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# Angiographic and Intravascular Ultrasound Predictors of In-Stent Restenosis

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***Objectives.*** **This study was performed to determine predictors of in-stent restenosis from a high volume, single-center practice.**

***Background.*** **Intracoronary stents have been shown to reduce the restenosis rate as compared with balloon angioplasty, but in-stent restenosis continues to be an important clinical problem.**

***Methods.*** **Between April 1993 and March 1997, 1,706 patients with 2,343 lesions were treated with a variety of intracoronary stents. The majority of stents were placed with high pressure balloon inflations and intravascular ultrasound (IVUS) guidance. Angiographic follow-up was obtained in 1,173 patients with 1,633 lesions (70%). Clinical, angiographic and IVUS variables were prospectively recorded and analyzed by univariate and multivariate models for the ability to predict the occurrence of in-stent restenosis defined as a diameter stenosis ≥50%.**

***Results.*** **In-stent restenosis was angiographically documented in 282 patients with 409 lesions (25%). The restenosis group had a significantly longer total stent length, smaller reference lumen diameter, smaller final minimal lumen diameter (MLD) by angiography and smaller stent lumen cross-sectional area (CSA) by IVUS. In lesions where IVUS guidance was used, the restenosis rate was 24% as compared with 29% if IVUS was not used ($p < 0.05$). By multivariate logistic regression analysis, longer total stent length, smaller reference lumen diameter and smaller final MLD were strong predictors of in-stent restenosis. In lesions with IVUS guidance, IVUS stent lumen CSA was a better independent predictor than the angiographic measurements.**

***Conclusions.*** **Achieving an optimal stent lumen CSA by using IVUS guidance during the procedure and minimizing the total stent length may reduce in-stent restenosis.**

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Intracoronary stents have been shown to reduce the rate of restenosis as compared with balloon angioplasty (1–4), but in-stent restenosis continues to be an important clinical problem (5–9). It has been reported that final minimal lumen diameter (MLD) by angiography is the best inverse predictor of restenosis (10); however, Nakamura et al. (11) showed that angiography overestimated the adequacy of acute stent expansion and the size of post-stent lumen diameters. Intravascular ultrasound (IVUS) permits detailed cross-sectional imaging of the coronary arteries (12) and has been used to optimize stent deployment (13,14). The incremental effect of this approach on restenosis is unclear. The purpose of the present study was to evaluate the clinical, angiographic and ultrasound predictors of in-stent restenosis from a single-center, large-volume experience.

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## Methods

**Patients.** Intracoronary stents were deployed in 1,706 consecutive patients with 2,343 lesions between April 1993 and March 1997. Angiographic follow-up was requested in all patients within 6 months and was obtained in 1,173 patients (69%) with 1,633 stented lesions (70%). This group of patients with angiographic follow-up constituted the study group. The only patients excluded from this analysis were those with restenosis lesions from a previous stent implantation.

Clinical, angiographic and IVUS variables were analyzed to describe the study group and to determine predictors of angiographic restenosis. Follow-up coronary angiography was performed at a median of 5.1 months (range 1 to 34) after stent implantation. Angiographic restenosis was defined as ≥50% diameter reduction of the mean proximal and distal reference lumens. Patients were classified into two groups: 891 patients (1,224 lesions) without restenosis and 282 patients (409 lesions) with restenosis.

**Stent implantation procedure.** Intracoronary stenting was performed by using techniques that have been previously described (13). The Palmaz-Schatz coronary stent (Cordis, Johnson & Johnson Company) was the stent most commonly used (46%). Other stents were used in 45% of lesions, and a combination of stents was used in 9% of lesions. After


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**Abbreviations and Acronyms**

CSA = cross-sectional area
%DS = percent diameter stenosis
IVUS = intravascular ultrasound
MLD = minimal lumen diameter
OR = odds ratio

intracoronary stent implantation, angiographic optimization was performed by using high pressure balloon dilations (>14 atm) to achieve a satisfactory angiographic result with <20% residual stenosis by visual estimate. The mean final balloon pressure was 16.1 ± 3.2 atm. After the angiographic result was considered acceptable, such that the procedure would ordinarily be terminated, IVUS was performed. IVUS imaging was obtained in 921 patients (79%) with 1,248 lesions (76%). Alternatively, IVUS imaging was obtained before any intervention or after the first predilation in 218 lesions (13%). The measured IVUS lumen area was used to choose the balloon for expanding the stent. If IVUS imaging was not available, a balloon diameter was chosen that was ≥0.5 mm larger than the angiographic reference lumen diameter. The mean balloon/artery ratio was 1.2 ± 0.2. Total stent length was defined as the sum of the length of all stents implanted for each lesion.

