Lesion-to-Lesion Independence of Restenosis
After Treatment by Conventional Angioplasty,
Stenting, or Directional Atherectomy
Validation of Lesion-Based Restenosis Analysis

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Background. Since many restenosis trials include patients in whom more than one lesion is treated, analysis of the angiographic data on a “per lesion” basis might be confounded by potential correlations of restenosis among multiple treated lesions within each patient. The goals of this study were 1) to determine whether there was any correlation in the rate of restenosis among multiple lesions that underwent conventional angioplasty, stenting, or directional atherectomy within the same patient and 2) to determine whether lesions treated in a multilesion intervention experience a different magnitude of restenosis than lesions undergoing single-lesion procedures.

Methods and Results. Of 441 patients treated by Palmaz-Schatz stenting (n=114), directional atherectomy (n=100), or conventional balloon angioplasty (n=227), 67 underwent multilesion procedures involving treatment of 146 lesions. A general linear model with intraclass correlation (GLIMIC) was used to calculate the coefficient of correlation (r) of the change in the measured minimum lumen diameter (late loss) from the time of the initial procedure to 6-month angiogram among the multiple lesions within the same patient for all 441 patients. This showed no correlation among multiple lesions within the same patient for the late loss in minimum lumen diameter (r=−0.12 [95% CI: −0.40, 0.12]), among lesions in the same vessel (r=0.14 [95% CI: −0.34, 0.62]), or among different vessels (r=−0.18 [95% CI: −0.52, 0.16]), suggesting that the magnitude of late loss is independent among multiple lesions within the same patient. There was no difference (p=0.96) between the observed incidence of zero-, one-, and two-vessel restenosis (≥50% diameter stenosis at follow-up) for patients with multiple-lesion treatment and that predicted assuming lesion-to-lesion independence. Similarly, there was no difference in late loss or in the overall binary restenosis rate when single-lesion procedures were compared with multilesion procedures. Multivariable analysis of the late loss in lumen diameter (which adjusted for the effects of the acute result and the device used) demonstrated no independent effect (p=0.20) of single-lesion versus multilesion status.

Conclusions. Luminal encroachment appears to occur at independent rates among multiple lesions treated in a single patient. The observed incidence of restenosis for patients with multiple treated lesions is accurately predicted assuming independent probabilities of restenosis. Lesion-based analysis, even when including multiple treated lesions within the same patient, is thus valid for evaluating conventional angioplasty, stenting, or directional atherectomy. (Circulation 1993;87:1123–1129)

Key Words • restenosis • lesions

The analysis of coronary restenosis after conventional or new device interventions has traditionally been based on either late patient end points (recurrent symptoms or need for revascularization) or late angiographic end points (luminal narrowing). Because follow-up angiography provides objective quantitative data, a lesion-based angiographic analysis would be preferable.1 Many published retrospective and prospective trials that attempted to determine the effect of patient characteristics, lesion characteristics, or specific interventions (device or adjunctive pharmacologic therapy) on restenosis have thus relied on lesion-based analyses, even though many patients received treatment for more than one coronary obstruction.2–10 Such analysis requires two untested assumptions. First, for multiple lesions treated in the same patient, it is assumed that there is no correlation in the restenosis rate among the treated lesions. Otherwise, the calculated variance used for statistical comparison of the treated population would be underestimated.11–14 One approach to avoid this problem is to choose one lesion per patient for the analysis,15,16 but this method does not make efficient use
of all the available angiographic data and introduces obvious selection bias. The second untested assumption for lesion-based analysis is that restenosis behaves equivalently in patients with single-lesion intervention versus patients with multilesion intervention. We have previously reported that coronary restenosis is a continuous and near normally distributed process. Analysis of restenosis data as a continuous variable by regression techniques and application of a specialized statistical technique that analyzes the intraclass correlation can thus be helpful in determining whether restenosis occurs at independent rates within the same patient. Accordingly, the purpose of this study is both to test the validity of lesion-based analysis by determining whether there is correlation in the rate of restenosis among multiple lesions within the same patient and to test whether the magnitude of restenosis is equivalent among patients undergoing single-lesion or multilesion interventions.

