Reference Chart Derived From Post–Stent-Implantation Intravascular Ultrasound Predictors of 6-Month Expected Restenosis on Quantitative Coronary Angiography

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Reference Chart Derived From Post–Stent-Implantation Intravascular Ultrasound Predictors of 6-Month Expected Restenosis on Quantitative Coronary Angiography

P.J. de Feyter, MD, PhD; P. Kay, MD; C. Disco, MSC; P.W. Serruys, MD, PhD

Background—Intravascular ultrasound (IVUS)–guided stent implantation and the availability of a reference chart to predict the expected in-stent restenosis rate based on operator-dependent IVUS parameters may interactively facilitate optimal stent placement. The use of IVUS guidance protects against undue risks of dissection or rupture.

Methods and Results—IVUS-determined post–stent-implantation predictors of 6-month in-stent restenosis on quantitative coronary angiography (QCA) were identified by logistic regression analysis. These predictors were used to construct a reference chart that predicts the expected 6-month QCA restenosis rate. IVUS and QCA data were obtained from 3 registries (MUSIC [Multicenter Ultrasound Stenting in Coronaries study], WEST-II [West European Stent Trial II], and ESSEX [European Scimed Stent EXperience]) and 2 randomized in-stent restenosis trials (ERASER [Evaluation of ReoPro And Stenting to Eliminate Restenosis] and TRAPIST [TRapidil vs placebo to Prevent In-STent intimal hyperplasia]). In-stent restenosis was defined as luminal diameter stenosis $\geq 50\%$ by QCA. IVUS predictors were minimum and mean in-stent area, stent length, and in-stent diameter. Multiple models were constructed with multivariate logistic regression analysis. The model containing minimum in-stent area and stent length best fit the Hosmer-Lemeshow goodness-of-fit test. This model was used to construct a reference chart to calculate the expected 6-month restenosis rate.

Conclusions—The expected 6-month in-stent restenosis rate after stent implantation for short lesions in relatively large vessels can be predicted by use of in-stent minimal area (which is inversely related to restenosis) and stent length (which is directly related to restenosis), both of which can be read from a simple reference chart. (Circulation. 1999;100:1777-1783.)

Key Words: ultrasonics ▪ angiography ▪ restenosis ▪ stents

Intracoronary stent implantation has unequivocally been shown to reduce the frequency of 6-month in-stent restenosis in focal lesions in relatively large coronary vessels.1^4 Intravascular ultrasound (IVUS) has successfully been used to guide stent implantation and often results in a wider stented lumen, which may, according to the “bigger is better” principle, further reduce the restenosis rate.5^21 In the present study, we sought to identify post–stent-implantation IVUS predictors of in-stent restenosis. These parameters are partly operator dependent and are available online; thus, they can be adjusted by the operator during actual stent implantation to achieve the best possible result.

We performed a meta-analysis to determine final post–stent-implantation IVUS predictors of 6-month restenosis (diameter stenosis $\geq 50\%$) by quantitative coronary angiography (QCA) after stent implantation in focal lesions and large vessels. Patients were selected from 3 stent registries (MUSIC [Multicenter Ultrasound Stenting in Coronaries study],14 WEST-II [West European Stent Trial II],22 and ESSEX [European Scimed Stent EXperience]) and from 2 randomized trials investigating the efficacy of a pharmaceutical agent on in-stent restenosis (ERASER [Evaluation of ReoPro And Stenting to Eliminate Restenosis] and TRAPIST [TRapidil vs placebo to Prevent In-STent intimal hyperplasia]). The latter 2 trials did not demonstrate a significant difference between drugs and placebo, and thus for the present study, all patients groups were combined. The registries and trials have been considered together because the IVUS and QCA analyses used were performed in the same core laboratory.

The analysis was performed by a multistep approach. First, IVUS predictors for 6-month in-stent (QCA) restenosis were identified. Second, various univariate and multivariate models were constructed with these parameters to predict the observed restenosis. Third, models were selected that had the best fit on the Hosmer-Lemeshow goodness-of-fit test. Finally, from the best-fit models, the model with the most easily obtainable and clinically relevant parameters was selected.
and a reference chart was constructed that predicted the expected angiographic in-stent restenosis rate after stent implantation of short lesions in relative large vessels.

