Predictive Factors of Restenosis After Coronary Stent Placement

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Objectives. The objective of this study was to identify clinical, lesional and procedural factors that can predict restenosis after coronary stent placement.

Background. Coronary stent placement reduces the restenosis rate compared with that after percutaneous transluminal coronary angioplasty (PTCA). However, restenosis remains an unresolved issue, and identification of its predictive factors may allow further insight into the underlying process.

Methods. All patients with successful coronary stent placement were eligible for this study unless they had had a major adverse cardiac event during the 1st 30 days after the procedure. Of the 1,349 eligible patients (1,753 lesions), follow-up angiography at 6 months was performed in 80.4% (1,084 patients, 1,399 lesions). Demographic, clinical, lesional and procedural data were prospectively recorded and analyzed for any predictive power for the occurrence of late restenosis after stenting. Restenosis was evaluated by using three outcomes at follow-up: binary restenosis as a diameter stenosis ≥50%, late lumen loss as lumen diameter reduction and target lesion revascularization (TLR) as any repeat PTCA or coronary artery bypass surgery involving the stented lesion.

Results. Multivariate analysis demonstrated that diabetes mellitus, placement of multiple stents and minimal lumen diameter (MLD) immediately after stenting were the strongest predictors of restenosis. Diabetes increased the risk of binary restenosis with an odds ratio (OR) [95% confidence interval] of 1.86 [1.56 to 2.16] and the risk of TLR with an OR of 1.45 [1.11 to 1.80]. Multiple stents increased the risk of binary restenosis with an OR of 1.81 [1.55 to 2.06] and that of TLR with an OR of 1.94 [1.66 to 2.22]. An MLD <3 mm at the end of the procedure augmented the risk of binary restenosis with an OR of 1.81 [1.55 to 2.06] and that of TLR with an OR of 2.05 [1.77 to 2.34]. Classification and regression tree analysis demonstrated that the incidence of restenosis may be as low as 16% for a lesion without any of these risk factors and as high as 59% for a lesion with a combination of these risk factors.

Conclusions. Diabetes, multiple stents and smaller final MLD are strong predictors of restenosis after coronary stent placement. Achieving an optimal result with a minimal number of stents during the procedure may significantly reduce this risk even in patients with adverse clinical characteristics such as diabetes.

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Coronary stent placement is increasingly used to improve the early outcome (1,2) and reduce late restenosis after percutaneous transluminal coronary angioplasty (PTCA) (3,4). The problem of early stent occlusion has been minimized by a better antithrombotic regimen after PTCA (5). The Intracoronary Stenting and Antithrombotic Regimen (ISAR) trial has shown that this strategy is particularly effective in high risk patients (6); hence, the broadening of indications for stent placement is now well justified. However, even a restenosis rate of 20% to 30% after stenting (3,4,7), often achieved in rather selected lesions (3,4), continues to impose a relevant limitation to the management of patients with coronary artery disease. The pathogenesis of restenosis is not completely understood (8), and identifying predictive factors may allow some insight into this complex process. Numerous studies have examined the role of various clinical, angiographic and procedural factors in predicting restenosis after PTCA. However, specific aspects of stent placement technique as well as of stent-induced vascular injury and repair may not justify extrapolation of these findings to patients after coronary stent implantation. Intravascular ultrasound studies suggested that neointimal hyperplasia might be the sole mechanism responsible for restenosis after stenting (9), in contrast to conventional coronary angioplasty where arterial remodeling has a predominant role in late lumen renarrowing (10). Furthermore, knowledge of risk factors for restenosis after coronary stent placement may help to optimize indications and stent deployment technique and to guide strategies against this vexing problem. The objective of the present study was to identify clinical, lesional and procedural factors able to predict restenosis after coronary stenting.