Methods

Study Population

Between June 1988 and January 1991, 143 lesions in 132 patients were treated by Palmaz-Schatz stenting, and 160 lesions in 134 patients were treated by directional coronary atherectomy at the Beth Israel Hospital (Boston). Between January 1986 and January 1988, 229 patients underwent conventional angioplasty of 288 coronary segments at Kokura Memorial Hospital. Protocols approved by the committee on clinical investigations were followed. Follow-up angiography was performed at 3–6 months after coronary intervention in 441 patients (123 stent lesions, 112 directional atherectomy lesions, and 285 conventional angioplasty lesions) representing 89% angiographic follow-up. “Multilesion” intervention was performed on 146 lesions using the same device in the same patient either within the same vessel (68 [46.5%]) or in different vessels (78 [53.5%]).

Angiographic Analysis

Angiographic analysis was performed immediately before and after each new intervention and was repeated 6 months after intervention using the view in which the initial stenosis appeared most severe. Coronary arterial dimensions were determined by caliper measurements made on projected flat images of selected optically magnified cineframes and referenced to the known diameter of the angiographic catheter for stent and atherectomy lesions, with videodensitometry using a Vanguard XR-70 coronary analyzer for conventional angioplasty lesions. Almost all views for analysis were performed on a magnified 5-in. mode with the target lesion and reference guide catheter centered whenever possible. Measurements included the minimal luminal diameter of the treated coronary segment and the reference diameter (taken as the mean diameter of the normal-appearing proximal and distal segment) before and after each intervention and at follow-up. Intravenous nitroglycerin (200 μg) was administered immediately before and after intervention.

Statistical Analysis

Values are reported as mean±SD. Categorical variables were compared by χ² analysis, and continuous data was compared by t test or ANOVA. The late (3–6-month follow-up angiogram) percent diameter stenosis for single-lesion versus multilesion procedures was also compared using a display of the complement of a cumulative distribution. This function plots the proportion of patients exceeding a given percent diameter stenosis on the y-axis versus the percent diameter stenosis of interest on the x-axis.

The independent effect of multilesion intervention versus single-lesion intervention on restenosis was examined using multivariable techniques. Restenosis was analyzed in two ways: 1) as the late loss or the absolute loss in minimum luminal diameter between the immediate postprocedure lumen and the late (3–6-month) lumen and 2) as binary restenosis defined as >50% diameter stenosis at follow-up angiography. The association between the late loss in luminal diameter and selected explanatory variables was tested using linear regression. Independent determinants of restenosis were constructed using step-up multivariable regression techniques in which significant (p<0.10) explanatory variables from univariable models were entered into the multiple model.

A general linear model with intraclass correlation was used to analyze potential correlation among lesions within patients who had multilesion intervention. This method tests for the presence of significant correlation between treated lesions within individual patients, since such correlation would introduce important methodological errors for the variance calculation. The finding of no significant correlation would thus validate lesion-based analysis. The statistical details of this method are presented in the “Appendix.”

The probability of zero-, one-, or two-lesion restenosis per patient may be accurately estimated by simple multiplication of independent probabilities of restenosis if binary restenosis occurs as an independent event in multiple treated lesions within any given patient. The per-lesion restenosis rate was first calculated from all lesions in patients undergoing a two-lesion procedure. Based on this per-lesion restenosis rate, the predicted incidence of zero-, one-, or two-lesion restenosis on a per-patient basis was then calculated. The predicted incidence of zero-, one-, or two-lesion restenosis was then compared with the observed incidence rate of zero-, one-, or two-lesion restenosis on a per-patient basis, using the χ² test.

Results

Clinical Characteristics

Among 441 patients who had angiographic follow-up after either coronary angioplasty (n=227), Palmaz-Schatz stenting (n=114), or directional coronary atherectomy (n=100), 374 had single-lesion intervention and 67 had multilesion intervention. The distribution of the number of lesions treated per patient stratified by the device type is displayed in Table 1. The single-lesion intervention group had a higher percent prior restenosis (43% versus 29%, p<0.002, Table 2) than the multilesion group, but there was no difference in age or the proportion of men between the two groups. Examination of the coronary distribution demonstrated that single-lesion interventions were performed on a higher percentage of left anterior descending arteries.
(51.3\% versus 40.4\%,  p = 0.03). Single-lesion procedures were performed in men in 78\% of cases while multivessel procedures were performed in men in 68\% of cases, but this 10\% difference did not achieve statistical significance (p = 0.09).

