Robustness of Late Lumen Loss in Discriminating Drug-Eluting Stents Across Variable Observational and Randomized Trials

Laura Mauri, MD, MSc; E. John Orav, PhD; Susana C. Candia, BSc; Donald E. Cutlip, MD; Richard E. Kuntz, MD, MSc

Background—Binary angiographic and clinical restenosis rates can vary widely between clinical studies, even for the same stent, influenced heavily by case-mix covariates that differ among observational and randomized trials intended to assess a given stent system. We hypothesized that mean in-stent late loss might be a more stable estimator of restenosis propensity across such studies.

Methods and Results—In 46 trials of drug-eluting and bare-metal stenting, increasing mean late loss was associated with higher target lesion revascularization (TLR) rates (P<0.001). When the class of bare-metal stents was compared with the class of effective drug-eluting stents, late loss was more discriminating than TLR as measured by the high intraclass correlation coefficient (ρ) (late loss, ρ=0.71 versus TLR, ρ=0.22; 95% CI of difference=0.33, 0.65). When the individual drug-eluting stents and bare-metal stents were compared, late loss was a better discriminator than TLR (0.68 versus 0.19; 95% CI of difference=0.24, 0.60). Greater adjustments of study covariates are needed to stabilize assessments of TLR compared with late loss because of greater influence of reference vessel diameter on TLR than on in-stent late loss. Optimization of late loss with the use of a novel method of standardization according to diabetes prevalence and mean lesion length resulted in minor adjustments in late loss (<0.08 mm for 90% of reported trials) and an ordered array of mean late loss values for the stent systems studied.

Conclusions—Late loss is more reliable than restenosis rates for discriminating restenosis propensity between new drug-eluting stent platforms across studies and might be the optimum end point for evaluating drug-eluting stents in early, nonrandomized studies. (Circulation. 2005;112:2833-2839.)

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

Rates of restenosis after stenting of coronary artery obstructions vary widely depending on the prevalence of known and unknown predictors of restenosis. Some bare-metal stent registries have shown clinical restenosis rates of <5%,2,3 on a par with rates observed recently in drug-eluting stents.4,5 However, these low rates of restenosis for bare-metal stents are attributable to the lower risk of the populations in which they were tested rather than to a lower restenosis propensity of bare-metal stents. When tested across broad ranges of risk, the same stent may be observed to have restenosis rates that vary by as much as 4-fold.3,6 Clinical restenosis rates therefore do not allow objective comparison of the restenosis propensity across randomized or observational studies.

Late lumen loss, defined as the difference between the minimum lumen diameter (MLD) immediately after stenting and the MLD at 6-to 8-month follow-up, has been used in pilot studies of drug-eluting stents as a marker for restenosis propensity.7 The mean in-stent late loss observed in a study can be used to predict restenosis risk for bare-metal and drug-eluting stents.8,9

We sought to determine whether mean late loss was more stable for stent systems across studies and thus superior to observed clinical restenosis rates for distinguishing drug-eluting stent performance.

Methods
To evaluate the utility of mean late loss to differentiate drug-eluting stent performance, 2 types of data were analyzed. First, a comprehensive literature search was performed to identify the relationship between reported mean late loss and target lesion revascularization (TLR) across studies of different types of stents. Second, primary data from 8 randomized trials of drug-eluting and bare-metal stenting were used to identify predictors of late loss and to standardize the late loss metric for comparison of drug-eluting stents.

Literature Selection and Data Evaluation
A comprehensive literature search of MEDLINE and clinical trials presented at major international meetings (American College of

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Cardiology, Paris Course on Revascularization, Transcatheter Therapeutics, American Heart Association) from January 2003 to April 2005 produced original reports of 46 clinical trials testing drug-eluting or bare-metal stents in the treatment of de novo coronary lesions in which both mean late loss at 4 to 9 months and TLR at 6 to 12 months were reported.\textsuperscript{2,5,10–49} For drug-eluting stent trials, at least 2 studies of the same stent were required for inclusion.

