Intravascular Ultrasound Predictors of Angiographic Restenosis in Lesions Treated With Palmaz-Schatz Stents

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Objectives. This study sought to evaluate the clinical, procedural, preinterventional and postinterventional quantitative coronary angiographic (QCA) and intravascular ultrasound (IVUS) predictors of restenosis after Palmaz-Schatz stent placement.

Background. Although Palmaz-Schatz stent placement reduces restenosis compared with balloon angioplasty, in-stent restenosis remains a major clinical problem.

Methods. QCA and IVUS studies were performed before and after intervention (after stent placement and high pressure adjunct balloon angioplasty) in 382 lesions in 291 patients treated with 476 Palmaz-Schatz stents for whom follow-up QCA data were available 5.5 ± 4.8 months (mean ± SD) later. Univariate and multivariate predictors of QCA restenosis (≥50% diameter stenosis at follow-up, follow-up percent diameter stenosis [DS] and follow-up minimal lumen diameter [MLD]) were determined.

Results. Three variables were the most consistent predictors of the follow-up angiographic findings: ostial lesion location, IVUS preinterventional lesion site plaque burden (plaque/total arterial area) and IVUS assessment of final lumen dimensions (whether final lumen area or final MLD). All three variables predicted both the primary (binary restenosis) and secondary (follow-up MLD and follow-up DS) end points. In addition, a number of variables predicted one or more but not all the end points: 1) restenosis (IVUS preinterventional lumen and arterial area); 2) follow-up DS (QCA lesion length); and 3) follow-up MLD (QCA lesion length and preinterventional MLD and DS and IVUS preinterventional lumen and arterial area).

Conclusions. Ostial lesion location and IVUS preinterventional plaque burden and postinterventional lumen dimensions were the most consistent predictors of angiographic in-stent restenosis.

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Palmaz-Schatz stents have been shown to improve procedural outcomes (1,2) and to reduce restenosis rates compared with balloon angioplasty (3,4). The risk of subacute stent thrombosis has been minimized by using better stent deployment techniques and aggressive antiplatelet therapy (5,6). However, restenosis rates of 20% to 30% after stenting (7) continue to be a significant limitation, especially since the treatment of in-stent restenosis (especially diffuse in-stent restenosis) remains unsatisfactory (8,9).

Risk factors for restenosis after balloon and nonstent new device angioplasty have been identified. However, the mechanism of restenosis is different for stented versus nonstented lesions (10–12). Thus, geometric factors important for development of restenosis after balloon and nonstent new device angioplasty might be of little importance in stented lesions.

The object of the present study was to evaluate the clinical, procedural, preinterventional and postinterventional quantitative coronary angiographic (QCA) and intravascular ultrasound (IVUS) predictors of angiographic in-stent restenosis.

Methods

Patient and lesion demographics. Preinterventional and postinterventional (post–Palmaz-Schatz stent implantation plus adjunct balloon angioplasty) IVUS and QCA studies were performed in 382 lesions in 291 patients for whom follow-up angiographic data were available 5.5 ± 4.8 months (mean ± SD) later (220 men, 71 women; mean age 61.7 ± 10.9 years, range 30 to 86). Target lesion location was a native coronary artery in 232 lesions and a saphenous vein graft in 150. Fourteen native artery lesions were in the left main coronary artery, 84 in the left anterior descending coronary artery, 40 in the left circumflex coronary artery and 94 in the right coronary artery. Nine lesions (2.4%) were total occlusions; 62 (16.2%) were ostial in location. A total of 476 stents were placed; 295 lesions were treated with a single stent, 80 with two stents and 7 with three stents. Articulated “biliary” stents (PS204) were used in 121 lesions and “coronary” stents in 261. Of those lesions treated with coronary stents, 108 stents were 3.0 mm in...
Abbreviations and Acronyms

CI = confidence interval
CSA = cross-sectional area
CSN = cross-sectional narrowing
DS = percent diameter stenosis
EEM = external elastic membrane
IVUS = intravascular ultrasound
MLD = minimal diameter stenosis
OR = odds ratio
P+M = plaque plus media
QCA = quantitative coronary angiography (angiographic)

Diameter, 86 stents were 3.5 mm in diameter, and 67 stents were 4.0 mm in diameter.