**Analysis of the Intraclass Correlation of Late Loss**

The intraclass correlation (\(\rho\)) of late loss in minimum luminal diameter for multiple treated lesions was \(-0.12\) (95\% CI: \(-0.40, 0.12\)). Thus, late loss in minimum luminal diameter for multiple lesions within the same patient was not significantly correlated, implying that luminal renarrowing was an independent process among multiple treated lesions within the same patient. Furthermore, subset analysis demonstrated no significant correlation for the late loss among multilesions within the same coronary vessel \((n = 68, \rho = 0.14 \text{ [95\% CI: } -0.34, 0.62])\) or among different coronary vessels \((n = 78, \rho = -0.18 \text{ [95\% CI: } -0.52, 0.16])\).

**Actual and Predicted Incidence of Restenosis in Patients With Single-Lesion and Multilesion Intervention**

In the above continuous-variable analysis, luminal renarrowing (late loss) occurred at independent rates among multiple treated lesions within individual patients. To confirm this independent behavior in a traditional restenosis model, we compared observed incidence of zero-, one-, or two-lesion restenosis as a binary outcome in patients with two-lesion intervention with the predicted incidence assuming independent rates of restenosis. Using a restenosis rate of 36.6\% (the per-lesion restenosis rate among two-vessel procedures) the predicted rate of zero-, one-, or two-lesion restenosis per patient was calculated by multiplying probabilities of restenosis assuming independence of the events. The observed incidence of zero-, one-, and two-lesion restenosis among 56 patients undergoing two-vessel angioplasty was not statistically different from the predicted incidence, assuming lesion independence as shown in Figure 1 (\(p = 0.958\)).

**Angiographic Measurements Comparing Single-Lesion Multilesion Intervention**

Comparison of single-lesion and multivessel angiographic measurements on a per-lesion basis using ANOVA demonstrated no significant differences in the baseline, procedural, or late (6-month) angiographic measurements for the lesions treated by stenting or directional atherectomy or conventional angioplasty (Table 3) except for a larger preprocedure minimum lumen diameter in the multivessel conventional angioplasty group (\(p = 0.03\)). The overall binary restenosis rate was 37.4\% for single-lesion intervention and 34.9\%.
for multilesion intervention \( p = 0.60 \). Figure 2 shows similar cumulative distributions of the late percent stenosis between single-lesion and multilesion intervention for the overall group. Thus, the binary restenosis rate is similar for single-lesion and multilesion procedures irrespective of the dichotomous definition of restenosis.

**Multiple Linear Regression Model**

There was no difference in binary restenosis \( p = 0.60 \) between single-lesion versus multilesion intervention. To examine the possibility that patients with multilesion intervention had different restenosis characteristics than patients with single-lesion intervention (based on continuous variables), a linear regression model of late loss in lumen diameter was constructed (Table 4). Linear regression demonstrated that the immediate postprocedure luminal diameter was an independent determinant of late loss but not whether the treated lesions were from a single-lesion intervention or multilesion intervention.