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Methods

 Patients. Stenting was attempted in 1,494 patients at our institution during the period from May 1992 through April 1996. Indications for stenting were extensive coronary artery dissections or suboptimal results (residual stenosis >30%) after PTCA and lesions in venous bypass grafts. We excluded from this study patients with coronary stent implantation in the setting of cardiogenic shock complicating acute myocardial infarction (37 patients, 2.5%); patients with unsuccessful stenting, defined as failure to place the stent at the desired site or to achieve a satisfactory angiographic result (i.e., residual stenosis <30%) (41 patients, 2.7%); patients with stenting intended primarily as a bridge to coronary bypass graft surgery (CABG) (11 patients, 0.7%); patients with any major adverse cardiac event during the 1st 30 days after the procedure such as death, myocardial infarction, CABG, repeat PTCA or stent vessel occlusion (56 patients, 3.7%). Thus, 1,349 patients with successful stent placement in 1,753 coronary lesions were eligible for this study. All were asked to undergo control angiography and clinical follow-up at 6 months (or earlier in case of symptoms or objective signs of ischemia). If the angiographic control study had taken place before the preset time and had not resulted in a reintervention at the target lesion, the patients were encouraged to undergo repeat angiography. Follow-up angiography at a median of 188 days (interquartile range 173 to 203 days) was carried out in 1,084 patients (80.4%), representing 1,399 lesions for analysis.

Stent placement and post-stenting treatment. The stent implantation technique has been described previously (2). All patients received heparin (15,000 U) and aspirin (500 mg) intravenously before PTCA. Short 7-mm or articulated 15-mm Palmaz-Schatz stents (Johnson & Johnson) were delivered under fluoroscopic guidance after having been hand-crimped on conventional angioplasty balloons. In all cases conventional balloon angioplasty was the only procedure performed before stent placement. Balloon size and pressure were at the operator’s discretion. Multiple stents were deployed if necessary to cover the full extent of the target lesion or the dissection if it occurred. Adequacy of the final result was based solely on the angiographic assessment; intravascular ultrasound was used in <10% of cases.

After sheath removal and application of a pressure bandage, heparin infusion was started in all patients and continued for 12 h. All patients were given aspirin (100 mg orally twice daily) throughout the study. Subsequent therapy depended on the treatment strategy selected, reflecting the overall changing attitude in this respect. In the 1st 2 years of this study patients were treated with an anticoagulation regimen comprising heparin for 5 to 10 days and phenprocoumon (Marcumar, Hoffmann-La Roche, Grenzach-Wyhlen, Germany) for 4 to 6 weeks, whereas most patients in the last 2 years were treated with combined antiplatelet therapy with ticlopidine (250 mg twice daily) in addition to aspirin.

Coronary angiographic evaluation. Qualitative angiographic assessment was done by the operator during or immediately after the procedure. The angiogram was assessed for the presence of vessel occlusion before PTCA or stenting and dissections (11) immediately before stent placement. The vessel was considered occluded in the presence of Thrombolysis in Myocardial Infarction (TIMI) flow grade 0 or 1. The occlusion was considered recent in the setting of acute myocardial infarction or if it occurred as a complication of the PTCA procedure preceding stent implantation; otherwise it was considered chronic.

Quantitative angiographic analysis was made by operators not involved in the intervention who used the automated edge detection system CMS (Medis Medical Imaging Systems, Nuenen, The Netherlands). The contrast-filled nontapered catheter tip was used for calibration. Minimal lumen diameter (MLD), reference diameter (RD), percent diameter stenosis as well as the diameter of the maximally inflated balloon were obtained from this analysis system. The measurements were done for the angiogram before and immediately after stenting, and for that recorded at follow-up. Balloon/vessel ratio was calculated as diameter of the inflated balloon divided by the coronary RD. Late loss was computed as the difference between the final post-stenting MLD and the MLD found at follow-up angiography.

Risk factors analyzed and study end points. All demographic, clinical, angiographic and procedural characteristics were recorded prospectively. They were selected as potential risk factors for restenosis on the basis of earlier experience with PTCA. Age, gender, the presence of hypercholesterolemia, systemic arterial hypertension, smoking, diabetes mellitus, acute myocardial infarction, unstable angina pectoris, multivessel disease, previous PTCA, recent occlusion, chronic occlusion and dissection, as well as vessel stented, RD and MLD before stenting, maximal balloon pressure, balloon/vessel ratio and MLD immediately after stenting were variables included in the list. It had previously been shown (12,13) that lesions in the left anterior descending coronary artery (LAD) have a higher risk of restenosis. Therefore, the target vessel was simplified here by distinguishing LAD and non-LAD. In addition, a specific factor for stenting, the number of stents implanted, was included. Because of the frequent use of short (7-mm) stents, the 7-mm stent was used as the unit of measure of this variable. Therefore, a standard articulated Palmaz-Schatz stent was counted as two stent units. Multiple
This method with its flow chart–like graphic presentation helps outcomes (S-Plus version 3.3, StaSci Division, MathSoft, Inc.).