**Methods**

Patients were selected from 3 stent registries and 2 randomized restenosis trials (Table 1). Only patients who underwent single-lesion treatment were enrolled. Various stent types were implanted: 2 balloon-expandable stents (15-mm Palmaz-Schatz, Cordis Corp; and 15-mm Multi-Link, Guidant/Advanced Cardiovascular Systems) and 2 self-expanding stents (14-mm Radius, Scimed Life Systems; and the Wallstent, Schneider Europe [various stent lengths]) were used. All registries and trials used intracoronary ultrasound as guidance for optimal stent implantation. Patients were included in the present study if they had both an adequate final post-stent-implantation IVUS examination and a 6-month coronary angiogram to establish the restenosis rate. Six-month in-stent restenosis was determined with QCA and was defined as an in-stent luminal diameter stenosis $\geq 50\%$. The restenosis rate in the above-mentioned studies varied from 9.8% to 25.7%.

Baseline clinical characteristics are shown in Table 2. Overall, there were only small differences between the various patient groups except for the severity of angina, which was less severe in the WEST-II and ESSEX registries, and the higher frequency of prior myocardial infarction in the ERASER and TRAPIST randomized trials.

**Intravascular Ultrasound**

Three different intracoronary ultrasound imaging devices were used. The CVIS (Microview) has a 30-MHz single-element bevelled transducer that rotates at 1800 rpm within a 3.5F short-monorail imaging catheter. The Endosonics Europe device consists of 64 elements mounted on the end of a flexible shaft that rotates at 1800 rpm within a 3.2F short-monorail imaging catheter. The Hewlett-Packard/Boston Scientific Corp device incorporates a single-element 30-MHz bevelled monorail transducer that rotates at 1800 rpm within a 3.5F short-monorail imaging catheter. The video signal was recorded on a high-resolution super-VHS tape. The videotape was used to obtain manual online in-stent IVUS measurements to guide stent implantation. In-stent diameter (mm), in-stent minimum area (mm$^2$), and lumen measurements at the 3- to 5-mm reference area proximal and distal to the stented segment were obtained. Stent apposition to the vessel wall and symmetrical stent expansion were reviewed over the entire stented segment. Optimal IVUS-guided stent implantation was attempted with the MUSIC criteria (complete stent apposition, symmetrical expansion, and adequate in-stent cross-sectional area), but it was left to the discretion of the operator to stop further attempts to achieve these criteria if additional dilation might pose a significant risk of dissection or rupture.

**Quantitative IVUS Measurements**

A Microsoft Windows-based contour-detection program was used for automated 3D analysis of IVUS images. The contour-detection program was performed in 2 steps. First, 2 longitudinal sections were constructed from the 3D data set, and an automated contour-detection algorithm determined lumen-intima and media-adventitia boundaries of nonstented segments and lumen-stent boundary in stented segments. The contour-detection program uses a minimum-cost–based algorithm. These longitudinal contours were used to define regions of interest in the individual cross-sectional IVUS images. Next, the regions of interest were used to guide the second-final automated contour detection in these cross sections. A cursor on the longitudinal sections indicated the individual cross sections and allowed scrolling through the entire cross-sectional data set, to allow the technician to assess the automatically detected

<table>
<thead>
<tr>
<th>Trial</th>
<th>Stent</th>
<th>Patients Recruited in Study, n</th>
<th>Patients With IVUS at Baseline, n</th>
<th>Study Patients With IVUS at Baseline and QCA at Follow-Up, n</th>
<th>Type of Study</th>
<th>IVUS-Guided Stenting</th>
<th>Restenosis by QCA, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Balloon-expandable stents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MUSIC</td>
<td>P-S (15 mm)</td>
<td>161</td>
<td>151</td>
<td>140</td>
<td>Registry</td>
<td>Yes</td>
<td>9.8</td>
</tr>
<tr>
<td>WEST-II</td>
<td>Multi-Link (15 mm)</td>
<td>165</td>
<td>151</td>
<td>137</td>
<td>Registry</td>
<td>Yes</td>
<td>11.7</td>
</tr>
<tr>
<td>ERASER</td>
<td>P-S (15 mm)</td>
<td>215</td>
<td>190</td>
<td>162</td>
<td>Randomized</td>
<td>Yes</td>
<td>19.8</td>
</tr>
<tr>
<td><strong>Self-expanding stents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESSEX</td>
<td>Radius (14 mm)</td>
<td>103</td>
<td>92</td>
<td>89</td>
<td>Registry</td>
<td>Yes</td>
<td>21.3</td>
</tr>
<tr>
<td>TRAPIST</td>
<td>Wallstent (29 mm)</td>
<td>312</td>
<td>274</td>
<td>245</td>
<td>Randomized</td>
<td>Yes</td>
<td>25.7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>956</td>
<td>858</td>
<td>773</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P-S indicates Palmaz-Schatz.
The SD of differences varied between 4% and 9.5%.\(^{16,17}\)

Both adjacent images.