Stents were implanted according to standard protocols (5,13). The sheath-based stent delivery system was used to deliver the coronary stent. Biliary stents were hand-crimped on conventional coronary or peripheral angioplasty balloons. Operators were not blinded to the IVUS findings during stent implantation. All stents were implanted with high pressure adjunct balloon angioplasty (14.5 ± 4.5 atm) to achieve targeted stent expansion. The targeted stent expansion was a minimal stent cross-sectional area (CSA) ≥80% of the average of the proximal and distal reference lumen CSA by IVUS (or an absolute minimal lumen CSA ≥7.5 mm² in native arteries or ≥9.0 mm² in vein grafts) as well as complete stent–vessel wall apposition. Forty-two lesions were pretreated with atheroablative devices before stent implantation: 15 lesions with directional coronary atherectomy (Devices for Vascular Intervention), 21 with high speed rotational atherectomy (Heart Technology) and 15 with excenter laser coronary angioplasty (Spectranetics/Advanced Interventional Systems).

Patients were studied only after giving written informed consent; all IVUS studies have the ongoing approval of the Washington Hospital Institutional Review Board.

Clinical demographics. Baseline clinical demographics were obtained by independent hospital chart audit performed by a registered nurse. Angina status was recorded according to the classification of the Canadian Cardiology Society. Unstable angina was defined as a recent acceleration of angina by IVUS (or an absolute minimal lumen CSA ≥7.5 mm² in native arteries or ≥9.0 mm² in vein grafts) as well as complete stent–vessel wall apposition. Forty-two lesions were pretreated with atheroablative devices before stent implantation: 15 lesions with directional coronary atherectomy (Devices for Vascular Intervention), 21 with high speed rotational atherectomy (Heart Technology) and 15 with excenter laser coronary angioplasty (Spectranetics/Advanced Interventional Systems).

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lumen CSA); and 5) CSN (%) (equals P+M CSA divided by EEM CSA).

Acoustic shadowing caused by lesion calcification at times made identification of the EEM difficult. In these cases, circumferential or axial extrapolation was used, as previously described (19,20). When the tissue encompassed the catheter, the lumen was assumed to be the physical (not acoustical) size of the imaging catheter. Therefore, 1.0 mm was the smallest MLD, and 0.8 mm² was the smallest lumen CSA that could be measured before intervention.

Target lesion plaque composition was evaluated visually (21). The presence of significant amounts of calcium, dense fibrous tissue or soft plaque, as well as dissections at the stent edges, after intervention was assessed as described previously (22–24) and tabulated independently for each lesion. The arc of calcium was measured with a protractor centered on the lumen (25).

The target lesion was normalized for the reference segment. Reference segment dimensions were calculated as the mean value of the proximal and distal reference lumen CSA. For reference segment, the most normal-looking cross-section within 10 mm proximal or distal to the target lesion, but before a major side branch, was selected. If either the proximal or distal reference segment could not be analyzed (e.g., ostial lesion location, diffuse disease or major side branch close to the lesion), then only one reference segment measurement was used. Cross-sectional reference site measurements were similar to those made for the target lesion and included the EEM, lumen, P+M CSA, CSN, MLD and arc of calcification.

The target lesion was also assessed after intervention (after the last adjunct balloon inflation). Final IVUS measurements included 1) stent CSA (mm²); 2) lumen CSA (mm²); 3) MLD (mm); and 4) stent symmetry (minimal stent diameter divided by maximal stent diameter). Stent expansion was calculated as the stent CSA divided by the average of the proximal and distal reference lumen CSAs. Preinterventional and postinterventional IVUS studies were compared to calculate acute lumen gain (increase in minimal lumen CSA).