The end points of the study were three different measures of lesion restenosis at 6 months: binary restenosis defined as a \( \geq 50\% \) diameter stenosis at follow-up, late lumen loss as defined above and target lesion revascularization (TLR) as a binary variable. TLR was defined as repeat PTCA or CABG involving the stented lesion, driven by clinical signs of ischemia in the presence of angiographic restenosis. We used these three measures of restenosis to correct for the weaknesses presented by each of them alone.

**Data analysis.** Possible differences in the risk factor profile for restenosis between the groups with and without follow-up angiography were checked by means of the \( t \) test for independent samples (two-sided test) for continuous data and chi-square test for discrete data. To control for the errors produced by possible deviations of the continuous variables from a normal distribution, this analysis was validated by using nonparametric methods such as the Mann-Whitney test, which yielded similar results.

The main analysis tested the association of any risk factor with a worse outcome at follow-up in terms of the three end points of this study. We chose to make an analysis on a per lesion basis because there is convincing evidence (14,15) for a lesion dependence of restenosis. However, we checked the validity of this approach by repeating the most important analyses on a per patient basis as well. All continuous variables were first transformed to binary data with 1 for the presence of the assumed risk factor and 0 otherwise. We used the median of each variable as the cutoff point for this division, avoiding the use of any other arbitrary value.

We used three methods of analysis. 1) The risk each factor presents for the three end points of the study was estimated by means of univariate analysis, performing chi-square tests and calculating the relative risk in the case of binary restenosis and TLR and \( t \) test for independent samples (two-sided) for late lumen loss. 2) Multivariate stepwise logistic regression analysis was carried out to identify independent correlates of restenosis and TLR. All potential risk factors were part of the model. We did not preselect independent variables to enter into the model in order to avoid a bias by arbitrarily canceling possible independent or interaction effects of some variables. The significant risk factors are presented with their respective odds ratio (OR) calculated by the logistic regression program (SPSS version 7.0, SPSS Inc.). Stepwise multiple linear regression was used for late lumen loss; the results presented consist of the regression coefficients for the significant correlates. 3) We used a tree-based modeling technique of predictive factors for restenosis and TLR rates. This was done by constructing classification and regression trees (CART) for both binary outcomes (S-Plus version 3.3, StaSci Division, MathSoft, Inc.). This method with its flow chart–like graphic presentation helps in a simple and very demonstrative way to predict the outcome of patients in the presence of one or more risk factors before a decision is made on the treatment strategy. A disadvantage of this method is that it does not take into account a possible interplay of the risk factors entered into the model. For this reason we constructed the CART using only the independent correlates of the outcome as determined by logistic regression analysis. Only the first four divisions of the tree were retained, because the tree becomes less stable with more levels and loses its informative power.

Data are expressed as percent for discrete variables and as mean value \( \pm \) SD for continuous variables. Statistical significance was accepted for all \( p \) values \(<0.05\).