**Table 3.** Angiographic Measurements Stratified by Single-Lesion Versus Multilesion Intervention and by Device Type

<table>
<thead>
<tr>
<th></th>
<th>Stents</th>
<th></th>
<th>Atherectomy</th>
<th></th>
<th>PTCA</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Single-lesion</td>
<td>Multilesion</td>
<td>Single-lesion</td>
<td>Multilesion</td>
<td>Single-lesion</td>
<td>Multilesion</td>
</tr>
<tr>
<td></td>
<td>( n = 106 )</td>
<td>( n = 8 )</td>
<td>( n = 88 )</td>
<td>( n = 12 )</td>
<td>( n = 180 )</td>
<td>( n = 47 )</td>
</tr>
<tr>
<td>Reference diameter (mm)</td>
<td>3.38±0.66</td>
<td>3.60±0.60</td>
<td>3.15±0.69</td>
<td>3.23±0.75</td>
<td>2.90±0.68</td>
<td>2.74±0.61</td>
</tr>
<tr>
<td>Initial lesion diameter (mm)</td>
<td>0.77±0.54</td>
<td>1.0±0.61</td>
<td>0.68±0.34</td>
<td>0.77±0.52</td>
<td>0.70±0.49*</td>
<td>0.88±0.95*</td>
</tr>
<tr>
<td>Postprocedure diameter (mm)</td>
<td>3.48±0.65</td>
<td>3.64±0.62</td>
<td>2.96±0.57</td>
<td>2.98±0.73</td>
<td>1.94±0.51</td>
<td>1.85±0.55</td>
</tr>
<tr>
<td>Acute gain (mm)</td>
<td>2.71±0.72</td>
<td>2.64±0.76</td>
<td>2.29±0.62</td>
<td>2.22±0.80</td>
<td>1.23±0.57</td>
<td>0.97±0.98</td>
</tr>
<tr>
<td>Follow-up lumen diameter (mm)</td>
<td>2.13±0.96</td>
<td>2.34±1.06</td>
<td>1.84±0.98</td>
<td>2.16±0.92</td>
<td>1.41±0.72</td>
<td>1.39±0.69</td>
</tr>
<tr>
<td>Follow-up stenosis (%)</td>
<td>33.8±26.2</td>
<td>33.9±28.9</td>
<td>39.3±28.7</td>
<td>31.3±25.0</td>
<td>50±24.1</td>
<td>48.9±22.4</td>
</tr>
<tr>
<td>Late loss (mm)</td>
<td>1.35±1.0</td>
<td>1.30±1.48</td>
<td>1.12±0.95</td>
<td>0.82±0.87</td>
<td>0.52±0.64</td>
<td>0.46±0.62</td>
</tr>
</tbody>
</table>

PTCA, percutaneous transluminal coronary angioplasty.
*\( p < 0.05 \) comparing single-lesion and multilesion procedures for the same device.

**Discussion**

**The Problem of Multilesion Intervention in Restenosis Analysis**

The analysis of restenosis data is complicated by the fact that there are often multilesion procedures performed within the same patient, making several lesions available for analysis. One approach to the analysis of multiple treated lesions within the same patient is to average the data from each of the multiple lesions to provide single values comparable to patients who had single-lesion intervention. An analogous patient-based analysis has been used in atherosclerosis regression trials in which the single data point reflects the average lesion change within the patient as a whole. Such analysis may be oversimplified, since the behavior of individual lesions that are responsible for clinical events such as angina and myocardial infarction is obscured. For instance, in a patient who has undergone a multilesion procedure, severe restenosis within a single lesion may result in recurrent angina, whereas the other dilated lesions within the same patient may remain quiescent. Averaging the data from all the lesions in such a patient would thus dissociate the clinical event of angina from an unremarkable or favorable average change in percent stenosis.

A lesion-based approach would be desirable compared with the patient-based approach because it makes more efficient use of limited angiographic data and increases the statistical power of the study. Although a lesion-based analysis is appealing, potential methodological problems limit its use. If there is homogeneity or correlation in the magnitude of restenosis (luminal narrowing) among multiple lesions within the same patient, then the variance of the population will be underestimated, leading to spurious significant differences between groups, when in fact, no such differences exist. Because of these concerns, some investigators have selected only one lesion at random for restenosis analysis in patients in whom multiple lesions were dilated. This approach, however, is limited by potential selection bias and by its failure to make the most efficient use of all the available angiographic data.

Previously, we have applied a general linear model with intraclass correlation to the analysis of atherosclerosis regression data to correct for any correlation among multiple lesions within individual patients in a
lesion-based analysis. In that study, we found that atherosclerosis progression occurred at independent rates in multiple undilated lesions within the same patient. The present study extends these findings to the process of restenosis, in which case multiple dilated lesions within the same patient appear to develop luminal renarrowing at independent rates. Furthermore, dilated lesions either within the same vessel or between two different vessels behaved independently. The findings are supported by Vandormael et al’s multivariable analysis, which did not identify any patient-related variables that were predictive of multilesion restenosis. A potential explanation for the independent rate of restenosis may be found in the heterogeneity of shear stresses and other local mechanical forces to which the individual lesions are exposed. We have previously reported that low shear stress is correlated with an increased rate of luminal narrowing in undilated coronary artery lesions.