Clinical, procedural, angiographic and IVUS predictors of the follow-up angiographic results were determined using a lesion-based assessment. Previous studies have shown that stented lesions behave independently with regard to restenosis when multiple lesions are treated in the same patient (26).

Multivariate logistic regression analysis was used to determine the best predictors of the primary end point: the binary angiographic definition of restenosis (follow-up QCA DS ≥50%) (27). Univariate predictors of angiographic restenosis with a p value <0.2 were entered into the multivariate model. The best independent predictors of restenosis and their 95% confidence intervals were calculated.

Multivariate linear (or logistic regression) analysis was used to determine the best predictors of the secondary end points: 1) follow-up QCA MLD, and (2) follow-up QCA DS. Univariate predictors of these secondary end points with a p value <0.2 were entered into the multivariate model. The best independent predictors and their correlation coefficients (or odds ratios for the final models) were calculated.

**Results**

**Univariate clinical predictors of in-stent restenosis.** Clinical demographics in the overall cohort were as follows: 76% were male; 70% had a history of myocardial infarction; 70% had a history of coronary artery bypass graft surgery; 29% had unstable angina; 71% had hypertension; and 87% had hypercholesterolemia. Only insulin-dependent diabetes (present in 56 patients, 63% of whom developed restenosis) was a univariate clinical predictor of in-stent restenosis (odds ratio [OR] 2.00, 95% confidence interval [CI] 1.07 to 3.71, p = 0.0289). Diabetes treated with oral agents or diet was also tested and was not found to be significant.

**Procedural characteristics as univariate predictors of in-stent restenosis (Table 1).** The number of stents/lesion and maximal adjunct balloon inflation pressure were univariate procedural predictors of restenosis. Other procedural variables, such as “coronary” (vs. “biliary” stent) use and balloon/artery ratio, were not.

**QCA results and angiographic predictors of restenosis.** Preinterventional lesion length measured 9.8 ± 6.3 mm. MLD increased from 1.06 ± 0.53 mm before to 2.97 ± 0.56 mm after intervention; DS decreased from 64 ± 16% before to 5 ± 13% after intervention. At follow-up, a mean of 5.5 ± 4.8 months after intervention, MLD decreased to 1.56 ± 0.82 mm, and DS increased to 48 ± 27%. In this cohort, 191 lesions (50%) were

<table>
<thead>
<tr>
<th>No. of stents/lesion</th>
<th>Restenosis (n = 191)</th>
<th>No Restenosis (n = 191)</th>
<th>OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.29 ± 0.49</td>
<td>1.33 ± 0.51</td>
<td>1.16 ± 0.41</td>
<td>2.20 (1.33–3.61)</td>
<td>0.0020</td>
</tr>
<tr>
<td>Max inflation pressure (atm)</td>
<td>14.5 ± 4.3</td>
<td>15.2 ± 4.1</td>
<td>14.0 ± 4.4</td>
<td>1.06 (1.07–1.12)</td>
</tr>
</tbody>
</table>

Data presented are mean value ± SD, unless otherwise indicated. CI = confidence interval; Max = maximal; OR = odds ratio.
restenotic at follow-up. Acute gain was 1.92 ± 0.66 mm. The univariate angiographic predictors of in-stent restenosis are shown in Table 2.

**IVUS results and predictors of restenosis.** Minimal lumen CSA increased from 2.4 ± 1.6 mm² before to 7.6 ± 2.5 mm² after intervention (p < 0.0001). MLD measured by IVUS correlated with QCA before (r = 0.476, p = 0.0001) and after intervention (r = 0.503, p < 0.0001). The final stent expansion measured 83 ± 20% of the reference lumen CSA, with a stent symmetry index of 0.83 ± 0.08.

