a 1101-patient, multicenter, randomized, double-blind evaluation of the sirolimus-eluting Bx Velocity stent compared with the standard Bx Velocity stent. Patients with a de novo coronary artery stenosis 15 to 30 mm in length in a 2.5- to 3.5-mm diameter vessel were eligible. E-SIRIUS was a 353-patient, multicenter, randomized trial of the same active and control stent arms, performed in Europe. Patients with a de novo coronary artery stenosis 15 to 32 mm in length in a 2.5- to 3.0-mm diameter vessel were eligible. Other clinical inclusion and exclusion criteria were similar to the SIRIUS trial. All investigational sites received approval from their local hospital institutional review boards.

The first 850 patient observations from the SIRIUS trial, the 8-month angiographic follow-up cohort, were used to develop the late-loss models (prediction cohort; complete follow-up in 703 patients). The 353-patient E-SIRIUS trial required 8-month follow-up in all subjects (completed in 308 subjects) and was used as the test cohort for the late-loss models generated from the SIRIUS study. Further predictions of relative restenosis based on late-loss estimates were made for the TAXUS (TAXUS Express Paclitaxel-Eluting Stent for Treatment of De Novo Lesions) IV trial.11

Angiographic Analysis
Standard image acquisition was performed at the clinical sites as described previously.10,19 Cineangiograms for both trials were forwarded to the Brigham and Women’s Hospital Angiographic Core Laboratory for review by observers blinded to the treatment assignment. All procedural and follow-up angiograms were reviewed with standard morphological criteria.20–22 Quantitative angiographic analysis was performed with a validated automated edge-detection algorithm (Medis CMS). A 5-mm segment of reference diameter proximal and distal to the stenosis was used to calculate the average reference vessel diameter. MLDs were measured within the stent (in-stent analysis) and within the segment including 5 mm proximal and distal to the stent margins (in-segment analysis).23

Definitions
Late loss was defined as the MLD immediately after the procedure minus the MLD at 8-month follow-up. Percent diameter stenosis was defined as $1 - (\text{MLD/reference vessel diameter}) \times 100$. BAR was defined as a $>50\%$ diameter stenosis at follow-up. Lesion length was defined as the axial extent of the lesion that contained a shoulder-to-shoulder lumen reduction by $\geq 20\%$. TLR was defined as clinically driven revascularization of the target lesion by 9 months of follow-up and was adjudicated by an independent Clinical Events Committee.

Statistical Analysis
Ordinal variables are expressed as frequencies, and continuous variables are expressed as mean±SD. Binary variables were compared with $\chi^2$ analysis, and continuous variables were evaluated with the Student’s $t$ test. A 2-sided probability value $\leq 0.05$ was considered significant. Statistical analyses were performed in SAS (version 8.2) unless otherwise noted.

Prediction of Angiographic Restenosis Rate From Late Loss

The normality of the distributions of late loss (in-stent and in-segment) were tested in each arm (active and control) of the SIRIUS trial with the Kolmogorov-Smirnov test. The fit of other parametric distributions (Gamma, Weibull) and the following transformations of late loss were examined systematically: log, square root, log normal, log-logistic, and power. The power-transformation procedure was the most flexible in transforming the late-loss distribution. The BOXCOX procedure (STATA) was used to screen the fit of the power transformation, then the optimum power (ranging from 0 to 1) was selected to predict the BAR rate observed in each arm of the SIRIUS trial (prediction cohort). The new transformed mean and SD were computed to correct for the rightward skew of the data (see online-only Data Supplement Appendix).

Predicted BAR rates were computed for the standard (normal assumption with the expected value of late loss required to result in a $>50\%$ diameter stenosis) and transformed models and compared with the observed BAR rates for SIRIUS and E-SIRIUS (the test cohort) trials. Confidence intervals (2-sided, 95%) were obtained by simulating 1000 bootstrap samples.24 Percent error was defined as 100 times the difference between the observed rate and the predicted rate divided by the observed rate. Finally, we applied a simple interpolation of the published in-stent late-loss result in the active arm of the TAXUS IV trial10 between the active and control arms of the SIRIUS trial to yield a power-transformation value for TAXUS IV.

Correlation of Late Loss With Clinical Restenosis
The ability of late loss to predict clinical restenosis in the SIRIUS trial was examined with logistic regression models of TLR as the outcome variable and either in-stent or in-segment late loss as the dependent variable. The c-statistic was measured and compared for each (1.0 signifying perfect accuracy).