The number of images analyzed multiplied by the distance between 2 encompassing the index volume. In-stent length was calculated as

\[ V = \sum_{i=1}^{n} A_i \cdot H \]

where \( V \) is volume, \( A \) is cross-sectional area of stent, \( H \) is thickness of the coronary slice, and \( n \) is the number of digitized cross sections encompassing the index volume. In-stent length was calculated as the number of images analyzed multiplied by the distance between 2 adjacent images.

The intraobserver and interobserver variabilities were <1.0%, and the SD of differences varied between 4% and 9.5%.\(^{16,17}\)

**Quantitative Coronary Angiography**

The minimal in-stent lumen diameter was determined on an end-diastolic frame by use of a computer-based Coronary Angiography Analysis System (CAAS II: Pie Medical). The edge-detection algorithm is based on the weighted sum of the first- and second-derivative functions applied to the digitized brightness silhouette.\(^{23}\)

The diameter function of the coronary artery lumen was determined by computing the shortest distance between the edge points of the right and left boundaries. The minimum lumen diameter was defined as the shortest distance between all measured left and right boundaries. The interpolated diameter was based on a computer estimation of the original lumen diameter, determined at the site of the minimum lumen diameter by taking into account the diameter function of the proximal and distal references. The diameter stenosis was derived from the measured minimum lumen diameter and the interpolated reference diameter.

**Statistical Analysis**

Statistical analysis was performed with SAS version 6.12. Quantitative data are given as mean±SD and qualitative data as frequencies.

IVUS parameters concerning volumetric measurements were not available in ∼67% of the patients selected from the MUSIC trial because a manual IVUS pullback was performed. Multiple IVUS parameters were tested by univariate logistic regression analysis to determine 6-month QCA restenosis predictors. With multivariate logistic regression analysis, multiple models containing IVUS parameters predictive of 6-month restenosis were constructed. These models were then tested by use of the Hosmer-Lemeshow goodness-of-fit test to choose the most appropriate model. In the Hosmer-Lemeshow goodness-of-fit test, an estimated event probability is calculated from the observations by use of a model. These observations are then sorted in order of their estimated event probability and divided into ∼10 groups (g) of approximately equal size. The Hosmer-Lemeshow goodness-of-fit statistic is obtained by calculating the Pearson \( \chi^2 \) test from the \( 2 \times g \) table of the observed and expected frequencies. The greater the \( P \) value, the better the model fits the data.

**Results**

The final post–stent-implantation IVUS measurements that were obtained in the various studies are tabulated in Table 3. In the MUSIC registry, the largest minimal in-stent cross-sectional area was achieved. The length of the implanted stent was longer, and consequently the in-stent volume was higher in the TRAPIST trial, which used Wallstents. The reference vessel diameter was smallest in the ESSEX registry. Univariate analysis of postprocedure final IVUS parameters showed that type of stent and all dimensional in-stent parameters except in-stent volume were significant predictors of restenosis (Table 4).

Multiple models were constructed with the IVUS parameters in univariate and multivariate analyses. When the Hosmer-Lemeshow goodness-of-fit test was used, 4 potentially appropriate models emerged (Table 5). One model was based on 1 parameter only (minimum in-stent area); the other 3 models were based on 2 parameters, and all 3 used stent length in combination with stent volume, mean stent area, or minimum stent area. Addition of any third parameter to a model did not significantly improve the predictive power. The combination of stent length and minimum in-stent area was chosen as the most easily obtainable and clinically

**TABLE 3. Final IVUS Measurements After Stent Implantation**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MUSIC (n=151)</th>
<th>WEST-II (n=151)</th>
<th>ERASER (n=190)</th>
<th>ESSEX (n=92)</th>
<th>TRAPIST (n=274)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum in-stent area, mm(^2)</td>
<td>7.85±0.2</td>
<td>7.39±1.9</td>
<td>7.04±2.0</td>
<td>6.96±2.0</td>
<td>6.17±1.9</td>
</tr>
<tr>
<td>Projected minimum lumen diameter, mm</td>
<td>2.77±0.4</td>
<td>2.78±0.4</td>
<td>2.67±0.4</td>
<td>2.67±0.4</td>
<td>2.59±0.4</td>
</tr>
<tr>
<td>Mean in-stent area, mm(^2)</td>
<td>9.45±2.4</td>
<td>8.95±2.2</td>
<td>8.71±2.3</td>
<td>8.53±2.3</td>
<td>7.83±2.1</td>
</tr>
<tr>
<td>Stent volume, mm(^3)</td>
<td>NA</td>
<td>154.7±5</td>
<td>168.113</td>
<td>128.58</td>
<td>227.131</td>
</tr>
<tr>
<td>Stent length, mm</td>
<td>NA*</td>
<td>17.4±6.6</td>
<td>19.5±11.9</td>
<td>14.8±4.2</td>
<td>28.6±13.2</td>
</tr>
<tr>
<td>Mean reference lumen area, mm(^2)</td>
<td>9.45±2.5</td>
<td>9.59±3.1</td>
<td>9.0±3.3</td>
<td>8.72±2.9</td>
<td>9.34±4.1</td>
</tr>
</tbody>
</table>