Harvard Clinical Research Institute Stent Database

The Harvard Clinical Research Institute (HCRI) Stent Database consists of 8 major clinical trials of stenting of de novo lesions in native coronary arteries conducted during 1996–2003 with the use of either bare-metal stents (STARS, ASCENT, SMART, NIRVANA, EXTRA, CCS) or drug-eluting stents (SIRIUS, E-SIRIUS).\textsuperscript{4,11,12,22,42,50} Data were derived from the total study sample of 7244 patients and the subgroup with mandated angiographic follow-up (n=3138) performed at 6 months after the index procedure for bare-metal stent studies and at 8 months for drug-eluting stent studies. The end point of interest, in-stent late loss, was complete in 2426 (77%) of those eligible for angiographic follow-up. Informed consent was obtained from each patient, and all investigational sites received approval from their institutional review boards.

Definitions

Acute gain was defined as the MLD immediately after the procedure minus the MLD at baseline. Late loss was defined as the MLD immediately after the procedure minus the MLD at angiographic follow-up, within the stent. Percent diameter stenosis was defined as \(1−(\text{MLD/reference vessel diameter})×100\). Binary angiographic restenosis 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 ≥20%. Diabetes was defined as the diagnosis of diabetes mellitus requiring medical treatment.

Statistical Analysis

Binary variables are expressed as frequencies, and continuous variables are expressed as mean±SD. Binary variables were compared with the use of \(χ^2\) analysis, and continuous variables were evaluated by the Student \(t\) test. A 2-sided probability value ≤0.05 was considered significant. Linear regression was performed to evaluate the relationship between mean late loss and observed TLR rate across trials. The addition of second-order polynomial terms was performed only when model fit was significantly improved. Statistical analyses were performed in SAS (version 8.2).

Intraclass Correlation: TLR Versus Late Loss

We measured the reliability of TLR versus late loss across 46 trials of bare-metal stent systems and 3 drug-eluting stent systems as estimated by the intraclass correlation coefficients (\(ρ\)).\textsuperscript{51} We first treated the drug-eluting stent systems and the bare-metal stent systems as 2 classes and estimated the intraclass correlation coefficient. We then estimated intraclass correlation coefficient treating the individual drug-eluting stent systems and bare-metal stents as 4 separate classes. The intraclass correlation coefficient should be highest for the restenosis end point that best discriminates the stent classes. The Mixed Procedure in the SAS statistical package was used to calculate maximum likelihood estimates of the within-class and between-class variance components. The ratio of the between-class variance divided by the sum of the variances was used to estimate the intraclass correlation coefficient for each restenosis end point (\(ρ\_{\text{LL}}, ρ\_{\text{TLR}}\)). The 2 correlation coefficients were then compared, and a 95% CI for the difference (\(ρ\_{\text{LL}}−ρ\_{\text{TLR}}\)) was constructed by random generation of 1000 bootstrap samples. Finally, to test the robustness of these results without relying on the assumption that all bare-metal stents have the same restenosis properties, the intraclass correlation coefficients were calculated excluding bare-metal stents.

Predictors of Late Loss

A multivariable linear regression model was constructed to predict in-stent late loss with the use of the HCRI Stent Database. Known predictors of restenosis (diabetes mellitus, reference vessel diameter, lesion length, postprocedure residual stenosis, acute gain, and sirolimus-eluting versus bare-metal stent treatment) were evaluated for their relative effects on late loss.

Standardization of Mean Late Loss

Standardization of mean late loss was performed in reference to a representative population derived from the first Food and Drug Administration–approved drug-eluting system,\textsuperscript{4,42} with an approximate diabetes prevalence of 25%, median lesion length of 14 mm, and median acute gain of 1.7 mm. The following 2 standardization methods were developed to compare the effectiveness of stents as measured by in-stent late loss in trials that deviate from these expected values.

Standardized Late Loss: Direct Method

If the distribution of all 3 variables (diabetes, lesion length, and acute gain) differs in the new trial compared with the reference population, then the study cohort is divided into 8 subgroups according to the presence or absence of diabetes, lesion length ≥14 or <14 mm, and acute gain ≥1.7 or <1.7 mm. Within each subgroup, we calculate the average late loss and combine these as a weighted average, in which the weights reflect prevalences in the reference population (Appendix A in the online-only Data Supplement: http://circ.aha.org/cgi/content/full/CIRCULATIONAHA.105.570093/DC1). If patients in a new trial differ from the reference population with respect to diabetes prevalence and median lesion length but have similar acute gain, then only 4 subgroups need to be created.