Results

Lesion Characteristics
The angiographic characteristics of the lesions are listed in Table 1, which demonstrates highly significant ($P<0.001$) differences in late loss between the randomized arms for the SIRIUS and E-SIRIUS trials for both in-segment and in-stent late-loss measurements. The control-arm in-segment late-loss means (0.81 mm SIRIUS, 0.80 mm E-SIRIUS) were lower than the in-stent late-loss means (1.00 and 1.05 mm, respectively). The active-arm in-segment late-loss mean was higher than the in-stent mean for the SIRIUS trial (0.24 versus 0.17 mm) but similar in the E-SIRIUS trial (0.19 versus 0.20 mm).

Late Loss Is Not Normally Distributed
The distribution of both in-stent and in-segment late loss was not normal for either arm of the trial (in-segment late loss: $P<0.01$ sirolimus, $P<0.01$ control; in-stent late loss: $P<0.01$ sirolimus, $P=0.047$ control), and the magnitude of right skewness (from a normal distribution where skew=0) was greatest in the sirolimus arm (in-segment late-loss skewness: 0.89 sirolimus, 0.43 control, in-stent: 1.23 sirolimus, 0.32 control; Figures 1 and 2).
Power transformation of in-stent late loss is the optimum method to predict BAR rates from mean late loss.

Compared with other transformations and nonnormal distributions, the 0.13 power transformation, ie, (late loss)0.13, was the optimum for restoring normality of the right tail of in-segment late loss in the active arm, and the 0.52 power transformation, ie, (late loss)0.52, was the optimum for the control arm. For in-stent late loss, the optimum powers were 0.13 for the active arm and 0.99 for the control arm. The in-segment and in-stent late-loss power transformations were then applied to predict BAR rates. The transformed and nontransformed predictions for both SIRIUS (prediction set) and E-SIRIUS (test set) were compared with the observed rates (Table 2).

Predictions based on the normal assumption underestimated restenosis rates in the active arms of SIRIUS and E-SIRIUS trials because of the lack of compensation for right-skewed late-loss distributions. For the SIRIUS trial, the active arm in-stent binary restenosis rate was underestimated by 81% (0.6% predicted rate compared with 3.2% observed rate), and the active in-segment binary restenosis rate was underestimated by 38% (5.5% predicted rate compared with 8.9% observed rate). Similarly, in the test cohort (E-SIRIUS), the transformed active-arm predictions matched better with the observed rates (Table 2). Transformed in-stent late loss was the most predictive of the E-SIRIUS observed BAR rates compared with in-segment transformed late loss and both in-stent and in-segment nontransformed late loss.

In-Stent Late Loss Is Correlated With TLR

We compared predictive models of TLR using in-stent and in-segment late loss. In the active arm, in-stent late loss was a more reliable predictor of TLR (c-statistic 0.915, versus 0.665 for in-segment), whereas TLR from the control arm was similarly predicted from in-stent or in-segment late loss (c-statistic 0.897 versus 0.916, respectively).

Predicting Restenosis Rates for Other DES Systems With In-Stent Late Loss

The optimum transformation power for prediction of BAR from late loss depends on the mean late loss, which varied from 0.13 mm in the active SIRIUS arm to 0.99 mm in the control arm. Interpolation of an in-stent late loss of 0.39 mm observed in the active arm of the TAXUS IV trial11 yielded a power-transformation parameter of 0.36. The published mean reference vessel diameter of 2.75 mm and postprocedural MLD of 2.66 mm in-stent were then used to predict the in-stent BAR rate. With the in-stent late-loss normal approximation (standard method), the predicted in-stent BAR was 3.7%, an underestimate of 39% compared with the observed in-stent BAR rate of 5.5%. The in-stent late-loss transforma-
tion approximation, on the other hand, predicted an in-stent BAR rate of 6.1%, an overestimate of only 10% (Figure 3).

Discussion
Percutaneous coronary therapies have generally been compared on the basis of their restenosis propensities.25 BAR rates and TLR rates ranging between 15% and 25% for stents and between 20% and 40% for other angioplasty devices5–8 allowed detection of modest differences in restenosis rates in clinical trials of fewer than 1000 subjects.26,27

The evaluation of restenosis in the DES era is more complex. In the SIRIUS and TAXUS experience, binary angiographic and clinical restenosis rates are below 10%,10,11 which makes comparison of competing DES treatments more difficult with sample sizes below 1000 subjects.26,27

The evaluation of restenosis in the DES era is more complex. In the SIRIUS and TAXUS experience, binary angiographic and clinical restenosis rates are below 10%,10,11 which makes comparisons between competing DES treatments more difficult with sample sizes below 1000 subjects. Moreover, the initial evaluation of future candidate DES will likely rely on smaller dose-finding studies of fewer than 100 subjects per test group, in which the infrequent binary restenosis end points will be too insensitive to be effective discriminators.