Table 3 shows the univariate IVUS predictors of in-stent restenosis at a p < 0.05 level. In addition, the preinterventional P+M CSA was predictive at the p < 0.2 level and was therefore tested in the multivariate model.

**Multivariate predictors of angiographic restenosis (Table 4).** Ostial lesion location, IVUS preinterventional lesion site CSN and IVUS assessment of final lumen dimensions (final lumen CSA or final MLD) were the most consistent predictors of the late angiographic results. These three variables predicted both the primary (binary restenosis) and secondary (follow-up MLD and follow-up DS) angiographic end points.

There were other predictors of one or two but not all three of the angiographic end points. The other predictors were as follows: binary restenosis (IVUS preinterventional EEM CSA and lumen CSA), follow-up DS (QCA lesion length) and follow-up MLD (QCA lesion length, preinterventional MLD and DS and IVUS preinterventional EEM CSA and lumen CSA). Importantly, postinterventional QCA MLD or DS did not predict any of the follow-up angiographic end points.

### Discussion

Serial IVUS studies have shown that the direction and magnitude of arterial remodeling are the predominant mechanisms for restenosis after balloon or nonstent new device angioplasty (12). Serial IVUS studies have also shown (10) that stents prevent negative (or pathologic) vessel remodeling and that the mechanism of in-stent restenosis is intimal hyperplasia. Thus, predictors of restenosis after stenting procedures may be different than those after nonstent procedures.

Some of the clinical, procedural and angiographic predictors of restenosis after Palmaz-Schatz stent implantation have been identified (3,28–31). The Stent Restenosis Study (3) demonstrated that lesion location, reference vessel diameter and final MLD were significant predictors of angiographic MLD at 6 months. In other studies, left anterior descending coronary artery lesion location (29); stenosis length and initial lumen gain (30); and multiple stent placement, stenting of restenotic lesions or chronic total occlusions and suboptimal angiographic results (31) were related to a higher restenosis rate. Recent angiographic studies (32,33) have suggested that increased vessel trauma caused by high pressure adjunct

| Table 2. Univariate Angiographic Predictors of In-Stent Restenosis |
|------------------|------------------|------------------|------------------|------------------|
|                  | Total            | Restenosis (n = 191) | No Restenosis (n = 191) | OR (95% CI) |
| Costal location  | n = 64           | n = 23             | n = 41             | 1.82 (1.02–3.23) | 0.0425 |
| Ref lumen diam (mm) | 3.01 ± 0.67     | 2.85 ± 0.66        | 3.16 ± 0.67        | 0.48 (0.34–0.68) | <0.0001 |
| Lesion length (mm) | 9.8 ± 6.3       | 10.5 ± 6.6         | 9.1 ± 5.8          | 1.04 (1.0–1.08)  | 0.0364 |
| Pre MLD (mm)      | 1.06 ± 0.53      | 0.96 ± 0.50        | 1.17 ± 0.56        | 0.45 (0.30–0.68) | 0.0002 |
| Pre PS (%)        | 64 ± 16          | 66 ± 16            | 62 ± 17            | 4.58 (1.23–17.01) | 0.0232 |
| Final MLD (mm)    | 2.97 ± 0.56      | 2.84 ± 0.57        | 3.09 ± 0.53        | 0.50 (0.34–0.74) | 0.0005 |

Data presented are mean value ± SD or number of lesions, unless otherwise indicated. DS = diameter stenosis; MLD = minimal lumen diameter; other abbreviations as in Table 1.