**Results**

Table 1 compares the two groups with and without control angiography at 6-month follow-up. The patients without angiography were older, had a higher incidence of acute myocardial infarction, multivessel disease and were more often treated with antiplatelet agents than their counterparts with follow-up angiography. They also had a lower incidence of smoking, unstable angina and dissections, a greater MLD before stenting and fewer stents implanted than the group with follow-up angiography.
Univariate analysis. Several analyzed factors were associated with differences with respect to the outcome variables of this study. Thus, the risk for restenosis was higher for lesions in older patients, patients with diabetes or previous PTCA and lesions with chronic occlusions or multiple stents, lesions located in the LAD and lesions with a smaller RD and MLD before stenting and with a smaller MLD after stenting (Fig. 1, left). In contrast, acute infarct-related lesions and, even more surprisingly, lesions of smokers were associated with a lower risk for restenosis. We sought specifically the influence on restenosis of the location of the stent in saphenous vein grafts. In the relatively small number of lesions located in vein grafts in the present study (only 3.4% of the total number of lesions), the restenosis rate of 27.1% did not differ significantly from that of 26.3% encountered in native vessels (p = 0.9). Late lumen loss (Table 2) was significantly greater for lesions in patients with diabetes and previous PTCA, for lesions with multiple stents, a smaller MLD before stenting, bigger balloon/vessel ratio and higher dilation pressure. A lesser late lumen loss was observed only in lesions with a smaller final MLD. The risk for TLR (Fig. 2, left) was associated with fewer factors, in one direction only. A higher risk for TLR was observed for lesions in older and diabetic patients, for lesions with multiple stents and those with smaller vessel size and an MLD <3 mm after stenting.

Multivariate analysis. The predictive model for binary restenosis demonstrated an overall accuracy of 74.2%. It identified six independent factors: multiple stents, diabetes mellitus, LAD location and more severe original stenosis as reflected by a smaller MLD before stenting, whereas the presence of dissections before stenting presented an inverse relation with lumen loss (Table 2). However, the strongest predictor of late lumen loss was the final MLD after stenting (value for its regression coefficient at least twice that of other factors). Its predominant influence in the model may explain the seemingly paradoxical finding of an inverse correlation between RD and late lumen loss. It simply means, for example, that achievement of a 3.00-mm final MLD will be associated with a greater lumen loss in a 2.75-mm vessel than in a 3.25-mm vessel, provided that the other factors remain constant. If we remove final MLD from the model, the relation between RD and lumen loss returns to positive, as expected.

Using the same models we calculated the predicted probabilities of binary restenosis (by means of logistic regression) and the predicted values for late lumen loss (by means of multiple linear regression) for all lesions, including those without follow-up angiography. Interestingly, despite some differences in baseline characteristics, lesions without

Figure 1. Graphic presentation of the results of the univariate and multivariate analysis of the potential risk factors for binary restenosis at follow-up (diameter stenosis ≥50%). Relative risk (left) and OR (right) with their 95% confidence intervals are displayed for the clinical, lesional and procedural variables analyzed.

Univariate analysis

- Age > 62 years
- Woman
- Hypercholesterolemia
- Systemic arterial hypertension
- Smoking
- Diabetes mellitus
- Acute myocardial infarction
- Unstable angina pectoris
- Multivessel disease
- Previous PTCA
- Antiplatelet therapy post-stenting
- Recent occlusions
- Chronic occlusions
- Dissections
- Multiple stents
- LAD lesions
- RD before stenting < 3.08 mm
- MLD before stenting < 0.7 mm
- Balloon to vessel ratio > 1.05
- Maximal balloon pressure > 14 atm
- MLD after stenting < 3 mm

Logistic regression

- Lower Risk
- Higher Risk

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follow-up angiography had only a slightly lower chance of restenosis (25.1% vs. 26.3%, p = 0.042) and a nonsignificant trend for a lower lumen loss (1.06 ± 0.24 vs. 1.08 ± 0.24 mm, p = NS) than did lesions with follow-up angiography.

Fewer variables were retained in the final logistic model for TLR, which showed an overall accuracy of 82%. Post-stenting MLD, multiple stents and diabetes mellitus, the strongest predictors of the previous analyses, were the sole independent risk factors for reintervention (Fig. 2, right panel), with ORs as high as 2.05 for a final MLD < 3 mm.