In the present study, we have evaluated late loss as a potential gauge of restenosis in the DES era. First, in the DES era, in which mean late loss is often a fraction of its SD, right skewness can be overcome with power transformation to allow accurate approximation of BAR rates. Second, late loss is correlated with restenosis: The models in the present study show a monotonic (nondecreasing) relationship between higher late loss and higher restenosis rates in the 2 SIRIUS trials studied, as well as the indirect prediction of the TAXUS IV restenosis rate. Third, in-stent late loss showed a better correlation with TLR than in-segment late loss for the DESs studied. With these robust features, in-stent late loss is a sensitive indicator of restenosis propensity.

Late loss was initially developed as a tool to compare the mechanisms of restenosis between different coronary interventions such as balloon angioplasty, stenting, and atherectomy.26 Within stents, late loss is an absolute measure of neointimal re-narrowing, with vascular contraction being prevented by the stent framework.29,30 In-stent neointimal re-narrowing, however, is still only 1 factor that determines the probability of restenosis, which is also influenced by the vessel diameter. Commonly reported measures of relative restenosis include percent diameter stenosis and BAR rates. In the pre-DES era, among coronary devices, stents had the lowest relative restenosis but, paradoxically, also had the highest late loss.25

As a result, comparisons of different mechanical percutaneous interventions (angioplasty, stents, atherectomy) relied on relative measures of restenosis. In the case of similar mechanical interventions, however, such as stents with similar acute gains, the need for relative adjustments is reduced, and late loss may be a valuable tool to gauge antirestenosis effect.

Late Loss and Its Skewed Distribution for DESs
With bare metal stenting, late loss has been observed to follow a near-normal distribution.1,31 Bare metal stent trials and registries have demonstrated mean late losses varying from 0.6 to 1.2 mm.5,6,26,27,32–35 The RAVEL trial of the sirolimus-eluting Bx Velocity stent was the first randomized trial to report a stent with an average late loss well below the expected historical range, as well as its own control arm (in-stent late loss \( \leq 0.01 \) mm active versus 0.80 mm control), which corresponded to a BAR rate of 0% for the active arm versus 26% in the control arm.36

As the positive mean of any normal distribution is reduced enough so that its spread becomes significantly bounded by zero, it becomes right-skewed. The distribution of late loss for bare metal stents is only marginally skewed by zero. In contrast, the mean late loss has ranged between \( \leq \) 0.01 and 0.24 mm, the late-loss distributions studied are markedly deviated from normal and skewed to the right. In such skewed distributions, the variance, as estimated from the sample SD, no longer accurately denotes the deviation from the mean. If the calculated SD is used to predict binary event rates in this right tail, the predicted binary rates will be underestimated (Figure 4). To accurately study the behavior of such a distribution, either transformation or selection of a distribution that more closely resembles the skewed data becomes necessary rather than reliance on traditional normal methods. The power transformation used in the present study restored a more predictable normal distribution and demonstrated a monotonic relationship between late loss and restenosis.

In-Stent Versus In-Segment Late Loss
Whereas in-stent measurements of follow-up MLD have been relied on for the evaluation of virtually all bare metal stents to...
The observation of an exuberant renarrowing at the margins of stents, despite a therapeutic effect within the stent observed in early brachytherapy trials and some pilot DES trials, termed “edge effect” or “candy-wrapper restenosis,” led to inclusion of the zones proximal and distal to the stent for analysis. When the binary variable angiographic restenosis is used, the more inclusive in-segment analysis has the attractive ability to capture events that occur only at the edges, whereas the in-stent analysis does not.

In the present examination of late loss, we also sought to determine whether the in-stent or in-segment analysis was more reliable. We found that for the control arm, in-stent and in-segment analyses were essentially equivalent, with similar c-statistics for predicting TLR. However, in the sirolimus-eluting stent arm, in-stent late loss was much better correlated with TLR than was in-segment late loss.

Ideally, an angiographic measure of neointimal renarrowing would represent the magnitude of maximum change in lumen diameter from the time of stenting to the follow up angiogram across the treatment site and margins. Such a measurement would require a comparison across the 2 time points slice by slice along the length of the vessel, within matched, fine (~1 mm) increments. Practically, however, standard techniques of measuring late loss have compared MLDs from a specified zone. The in-stent late-loss calculation compares MLDs both from within the stented zone. The in-segment late-loss calculation compares the minimum of the proximal, distal, and stent zone diameters (in-segment MLD) after stenting and at late follow-up, rather than the maximum late loss from these zones. Thus, the in-segment calculation has the possibility of comparing different regions rather than representing the maximum late loss from among the zones evaluated. Because the greatest acute gain and late loss are usually within the stented zone, the in-segment postprocedural MLD will tend to be measured outside of the stented zone and the follow-up MLD within the stented zone, such that in-segment late loss will necessarily underestimate the maximum late loss (within the stent). In the absence of an edge effect, it is not surprising that the in-stent late-loss measurement best reflects the likelihood of clinical restenosis. The difference in c-statistics for in-stent compared with in-segment late loss reflects the better correlation of in-stent late loss with the probability of TLR when sirolimus-eluting stents are used.