Other investigators have also shown that low shear stress is correlated with an increased rate of narrowing of undilated lesions in other vascular beds, and such local mechanical forces may modulate the response of multiple lesions within the same patient to lipid-lowering strategies. Furthermore, Simons et al have reported that the presence of activated smooth cells in a lesion is correlated with the subsequent development of restenosis, indicating that the composition of the individual lesion may be an important determinant of restenosis.

Our finding that the incidence of zero-, one-, and two-lesion restenosis in patients with multilesson procedures follows the distribution that was predicted assuming lesion independence differs from the findings of Lambert et al, who found that the incidence of restenosis in patients with multilesson procedures did not follow the expected binomial distribution. That study may have been limited, however, by a low angiographic follow-up rate (64%) and the fact that more symptomatic than asymptomatic patients were available for re-study, potentially biasing estimates of the restenosis rate.

Comparison of Single-Lesion and Multilesson Procedures

Coronary stenoses undergoing single-lesion intervention did not experience more late loss in lumen diameter compared with lesions involved in multilesson procedures. In the multivariable model of luminal renarrowing, the postprocedure luminal diameter was the only significant explanatory variable in the determination of the late loss in luminal diameter, not the variable denoting single-lesion versus multilesson intervention. There was also no difference in restenosis according to a traditional definition (≥50% diameter stenosis) for single-lesion and multilesson procedures. Furthermore, the cumulative distribution of late percent stenosis shown in Figure 2 shows that the late results were nearly identical for single-lesion and multilesson procedures independent of the definition of restenosis used. Vandormael et al have also reported no difference in the incidence of restenosis when single-lesion and multilesson procedures were compared.

The higher incidence of restenosis in patients undergoing multilesson procedures reported in some studies is probably due to the fact that there are simply more arteries available to experience restenosis in these patients rather than a higher rate of restenosis on a per-lesion basis in these lesions. This is demonstrated clearly in the per-patient analysis of the current data set. Whereas 37.4% of patients undergoing single-lesion procedures experienced restenosis, 10.4% of multilesson patients experienced multilesson restenosis (all lesions restenosed), and 52.2% of these patients experienced restenosis of at least one lesion (mixed restenosis response), for a total of 62.6% of multilesson patients experiencing restenosis in at least one lesion.

Limitations

The angiographic follow-up rate is incomplete (89%); however, it is higher than that reported in a previous study (64%) that addressed related questions. Electronic calipers were used to quantitate the luminal diameters; it has been shown in the past that there is no difference between electronic calipers and videodensi-

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**Table 4. Univariable and Multivariable Linear Regression Models of the Late Loss (6 Months) in Luminal Diameter**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intercept</th>
<th>β</th>
<th>p</th>
<th>β</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postprocedure diameter</td>
<td>-0.44</td>
<td>0.50</td>
<td>&lt;0.0001</td>
<td>0.58</td>
<td>0.49, 0.68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multilesson procedure</td>
<td>0.90</td>
<td>-0.28</td>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predilated lesion diameter</td>
<td></td>
<td></td>
<td></td>
<td>0.48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior restenosis</td>
<td>0.76</td>
<td>0.16</td>
<td>0.04</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td>0.24</td>
<td></td>
<td></td>
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<tr>
<td>LAD</td>
<td></td>
<td></td>
<td></td>
<td>0.42</td>
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<tr>
<td>Circumflex</td>
<td></td>
<td></td>
<td></td>
<td>0.004</td>
<td></td>
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<tr>
<td>RCA</td>
<td></td>
<td></td>
<td></td>
<td>0.85</td>
<td></td>
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<td>Saphenous vein graft</td>
<td>0.75</td>
<td>0.71</td>
<td>&lt;0.0001</td>
<td></td>
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<tr>
<td>Stent</td>
<td>0.66</td>
<td>0.68</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
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<tr>
<td>Atherectomy</td>
<td>0.75</td>
<td>0.30</td>
<td>0.002</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Conventional PTCA</td>
<td>1.20</td>
<td>-0.70</td>
<td>&lt;0.0001</td>
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</tr>
</tbody>
</table>

LAD, left anterior descending coronary artery; RCA, right coronary artery; PTCA, percutaneous transluminal coronary angioplasty.