All of these mentioned analyses were repeated on a per patient basis. This analysis included 1,084 patients enrolled in this study. In patients with multilesion intervention only the first dilated lesion was used for analysis. The three main

**Table 2. Analysis of the Influence of Clinical, Lesional and Procedural Factors on the Degree of Late Lumen Loss After Stenting of 1,399 Lesions in 1,084 Patients**

<table>
<thead>
<tr>
<th>Late Lumen Loss (mm)</th>
<th>Univariate Analysis</th>
<th>Multiple Linear Regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Age &gt;62 yr*</td>
<td>1.09 ± 0.77</td>
<td>1.07 ± 0.74</td>
</tr>
<tr>
<td>Women</td>
<td>1.13 ± 0.78</td>
<td>1.06 ± 0.75</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>1.07 ± 0.76</td>
<td>1.08 ± 0.76</td>
</tr>
<tr>
<td>Systemic arterial hypertension</td>
<td>1.09 ± 0.76</td>
<td>1.06 ± 0.75</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.04 ± 0.77</td>
<td>1.11 ± 0.75</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.27 ± 0.81</td>
<td>1.04 ± 0.74</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>1.09 ± 0.75</td>
<td>1.08 ± 0.76</td>
</tr>
<tr>
<td>Unstable angina pectoris</td>
<td>1.10 ± 0.78</td>
<td>1.07 ± 0.74</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>1.07 ± 0.77</td>
<td>1.12 ± 0.72</td>
</tr>
<tr>
<td>Previous PTCA</td>
<td>1.17 ± 0.80</td>
<td>1.06 ± 0.74</td>
</tr>
<tr>
<td>Antiplatelet therapy after stenting</td>
<td>1.09 ± 0.74</td>
<td>1.06 ± 0.80</td>
</tr>
<tr>
<td>Recent occlusions</td>
<td>1.12 ± 0.75</td>
<td>1.08 ± 0.76</td>
</tr>
<tr>
<td>Chronic occlusions</td>
<td>1.23 ± 0.84</td>
<td>1.07 ± 0.75</td>
</tr>
<tr>
<td>Dissections</td>
<td>1.08 ± 0.76</td>
<td>1.08 ± 0.75</td>
</tr>
<tr>
<td>Multiple stenting</td>
<td>1.26 ± 0.80</td>
<td>0.99 ± 0.72</td>
</tr>
<tr>
<td>LAD lesions</td>
<td>1.12 ± 0.73</td>
<td>1.05 ± 0.77</td>
</tr>
<tr>
<td>RD before stenting &lt; 3.08 mm*</td>
<td>1.09 ± 0.70</td>
<td>1.07 ± 0.81</td>
</tr>
<tr>
<td>MLD before stenting &lt; 0.7 mm*</td>
<td>1.13 ± 0.77</td>
<td>1.04 ± 0.74</td>
</tr>
<tr>
<td>Balloon/vessel ratio &gt; 1.05*</td>
<td>1.18 ± 0.75</td>
<td>0.98 ± 0.75</td>
</tr>
<tr>
<td>Maximal balloon pressure &gt; 14 atm*</td>
<td>1.13 ± 0.76</td>
<td>1.02 ± 0.75</td>
</tr>
<tr>
<td>MLD after stenting &lt; 3 mm*</td>
<td>0.97 ± 0.69</td>
<td>1.19 ± 0.80</td>
</tr>
</tbody>
</table>

*Entered as continuous variables in multiple linear regression analysis. Unless otherwise indicated, data are presented as mean value ± SD. CI = confidence interval; . . . = nonsignificant factors; other abbreviations as in Table 1.

![Figure 2](image-url)
independent factors by lesion-based analysis, namely post-stenting MLD, multiple stents and diabetes had the same predictive power in all three multivariate models constructed on a per patient basis. Whereas these three factors were the only independent factors for both binary restenosis and TLR models, the multiple linear regression model for late lumen loss also identified reference and MLD before stenting and lesion location in the LAD as additional independent factors, identical to the per lesion analysis.

The results of the CART analysis allow a very descriptive illustration of the risk of restenosis (Fig. 3) and TLR (Fig. 4).

A lesion with a single stent and an MLD $\geq$ 3 mm at the end of the procedure in a nondiabetic patient has a risk for restenosis as low as 16%. On the other extreme, a lesion in the LAD with multiple stents in a diabetic patient has a risk for restenosis as high as 59.4% (Fig. 3). Similar trends are shown in the tree model for TLR as well (Fig. 4). The lowest risk for reintervention of only 9.8% can be calculated for a lesion with a good final result (MLD $\geq$ 3 mm) after placement of a single stent. The worst outcome with a 43% risk of reintervention can be expected for a lesion in a diabetic patient with a final MLD < 3 mm after placement of multiple stents.