Although this method of direct standardization has the advantage of simplicity, it requires that the number of patients in the new trial be sufficiently large that stable estimates of mean late loss can be calculated in each of the (2 or 4) patient subgroups. If this requirement is not met, then the indirect method outlined below should be considered instead.

Standardized Late Loss: Indirect Method

From the reported mean late loss in a new trial and proportions of patients with diabetes mellitus, with lesion length ≥14 mm, and with acute gain ≥1.7 mm, the indirectly standardized late loss can be calculated by comparison with our standardized assumptions: 25% with diabetes; 50% with lesion length ≥14 mm; 50% with acute gain ≥1.7 mm; and multiplication by regression-derived effect estimates (Appendix B in the online-only Data Supplement).

Results

Summary of Stent Trials Reporting Late Loss and TLR

The 46 trials of coronary stenting were tabulated according to stent type in the study if a registry and in each arm if a randomized trial (12 Cypher, 6 TAXUS, 2 ENDEAVOR, 55 bare-metal stent arms; Appendix C in the online-only Data Supplement). Figure 1A depicts the crude positive relationship between late loss means and TLR rates (\(P<0.001, r^2=0.22\)) and the wide variability of TLR rates compared with the more clustered late loss means within stent systems.

Intraclass Correlation of TLR Versus Late Loss

Intraclass correlation coefficient comparing the 2 broad classes (effective drug-eluting stents versus bare-metal stents) was \(ρ=0.71\) for mean late loss and \(ρ=0.22\) for TLR (95% CI of difference =0.33, 0.65) (Figure 1B). The intraclass correlation coefficient for late loss was again higher when drug-eluting stent types and bare-metal stents were treated as 4 separate classes (\(ρ\_{\text{LL}}=0.68; ρ\_{\text{TLR}}=0.19\); 95% CI of difference =0.24, 0.60). When drug-eluting stent types alone were treated as 3 classes, there was greater separation of the
respective intraclass correlation coefficients ($\rho_{LL}=0.64$; $\rho_{TLR}=0.009$; 95% CI of difference $= -0.20, 0.92$), albeit with decreased power for the comparison because of the reduced sample size.

**HCRI Stent Database**

Pooled observations from 8 clinical trials yielded 2426 patients with angiographic assessment of late loss at 6 to 8 months (Table 1). The binary angiographic restenosis rates were 28.2% (542/1922) and 7.8% (39/502) in the bare-metal and sirolimus-eluting cohorts, respectively ($P<0.0001$), and in-stent late losses were 0.94±0.63 and 0.18±0.43, respectively ($P<0.0001$).

**Effect of Reference Vessel Diameter: TLR Versus Late Loss**

Reference vessel diameter has previously been shown to be an independent determinant of TLR in both bare-metal and drug-eluting stents.5 Reference vessel diameter, however, was not a significant determinant of late loss ($P=0.12$). Late loss was determined by the type of stent used (sirolimus-eluting versus bare-metal), diabetes mellitus, lesion length, and acute gain (Table 2). Residual stenosis was a significant predictor of late loss, but with a small magnitude of effect (0.0097-mm decrease in in-stent late loss per 1% increase in residual stenosis).

**Standardized Late Loss and Expected Adjustment Between Trials**

To evaluate whether the robustness of the late loss metric could be further improved, we developed 2 methods of standardization for the most influential determinants of late loss that could vary across trials: diabetes mellitus, lesion length, and acute gain (Appendices A and B in the online-only Data Supplement).

Within the trials reported, the magnitude of adjustment of late loss ranged from $0.14$ mm to $0.10$ mm (Figure 2). The 4 study arms (6%) that had adjustments of $>0.10$ mm were in trials that enrolled only diabetic patients.23,40 For $>90\%$ of the reported studies, the difference between the unadjusted and adjusted (standardized) late loss was within $0.08$ mm, which would result in very small differences in predicted angiographic restenosis rates.8 Thus, in the majority of drug-eluting stent trials, the unadjusted late loss serves as a stable estimator of binary restenosis propensity.

When limited to drug-eluting stents, separated by stent type, the intraclass correlation coefficient increased with standardization from 0.64 to 0.83. Finally, plotting of either mean or standardized late loss from each study arm resulted in an ordered array of stents (Figure 3).