Other Continuous Absolute and Relative Angiographic End Points
Two other angiographic variables should be considered as alternatives: an absolute measure of restenosis, late MLD, and a relative measure of restenosis, late percent diameter stenosis. Whereas percent diameter stenosis is directly linked to the likelihood of target-vessel revascularization in a given patient, late loss isolates the neointimal hyperplasia component of the restenosis process for a given DES.

Clinical Implications for In-Stent Late Loss
Proper binary restenosis rate estimation from late loss requires mathematical transformation of the data, because traditional extrapolation will diminish the actual differences in binary restenosis rates for any 2 comparable values of late loss. This underestimation error is most pronounced at low restenosis rates where current DES clinical trials range. This

<table>
<thead>
<tr>
<th>TABLE 2. Prediction of BAR</th>
<th>Observed Late Loss, mm</th>
<th>Observed BAR, %</th>
<th>Predicted BAR, %, Normal Assumption (95% CI)</th>
<th>Predicted BAR, %, Power-Transformed Method (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-segment BAR from in-segment late loss</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SIRIUS</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Control</td>
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<td>0.67</td>
<td>36.3</td>
<td>39.3 (35.1–43.9)</td>
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<td>Sirolimus</td>
<td>0.24</td>
<td>0.47</td>
<td>8.9</td>
<td>5.5 (3.0–8.0)</td>
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<td>E-SIRIUS</td>
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<tr>
<td>Control</td>
<td>0.80</td>
<td>0.57</td>
<td>42.3</td>
<td>47.7 (41.2–53.6)</td>
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<tr>
<td>Sirolimus</td>
<td>0.19</td>
<td>0.38</td>
<td>5.9</td>
<td>4.8 (1.4–10.5)</td>
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<tr>
<td>In-stent BAR from in-stent late loss</td>
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<tr>
<td>SIRIUS</td>
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</tr>
<tr>
<td>Control</td>
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<td>0.70</td>
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<td>35.4 (30.9–39.5)</td>
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<td>Sirolimus</td>
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<td>3.2</td>
<td>0.6 (0.15–1.6)</td>
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</tr>
<tr>
<td>Control</td>
<td>1.05</td>
<td>0.61</td>
<td>41.7</td>
<td>45.8 (39.7–51.3)</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>0.20</td>
<td>0.38</td>
<td>3.9</td>
<td>1.2 (0.05–4.3)</td>
</tr>
</tbody>
</table>

Note that power-transformation methods were developed on the basis of the SIRIUS trial results (prediction cohort) and tested in the E-SIRIUS trial (test cohort).
The method of transformation will require future validation as additional DES studies are published. Although higher late-loss values correlate positively with higher restenosis rates, to what extent small differences in late loss are clinically meaningful between comparative DES systems may be more difficult to answer. These small differences may have the most important effects in high-restenosis-risk groups.

**Study Limitations**

Although vessel diameter may have a smaller effect on late loss than on relative measures of restenosis, such as other restenosis end points, late loss is best used to compare stents between groups that have similar acute gain, lesion lengths, and diabetes prevalence, as in a randomized, controlled trial. Finally, although in-stent late loss was most reliable for prediction of angiographic and clinical restenosis in sirolimus-eluting stents, analysis of the proximal and distal zones is still mandatory to detect edge effects when new DESs are studied.

**Conclusions**

Late loss is a robust end point that may be used in future trials to discriminate between new DESs for which binary rates are anticipated to be low. An angiographic surrogate for neo-intimal hyperplasia, in-stent late loss is positively correlated with other measures of relative restenosis and clinical restenosis and may be useful, particularly in early trials in which sample size is limited.

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**Figure 3.** Comparison of observed BAR rates with predicted rates from in-stent late loss using either normal method or power-transformed method across several published DES trials. When BAR rates $\leq 0.10$% are observed in DES arms, normal method underestimates restenosis rates, and power-transformed method is closer to observed rates. Symbol - represents observed rate of BAR, and straight lines represent 95% CIs for this rate. Symbols * and # represent predicted rates from power-transformed and normal methods, respectively.

**Figure 4.** Density function of late loss. Assumed normal distribution (A) vs right-skewed distribution (B). By calculating late loss over which $\geq 50\%$ diameter stenosis would be present [late-loss threshold $= 0.5(RVD) - RVD$ (postprocedural MLD)], where RVD indicates reference vessel diameter, rate of BAR may be estimated from mean late loss (BAR = area under curve A or B beyond threshold). When mean late loss is small or BAR rates are low ($\leq 10\%$), estimation with normal distribution assumption underestimates rate of binary restenosis compared with modeling that takes right-skewed distribution of late loss into account.

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