Figure 3. Classification and regression tree (CART) model showing the variables that most strongly influence the likelihood of binary restenosis (diameter stenosis $\geq$ 50%) at follow-up. The solid area of the pie represents the percent of the lesions with restenosis, and the open area of the pie indicates the size of the subgroup relative to the total group. MLDPost = minimal lumen diameter immediately after stenting.

Figure 4. Classification and regression tree model showing the variables that most strongly influence the likelihood of TLR during follow-up. The solid area of the pie represents the percent of the lesions that needed reintervention, and the open area of the pie indicates the size of the subgroup relative to the total group. MLDPost = minimal lumen diameter immediately after stenting.
increased this risk to 54.0% and 43%, respectively. Only 9%, whereas the combined presence of all these factors had a restenosis rate of 16% and a TLR rate of 4.3%. This observation is in keeping with previous studies of stenting (16,17) and PTCA (12,18,19). This higher risk for restenosis and TLR, which confirms reports from previous studies (22,25) and PTCA (12,26–28) and further support the prevailing paradigm in interventional cardiology, “bigger is better” (29). Our finding of a positive correlation between the final MLD after stenting and the amount of lumen loss is in accord with previous clinical (24,28) and experimental studies (30) analyzing the relation between immediate gain and late lumen loss. It does not contradict the inverse relation between final MLD and restenosis, as discussed earlier. This simply signifies that hyperplasia is greater but its impact diminishes as the final result improves.

CART analysis illustrates well the negative impact of the combined presence of diabetes mellitus, multiple stents and smaller final result on the risk of restenosis and reintervention after stenting. With the exception of diabetes, these predictive factors are available only at the end of the procedure, thus discouraging any attempt to predict outcome from baseline characteristics alone. However, this finding helps to design a special procedural strategy for patients with diabetes mellitus before stent deployment. In these patients, the best possible final result should be achieved with the minimal number of stents.

Our study identified several other factors with a less relevant influence on restenosis. The location of the lesion in the LAD, a chronically occluded lesion and previous PTCA augmented the risk of restenosis, as described by previous studies (12,13,17,31,32). Moreover, smaller MLDs and RDs before the procedure were associated with more late lumen loss. Rensing et al. (18) found a similar relation between MLD before PTCA and late lumen loss but only a nonsignificant trend for the association of RD with late lumen loss. The presence of dissections before stenting appeared to play a slight protective role against lumen loss, as previously noted for PTCA (12).

This study illustrates the low accuracy of an analysis based solely on univariate analysis. In addition, some factors that are not significant in univariate analysis are significant only in a multivariate analysis. Thus, confining the entry in the multivariate model to only those variables significant in univariate analysis may yield imprecise results.

Several important points strengthen the validity of the results of this study. 1) The study group was not confined to certain patients with specific clinical and lesion-related characteristics; rather, it comprised patients with a broad spectrum of coronary artery disease, including acute ischemic syndromes. 2) During the study period the stent implantation protocol underwent substantial changes (use of higher balloon pressure [33] and antithrombotic therapy after stenting [5]), allowing analysis of their impact on restenosis. The type of post-stenting antithrombotic therapy—anticoagulant or antiplatelet agents—had no significant effect on restenosis. Our results on the role of balloon pressure on restenosis are more difficult to interpret. We found no significant effect of this procedural variable, in contrast to our expectation that a higher balloon pressure would lower the risk of restenosis.

Multiple stents, final MLD <3 mm and diabetes mellitus, the strongest predictors of a worse outcome as demonstrated by the logistic models for restenosis and TLR, were used for further analysis. Rates of angiographic restenosis and of TLR were calculated separately for the groups presenting with no, one, two or all three factors. There was a clear increase in the incidence of restenosis and reinterventions parallel to the number of risk factors present (Fig. 5). Lesions without any of these factors had a restenosis rate of 16% and a TLR rate of only 9%, whereas the combined presence of all these factors increased this risk to 54.0% and 43%, respectively.