*NA indicates not available in all patients.

*The length of the stent was 15.2±2.0, which was obtained from angiographic data.

**TABLE 4. IVUS Parameters After the Procedure: Univariate Analysis of Predictors of Restenosis Rate**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum in-stent area</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Projected minimum lumen diameter</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean in-stent area</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stent volume</td>
<td>0.174</td>
</tr>
<tr>
<td>Stent length</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean reference lumen area</td>
<td>0.020</td>
</tr>
</tbody>
</table>

Type of stent (Palma-Schatz, Radius, Multi-Link, Wallstent) 0.014
relevant parameters. The observed and expected restenosis rates of this model are depicted in Figure 1. The model remained accurate after the same analysis was performed with exclusion of Wallstent patients (who are known to have a higher restenosis rate), but the CIs were wider.

Next, a reference chart was developed (Table 6 and Figure 2) that can be used as a ready reference to estimate the expected in-stent restenosis rate with stent length and post–stent-implantation minimal in-stent area. The ranges of the 2 variables were divided into 10 groups each. The expected restenosis rate for the median of each range was calculated along with the 95% CIs for that particular value. The expected restenosis rate is given, as well as the CI.

The majority of observations were clustered around 15-mm-length stents and a minimum in-stent area of 8 mm$^2$ (Figure 3). Values in Table 6 that are marked by asterisks were calculated by extrapolation from the model because there were no actual observations in that range. The reference chart in these ranges should be used with caution.

**Discussion**

In-stent restenosis remains a significant clinical problem because it is difficult to treat. IVUS-guided stent implantation has optimized stent expansion, and the initial higher lumen area achieved has been associated with a lower 6-month restenosis rate.$^{14,18}$ We reasoned that construction of a reference chart based on simple, easily obtainable, clinically relevant IVUS post–stent-implantation parameters that predicts the expected 6-month restenosis rate would be clinically useful. First, online knowledge of an expected restenosis rate based on IVUS-determined post–stent-implantation lumen dimensions and stent length obtained while the procedure is being performed may serve as an extra stimulus to attempt to achieve the best possible result of stent implantation, whereas IVUS guidance may reduce the undue risks of dissection or vessel rupture.$^{12}$ Second, a priori knowledge of the expected restenosis rate based on the lesion length and vessel size, which are decisive in stent size and length selection, may be useful in counseling patients whether to select a percutaneous intervention or bypass surgery. Third, it may be helpful to discuss the probability of restenosis after stent implantation and accordingly plan closer monitoring of patients. Fourth, the reference chart may be helpful to plan and power future in-stent restenosis studies.

IVUS variables, including in-stent area, extent of preexisting plaque, smaller vessel size, stenting of total occlusions, and history of diabetes mellitus, as well as implantation of a long stent, have been shown to predict in-stent restenosis.$^{10,20,21,24–26}$ In the present study, we found that 2 IVUS variables (minimum in-stent area and stent length) were strong predictors of 6-month restenosis. Using these 2 variables, it was possible for us to construct a reference chart that predicts the 6-month expected restenosis rate. Basically, the chart demonstrates that the widest in-stent area has the lowest restenosis rate, and the longer the implanted stent, the higher the restenosis rate. The achievement of maximal in-stent

**Figure 1.** Reliability of model comparing observed vs expected 6-month restenosis rate (y axis) in various Hosmer-Lemeshow groups (x axis). Ideally, the observed and expected restenosis rates should be identical.
dimensions expressed in terms of diameter, area, or volume is in keeping with the “bigger is better” theory and thus is associated with a lesser likelihood of reaching the expected restenosis rate.8,10,13,20,27,28

The inverse relation of stent length and 6-month restenosis may be explained by the purely statistical fact that a longer stent has a higher chance of restenosis. However, a preexisting longer lesion, known to be associated with a higher restenosis rate, may be responsible. The inverse relation between stent length and restenosis may be taken as an argument for choosing a conservative stent-length implantation approach or “spot” stenting, but the efficacy of this approach should be tested in an appropriate randomized trial.