*Univariable model for late loss: (mm) = intercept + (variable × β).
†Final "step-up" multivariable linear regression model (intercept = -0.13): late loss (mm) = 0.58 × postprocedure luminal diameter (mm) - 0.13 mm.
tometric measurements in undilated lesions. This study assumes that there is also good agreement between electronic caliper and videodensitometric edge detection measurements in the assessment of post-PTCA lesions. There was a mean of 2.1 lesions per multilesson patient (range, 2–4). A larger number of lesions per patient would permit a more precise calculation of the intraclass correlation. The confidence intervals for the estimate of ρ are wide, but even if one assumes that ρ is the largest value in the 95% confidence interval (0.12), then this value is still small and indicates that the magnitude of intraclass correlation is minimal at best. In the subgroup analysis of multiple lesions within the same vessel, the 95% confidence interval for the intraclass correlation coefficient did extend as high as 0.62, indicating that a moderate correlation may exist. Further studies with a large number of lesions dilated in each patient would be needed to independently confirm these results. Although the majority of multilesson cases were conventional PTCA procedures, the general linear model of intraclass correlation controls for each of the various device types as a potential covariate. Further studies with a larger number of new devices per patient would also be useful. Although many years of follow-up would be useful to detect concordance in the behavior of lesions in an atherosclerosis regression trial, restenosis usually occurs within months of the procedure, and a longer period of follow-up in these patients would be unlikely to detect a significant correlation among lesions.

Conclusions

Luminal renarrowing occurs at independent within the same patient when multiple lesions are dilated. The fact that multiple lesions within the same patient seem to behave independently justifies a lesion-based analysis of angiographic restenosis data. There is also no apparent difference between single-lesion and multilesson procedures in the magnitude or incidence of restenosis, and therefore angiographic data from these two types of procedures can be analyzed together.

Acknowledgments

We would like to thank Marion McPhee for her statistical programming assistance and Cynthia Senerchia, RN, MS, for her assistance in creating the new device data base.

Appendix

A general linear model with intraclass correlation was used to calculate the coefficient of correlation among multiple lesions within the same patient for the late loss in luminal diameter according to the following procedure:

\[ y_i = \alpha + \beta x_i + \gamma_2 z_{i2} + \gamma_3 z_{i3} + \sum_{l=1}^{q} \lambda_1 w_{i1} + \epsilon_{i} \]  

(1)

where \( y_i \) = late loss in arterial diameter over 30 months, \( i = \) subject; \( j = \) lesion within subject, \( x_i = \) initial arterial diameter, \( z_{i2} \) and \( z_{i3} \) are the device type indicator variables, \( w_{i1}, \ldots, w_{i4} \) are a group of other covariates, and

\[ \epsilon_{i} \sim N(0, \sigma^2), \rho(\epsilon_{ij}, \epsilon_{ij}) = \rho, i = 1, \ldots, n; j = 1, \ldots, k_i \]  

(2)

where \( \rho \) is the correlation between residuals. Thus, there are \( n \) persons where the \( i^{th} \) person contributes \( k_i \) lesions to the analysis. Therefore, one can treat this as a general linear model problem with intraclass correlation and estimate both the regression coefficients and their statistical significance as well as the correlation among multiple lesions all in the same analysis. The covariates controlled for in this model included the initial lesion diameter, the postprocedure luminal diameter, the reference segment diameter, the lesion location, whether the lesion had restenosed previously, and patient age and sex. All lesions were included in the model in order to estimate the \( \beta \)-coefficients in the regression model. The calculation of the intraclass correlation coefficient was based on the analysis of all 520 lesions from 441 patients.

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