**Discussion**

The major finding of this study is that three factors—diabetes, multiple stents and final result after stenting—are the strongest independent predictors of restenosis in all three multivariate models, that is for binary restenosis, lumen loss and TLR. They explain most of the differences in the outcome at 6 months. The presence of diabetes mellitus increased the risk for restenosis and TLR by a factor of 1.86 and 1.45, respectively. This observation is in keeping with previous studies of stenting (16,17) and PTCA (12,18,19). This higher risk may be due to increased blood viscosity with resulting higher shear rates (20) and enhanced smooth muscle cell proliferation, abnormalities that are common in diabetic patients (21). The placement of multiple stents almost doubled the risk for restenosis and TLR, which confirms reports from previous studies (22,23). The increased risk may be due to a larger surface area covered by stent material, but also to a greater length of the primary lesion or of the incurred dissection, or both. Data on lesion length are missing in this study, but in a smaller group of patients for whom this measurement was available, we (24) found that lesion length rather than the number of stents implanted was a significant correlate of lumen loss at 6-month angiographic follow-up. Stent placement procedure with a final MLD <3 mm increased the likelihood of restenosis by 50% and doubled the likelihood of TLR. These data are in line with previous reports on stenting (17,22,25) and PTCA (12,26–28) and further support the prevailing paradigm in interventional cardiology, “bigger is better” (29).
through a better final post-stenting result. The use of higher balloon pressure in this study was generally dictated by the modifications in stenting protocol adopted in recent years. However, we cannot exclude that adverse lesion characteristics such as eccentricity and calcifications may have played a role in this choice, canceling the potential of high balloon pressure to reduce the risk of restenosis. Because these lesion characteristics were not available for analysis in this study, a controlled study is needed to clarify definitively the influence of balloon pressure on restenosis. 3) We used polyvalent tools for assessing restenosis, because of the dissociation between clinical and angiographic findings. We maintained the angiographic estimates as part of our restenosis analysis, because restenosis cannot be predicted from clinical variables only (12), and we added the TLR index in an attempt to mitigate justified concerns about pure “coronary luminology” (34).

Limitations of the study. The selection of variables examined was based on the experience at the time the study was designed. Although additional variables might be included in an analysis based on today’s knowledge, we wanted to confine our study to those variables with complete and prospectively recorded data. The only variable entered into the model retrospectively was the type of antithrombotic therapy, because such information has important clinical implications and is readily and unequivocally available. The absence in the analysis of lesion characteristics such as ostial location, eccentricity and calcifications remains a limitation of our study. Our analysis also did not include the length of stenosis. Although this index would not have been available for all lesions because of the presence of recent or chronic occlusions in our study patients, its omission deserves special attention because it prevents us from drawing definitive conclusions about the exact role of multiple stenting in restenosis. Future studies are warranted to clarify whether the number of stents itself or the original lesion length covered by stents is responsible for more restenosis at follow-up.

A further limitation of the study is the absence of intravascular ultrasound examination. This method would be able to introduce other lesion characteristics as independent variables in the model and might have added other end points to the study to offer better insights into the mechanisms of restenosis. However, the advantages of this method must be weighed against the certain added cost and risk related to this technique (29).

Our study may be flawed by the incomplete angiographic follow-up. A 2% to 3% overestimation of the true restenosis rate has been predicted even for a modest 20% rate of missing angiographic control data, as in the present study (35). In fact, our predicted values also suggested that the restenosis rate might have been 1.2% lower in the group without than in the group with control angiography. This factor may have influenced our final models of restenosis in a way that cannot be anticipated.

Conclusions and clinical implications. This study demonstrates that diabetes mellitus, multiple stents and MLD after stenting are the three most powerful independent predictors of restenosis after coronary stenting. Although the independent role of multiple stents should be further addressed by future analyses adjusting simultaneously for lesion length, our results suggest that to avoid clinical restenosis, the interventional cardiologist should achieve the optimal final post-stenting lumen and be cautious about using stents in diabetic patients. Ensuring the best possible balance between optimal final result and number of stents implanted may outweigh the negative effect of other predictive factors, such as diabetes, and improve long-term outcome. However, if only a suboptimal final result has been achieved after multiple stents have been placed in a diabetic patient, the patient should remain under close follow-up to prevent in due time restenosis-mediated events.

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