| Table 3. Univariate Intravascular Ultrasound Predictors of In-Stent Restenosis |
|------------------|------------------|------------------|------------------|------------------|------------------|
|                  | Total            | Restenosis (n = 191) | No Restenosis (n = 191) | OR (95% CI) |
| Ref              |                  |                  |                  |                  |                  |
| EEM CSA (mm²)    | 16.5 ± 6.2       | 15.5 ± 5.0       | 17.7 ± 7.1       | 0.94 (0.90–0.98) | 0.0028 |
| Lumen CSA (mm²)  | 9.4 ± 3.6        | 8.7 ± 3.0        | 10.1 ± 4.1       | 0.88 (0.82–0.95) | 0.0010 |
| Lesion site      |                  |                  |                  |                  |                  |
| Pre EEM CSA (mm²)| 17.1 ± 7.3       | 15.9 ± 6.6       | 18.6 ± 8.1       | 0.95 (0.91–0.99) | 0.0176 |
| Pre lumen CSA (mm²)| 2.4 ± 1.6       | 2.0 ± 1.3        | 2.7 ± 1.8        | 0.74 (0.61–0.90) | 0.0029 |
| Pre MLD (mm)     | 1.42 ± 0.40      | 1.33 ± 0.34      | 1.51 ± 0.45      | 0.32 (0.15–0.66) | 0.0022 |
| Pre CSN (%)      | 85.4 ± 7.5       | 86.7 ± 6.8       | 84.3 ± 8.3       | 60.27 (1.29–1.92) | 0.0367 |
| Final lumen CSA (mm²)| 7.6 ± 2.5       | 7.1 ± 2.1        | 8.1 ± 2.8        | 0.847 (0.76–0.94) | 0.0014 |
| Final MLD (mm)   | 2.74 ± 0.49      | 2.79 ± 0.55      | 2.67 ± 0.42      | 0.51 (0.31–0.84) | 0.0080 |

CSA = cross-sectional area; CSN = cross-sectional narrowing; EEM = external elastic membrane; other abbreviations as in Tables 1 and 2.
balloon inflations may induce more late lumen loss and even a higher restenosis rate. Higher restenosis rates have also been found in diabetic patients (34).

**Previous IVUS studies of in-stent restenosis.** IVUS has been used for optimizing stent deployment, resulting in improved stent expansion, stent apposition and final lumen dimensions (5,6); however, there are few data on IVUS predictors of in-stent restenosis. In three IVUS studies (35–37), the final lumen dimensions (either MLD or CSA) were important predictors of long-term results (either angiographic restenosis or target vessel revascularization). In two of these studies (35,36), the absolute dimensions were more significant predictors than the relative stent expansion (defined as the stent/reference lumen ratio). Another analysis from one of these studies (38) showed that stent symmetry (ratio of minimal to maximal stent dimensions) was also a predictor of target vessel revascularization.

Restenosis in lesions treated with Palmaz-Schatz stents has been found to occur more frequently at the central articulation of the stent. The reasons for this pattern of restenosis have been analyzed and include both acute tissue prolapse (causing smaller final lumen dimensions at the central articulation) and exaggerated neointimal proliferation (10,11). Special attention has also been focused on restenosis at the margins of Palmaz-Schatz stents (39), showing the importance of the plaque burden at the reference site.

**Univariate predictors of in-stent restenosis.** In the current study, there were a number of univariate predictors of in-stent restenosis that were eliminated from the multivariate model. However, some of these univariate predictors are still worthy of comment. Insulin-dependent diabetes mellitus was associated with a higher restenosis rate, in agreement with recent studies (34,40) indicating that diabetes mellitus results in exaggerated late lumen loss due to more intimal hyperplasia in stented lesions. Although insulin-treated diabetes mellitus increased restenosis in the current study, non-insulin-treated diabetic patients appeared to be more similar to nondiabetic patients.

Lesion length and number of deployed stents were both univariate predictors of restenosis and have been reported before by numerous investigators, including Haude et al. (41), Ellis et al. (31) and Kastrati et al. (28). Longer lesions tend to be treated with more stents. However, both lesion length and number of stents were eliminated from the multivariate models, suggesting that length may be less important than final lumen dimensions.