In the individual studies (Table 1), the restenosis rate was higher in self-expanding stents than balloon-expandable stents, which suggests that the stent design may be associated with differences in restenosis rates. However, in the multivariate analysis, once we used the parameters of stent length and an area or volume measurement, stent design did not retain significance. It has been suggested that Wallstent implantation confers a higher restenosis rate. Therefore, we performed an analysis excluding Wallstent patients. The model was still accurate, but because of the lesser number of observations, it obviously is less reliable, with wider CIs.

We selected QCA at 6 months as our restenosis end point because the angiographic criterion of 50% diameter stenosis is a generally accepted criterion and can also be used, in contrast to IVUS-obtained restenosis parameters, in case of severe in-stent restenosis or a totally occluded stent.29

**Table 6. Reference Chart**

<table>
<thead>
<tr>
<th>Stent Length, mm</th>
<th>Minimum In-Stent Area, mm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.0–3.9</td>
<td>0.30 (0.22–0.40)</td>
</tr>
<tr>
<td>3.9–4.8</td>
<td>0.25 (0.19–0.32)</td>
</tr>
<tr>
<td>4.8–5.7</td>
<td>0.21 (0.16–0.26)</td>
</tr>
<tr>
<td>5.7–6.6</td>
<td>0.17 (0.13–0.21)</td>
</tr>
<tr>
<td>6.6–7.5</td>
<td>0.13 (0.11–0.17)</td>
</tr>
<tr>
<td>7.5–8.4</td>
<td>0.11 (0.08–0.14)</td>
</tr>
<tr>
<td>8.4–9.3</td>
<td>0.08 (0.06–0.12)</td>
</tr>
<tr>
<td>9.3–10.2</td>
<td>0.07 (0.04–0.10)</td>
</tr>
<tr>
<td>10.2–11.1</td>
<td>0.05 (0.03–0.09)</td>
</tr>
<tr>
<td>11.1–12.0</td>
<td>0.04 (0.02–0.08)</td>
</tr>
</tbody>
</table>

From IVUS-determined post–stent-implantation minimum in-stent area and stent length, one can extrapolate the expected 6-month QCA restenosis rate. The range of the 2 variables is divided into 10 groups each. The expected restenosis rate for the median of each range was calculated along with the 95% CI for this particular value (indicated in parentheses).

*There were no actual observations in this range; figures presented are calculated by extrapolation from the model.

![Figure 2](image1.png) **Figure 2.** Three-dimensional representation of restenosis rate (y axis) in relation to minimum in-stent area (x axis) and stent length (z axis).

![Figure 3](image2.png) **Figure 3.** Frequency distribution of number of observations (y axis) according to minimum in-stent area (x axis) and stent length (z axis).
Study Limitations
The study was performed in patients with focal lesions in relative large coronary vessels. Additional studies are needed to confirm that our results are also applicable in smaller vessels or for longer lesions. Although this study was an analysis of >750 observations, the majority of these observations were clustered around a stent length of 15 mm and an in-stent minimum area of 8.0 mm², and many fewer observations were obtained for other stent lengths and in-stent cross-sectional areas, so that refinements may be expected from calculations obtained from a much larger data bank that includes a wide variety of in-stent cross-sectional areas and stent lengths.

The inclusion of stent length as a predictor of restenosis may be confounded by other factors, such as overlap of stent, implantation of long stents to cover initial long lesion, or long dissection, all of which may influence restenosis. However, the inclusion of these observations would more reliably reflect real-world stenting.

Currently, there is a wide variety of stent types commercially available. Our data are only applicable to the Palmaz-Schatz, Multi-Link, Radius, and Wallstents. Other stent designs (for instance, Gianturco-Roubin®) may behave differently, and additional studies are needed to confirm the applicability of our reference chart to other stent types.

Conclusions
We constructed a reference chart that, by use of the IVUS-determined length of the implanted stent and the minimum in-stent area, predicted the 6-month QCA restenosis rate. Thus far, this reference chart is only applicable for stent implantation in short lesions in relatively large vessels. The reliability of this reference chart must be confirmed in a prospective study.

Acknowledgments
We pay tribute to all investigators who were involved in the MUSIC, WEST-II, and ESSEX registries and ERASER and TRAPST randomized trials, without whose efforts this study would not have been possible. We wish to thank the core laboratory technicians and database managers at Cardialysis Rotterdam. Finally, we thank Claudia Sprenger de Rover for expert secretarial assistance.

References