**Discussion**

Estimation of treatment effects is subject to bias and confounding when observational and randomized results are evaluated across studies. When restenosis risk factors (diabetes, lesion length, reference vessel size) vary substantially, one can observe markedly different restenosis rates for the

**TABLE 1. Baseline and Procedural Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (n=2426)</th>
<th>Bare-Metal Stents (n=1922)</th>
<th>Sirolimus-Eluting Stents (n=502)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>22.4%</td>
<td>22.5%</td>
<td>22.3%</td>
<td>0.95</td>
</tr>
<tr>
<td>Reference vessel diameter, mm</td>
<td>2.88±0.50</td>
<td>2.92±0.51</td>
<td>2.73±0.44</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Residual percent diameter stenosis, %</td>
<td>7.1±10.0</td>
<td>7.4±10.4</td>
<td>6.2±8.2</td>
<td>0.01</td>
</tr>
<tr>
<td>Lesion length, mm</td>
<td>13.4±6.3</td>
<td>13.1±6.4</td>
<td>14.7±5.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Acute gain, mm</td>
<td>1.71±0.47</td>
<td>1.72±0.48</td>
<td>1.66±0.43</td>
<td>0.005</td>
</tr>
</tbody>
</table>
same stent in different trials or similar restenosis rates between different stent classes (eg, drug-eluting stents versus bare-metal stents). Traditional measures of restenosis, such as binary angiographic and clinical restenosis, are reliable when randomized arms within trials are compared because randomization balances restenosis risk factors, but these measures are not reliable when cohorts across trials are compared.

In-stent late loss is both theoretically and clinically correlated with monotonic and incremental binary restenosis risk. In this study we tested the robustness of late loss by considering its reproducibility within different stent systems under a variety of clinical trial conditions. Our findings demonstrate the robustness of late loss in terms of high intraclass correlation under the various reported clinical trials. We evaluated the notion of “stent class” (1) between bare-metal stents and effective drug-eluting stents and (2) between bare-metal stents and different drug-eluting stent systems. We hypothesized that mean late loss might be less subject to variation across studies of the same stent class and therefore might be a more reliable discriminator of drug-eluting stent performance.

In 46 trials of stenting, we found that when the class of bare-metal stents was discriminated from the class of effective drug-eluting stents, late loss was more consistent than TLR rates. The intraclass correlation coefficients for late loss were significantly and substantially higher than for TLR. The intraclass correlation coefficients for late loss were significantly and substantially higher than for TLR. The intraclass correlation coefficients for late loss were significantly and substantially higher than for TLR. The intraclass correlation coefficients for late loss were significantly and substantially higher than for TLR. The intraclass correlation coefficients for late loss were significantly and substantially higher than for TLR.

Stability of late loss is due in large part to its direct measurement of narrowing and lack of influence of other factors in its calculation, in contrast to the dependency of TLR rate estimation on reference vessel diameter. Furthermore, late loss was also better at discriminating the individual drug-eluting stent types within the drug-eluting stent class.

Although late loss estimates derived from clinical trials were highly stable, they could be further improved as a comparative metric by standardization, especially in studies with extremely high or low prevalence of risk factors. The magnitude of adjustment required for in-stent late loss, however, was relatively small, underscoring its stability, with 90% of adjustments falling within an absolute 0.08-mm difference from the observed mean value. This is in contrast to the highly variable binary restenosis metrics, which range by as much as 4-fold for TLR when compared in differing patient populations.

Is There a “Class Effect” for Drug-Eluting Stents?

The success in preventing coronary restenosis by combining a coronary stent platform with a polymer eluting one of a variety of effective agents (such as sirolimus, paclitaxel, or ABT-578) has led to the common label of drug-eluting stents. Currently, 3 drug-eluting stent systems (Cypher, TAXUS, and ENDEAVOR) have shown substantial reductions in clinical restenosis compared with simpler bare-metal stents in large multicenter randomized trials. Our analysis shows that measures of clinical restenosis, specifically TLR, do not discriminate well between the group of effective drug-eluting stent systems and the group of bare-metal stents. On the other hand, mean late loss in lumen diameter discriminates this group of drug-eluting stents from bare-metal stents with a high degree of separation. Specifically, when trials of effective drug-eluting stents are combined, a clustering at the lower half of the 0.1- to 1.2-mm spectrum of mean late loss is evident (Figure 1), supporting the concept of a class effect of effective drug-eluting stents.