Adjunct balloon inflation pressures were also found to be a univariate predictor of in-stent restenosis, in agreement with recent reports (32,33). However, the interrelation among adjunct balloon angioplasty inflation pressures (necessary to optimize stent implantation), vessel size, final lumen dimensions, stent design and mechanics and lesion and plaque characteristics have yet to be determined.

**Multivariate predictors of in-stent restenosis.** In the current study there were three variables that predicted both the primary angiographic end point and all three secondary angiographic end points. These variables were ostial lesion location, preinterventional IVUS lesion site plaque burden and postintervention IVUS lumen dimensions.

**Ostial lesion location** was a multivariate predictor of in-stent restenosis. Ostial lesions commonly recur after balloon angioplasty, which has in part, been attributed to suboptimal acute procedural results. Although acute results have improved during the era of new device angioplasty (particularly with stent implantation), one recent study (42) has shown that there may be an exaggerated neointimal hyperplastic response within
stents implanted into the aorto-ostial location compared with stents implanted in other locations.

Plaque burden before stent placement was a multivariate predictor of in-stent restenosis. Although lumen dimensions after stent placement can be optimized by deliberate use of high pressure inflations and oversized balloons (equalizing the acute postprocedural results for different preprocedural lesion substrates), only atheroablation can reduce plaque burden before stent placement. The mechanism by which plaque burden is related to restenosis is not clear. A number of explanations are possible. An excessive preinterventional plaque burden may limit stent expansion, necessitating aggressive adjunct balloon angioplasty to optimize stent dimensions, which could aggravate deep vessel wall trauma. Alternatively, the atherosclerotic plaque may be the source of the cells involved in the intimal hyperplastic process. Two recent reports (43,44) (one using high speed rotational atherectomy and one using directional coronary atherectomy) have shown superior acute and long-term results compared with stent placement alone.

Finally, IVUS postintervention lumen dimensions were an independent predictor of in-stent restenosis. Previous studies (45) have shown that the postinterventional lumen dimensions are the strongest predictors of restenosis, regardless of device use. In the current study, IVUS measures of postinterventional lumen dimensions (whether MLD or minimal lumen CSA) were stronger predictors of in-stent restenosis than QCA measurement of lumen dimensions. As shown in this and other studies, QCA has a limited ability to measure lumen dimensions accurately after stent placement; the correlation between the QCA and IVUS measurement of MLD in the current study was only fair.

Limitations of the study. There are a number of limitations to this study: 1) Although this was an inclusive series of lesions (and patients) studied before and after intervention and at follow-up, there was a potential for selection bias because of the reason for angiographic and IVUS follow-up (e.g., recurrent chest pain). As a result, the number of lesions that were restenotic at follow-up was high. However, because IVUS is routinely used for almost all stent procedures in our laboratory, there should not have been a bias in selecting lesions for imaging before or after stenting. 2) The operator was not blinded to the IVUS images; to the contrary, the ultrasound information was used to optimize the acute procedural results. Although use of IVUS for stent deployment has been recommended (5,6), this is by far not common practice. Thus, results might have been different for patients treated with angiographic guidance alone. 3) Most of the lesions were treated with a single stent, whereas the number of lesions treated with two or more stents was relatively small. 4) These findings may not apply to all stents. 5) The present study was not able to identify whether ablative therapy before stent placement had an impact on the development of in-stent restenosis. Several devices were used before stent placement; however, the absolute number of lesions treated with ablative techniques before stent placement was small. 6) The ability to identify clinical, procedural, angiographic or IVUS predictors for in-stent restenosis does not mean that an interventional approach modifying these variables will reduce the restenosis rate; this will need to be studied prospectively in randomized trials.

Conclusions. Ostial lesion location and IVUS preinterventional plaque burden and postinterventional lumen dimensions were the most consistent predictors of angiographic in-stent restenosis. These findings were more consistent predictors of in-stent restenosis than other clinical or angiographic variables.

References