Not all drug-eluting stent systems have shown effectiveness, however, as different stent, polymer, drug, and dose combinations have yielded markedly different results, some with average late loss exceeding that of bare-metal stents.

### TABLE 2. Multivariable Predictors of In-Stent Late Loss

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Effect Estimate (mm)</th>
<th>SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent type (sirolimus-eluting vs bare-metal)</td>
<td>-0.79</td>
<td>0.029</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.16</td>
<td>0.028</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lesion length (per 10 mm)</td>
<td>0.17</td>
<td>0.019</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Acute gain (per mm)</td>
<td>0.17</td>
<td>0.029</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Residual percent diameter stenosis (per 1%)</td>
<td>-0.0097</td>
<td>0.0014</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Reference vessel diameter (per mm)</td>
<td>-0.044</td>
<td>0.028</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Figure 2. Adjustment in late loss across drug-eluting and bare-metal stent trials. The magnitude of adjustment of late loss for 71 study arms reporting mean late loss was standardized according to diabetes prevalence and mean lesion length (indirect method), and the values of late loss and standardized late loss were plotted according to categories of stent type. An ordered relationship of stent type exists according to the mean late loss. BMS indicates bare-metal stent.
These examples demonstrate that not all drug-eluting stent systems are equal. In-stent late loss discriminates the differences in restenosis propensity between effective and ineffective drug-eluting stent systems, and thus the notion of a class effect can only be supported for effective stent systems with low in-stent late loss.

Can Late Loss Define Subclasses Within the Class of Effective Drug-Eluting Stents?

Further discrimination by subclass within the class of effective drug-eluting stents was possible in our analysis with the use of late loss. We measured a high intraclass correlation when the 3 effective drug-eluting stent systems were each treated as (sub)classes. Combined with the monotonic relationship between late loss and restenosis, this finding is in contradistinction to the notion advanced by others that there is a late loss “threshold” (such as 0.75 mm for in-stent late loss) below which all drug-eluting stents are exchangeable. As we have shown, when the risk of TLR is low, it is often difficult to distinguish between drug-eluting stents and bare-metal stents in nonrandomized comparisons of TLR rates. In contrast, mean late loss is a reliable indicator of anti-restenosis efficacy across studies, under all levels of TLR risk. In-stent late loss is a reliable and powerful indicator of the restenosis propensity of the stent system under question across the spectrum of bare-metal and drug-eluting stent trial experience, thus supporting the ability to distinguish stent performance within the drug-eluting stent class.

Clinical Application

The primary measure of effectiveness against restenosis for drug-eluting stents is the clinical restenosis rate determined within a randomized trial. These rates vary according to the risk of the population in which the stent is tested, as well as the type of stent used. Stent versus stent randomized trials are designed to control for these population risk factors and allow inference within the trial solely on the efficacy of the assigned stent platform. When deciding which treatment to use for a given patient with obstructive coronary disease, however, physicians may compare the results of several stent systems across different trials. To isolate the efficacy of existing stent systems, one would desire a metric that was consistent from study to study. We have previously shown that late loss is a valid estimator of restenosis risk associated with stents in trials that is also more efficient than clinical or angiographic binary end points. The present analyses demonstrate that when comparisons are made across separate prospective studies, either randomized or observational, late loss is more reliable than restenosis rates at discriminating the effectiveness of different drug-eluting stents. For the practicing physician, in-stent late loss provides a more reliable measure of anti-restenosis propensity than restenosis rates from any given trial source.

The relative invariance of late loss across study populations stands in contrast to the predictable increase in TLR rates or mean percent diameter stenosis with decreasing reference vessel diameter. The translation of incremental differences in late loss to significant increases in clinical restenosis is apparent in studies comparing different drug-eluting stents in higher-risk patient populations or in cases in which comparisons are made with greater power. In the context of diminishing binary rates of restenosis, reliability and power make in-stent late loss a more robust end point than TLR, particularly in early studies to evaluate efficacy, dose-finding studies, or evaluations of the effects of minor variations in stent design. Formal validation of this end point by relating differences in late loss across stent platforms to differences in clinical restenosis will be required for the assumption of true surrogacy. Pragmatically, the ability of late loss to discriminate small differences in efficacy may be informative for pilot or dose-finding studies before the formation of larger studies to evaluate safety and clinical efficacy.

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