Quantitative coronary angiographic analysis was performed using digital calipers by experienced angiographers not involved in the stent procedure. MLD, reference lumen diameter and percent diameter stenosis (%DS) before and after stent implantation and at follow-up were measured.

IVUS studies were obtained as previously described (13). The lumen cross-sectional area (CSA) was measured at the proximal and distal reference sites and at the most narrowed point within the stent.

**Statistical analysis.** Statistical analysis was performed on a Power Macintosh 8500 with commercially available software programs (Statview 4.5, Abacus Concept Inc., and JMP 3.1, SAS Institute Inc.). Data were expressed as the mean value ± SD. Differences between groups were evaluated by the chi-square test or the Fisher exact test for categoric variables and the Student *t* test for continuous variables. P values <0.05 were considered significant.

Univariate logistic regression analysis was used to select the clinical, angiographic or IVUS predictors of angiographic restenosis. Univariate predictors of angiographic restenosis with a p value <0.05 were entered into a multivariate logistic model. A backward elimination was used to select independent predictors. A p value <0.05 was required for all variables to be included in the final multivariate stepwise model. The odds ratios (OR) and 95% confidence intervals are presented in the tables for the final multivariate model. The OR was calculated as

$$OR = e^{(\beta * x)}$$

where $\beta$ is the estimate and x equals the unit measurement for continuous variables. For MLD and reference lumen diameter, the unit of measurement was taken as 1 mm; for stent length it was 10 mm; for CSA it was 1 $mm^2$; and for age it was 10 years. An OR >1 means an increase in the predicted risk of restenosis for the variable listed.

## Results

**Comparison of patients with and without restenosis.** In-stent restenosis was angiographically documented in 282 patients (24%) with 409 lesions (25%). As shown in Table 1, the restenosis group had older patients and had patients with a greater frequency of hypercholesterolemia, diabetes and previous coronary artery bypass graft surgery. The restenosis group also had a higher incidence of saphenous vein grafts, type C lesions, dissection and multiple stents and had a longer total stent length. Figure 1 demonstrates the correlation between the total stent length and in-stent restenosis rate. Palmaz-Schatz stents and IVUS guidance were used more frequently in the no-restenosis group.

**Angiographic analysis.** The restenosis group had a longer lesion length, a smaller angiographic reference lumen diameter, a smaller final MLD and a higher %DS after the stent procedure (Table 2). There was a significant inverse correlation between the in-stent restenosis rate and the angiographic reference lumen diameter (Fig. 2) or the final MLD (Fig. 3).

**IVUS analysis.** The restenosis group had a smaller final stent lumen CSA that occurred in smaller arteries with a smaller proximal or distal reference lumen CSA (Table 2). Figure 4 demonstrates the inverse correlation between stent lumen CSA and in-stent restenosis rate.

**Comparison between IVUS and no-IVUS guidance.** To achieve an optimal result, additional inflations were performed in 420 (34%) of 1,248 lesions with IVUS guidance, and additional stents were implanted in 241 lesions (19%). The lesions with IVUS guidance had a significantly larger final MLD (3.2 ± 0.6 vs. 3.0 ± 0.5 mm, $p < 0.0001$) and a smaller final %DS (−0.3 ± 13.2% vs. 4.3 ± 12.0%, $p < 0.0001$), as well as a larger acute gain (2.2 ± 0.7 vs. 2.0 ± 0.6 mm, $p < 0.0001$), as compared with lesions without IVUS guidance. In addition, the lesions with IVUS guidance had a significantly lower in-stent restenosis rate (24% vs. 29%, $p = 0.03$).

**Multivariate logistic regression analysis.** Eleven clinical variables (age, male gender, hypercholesterolemia, active smoking, diabetes, hypertension, previous myocardial infarction, previous bypass surgery, previous coronary angioplasty, unstable angina and indication for stenting), five procedural variables (IVUS guidance, Palmaz-Schatz stent, single stent, number of stents per lesion, and total stent length), and five angiographic variables (lesion type, lesion length, reference lumen diameter, pre MLD and final MLD) were assessed by univariate logistic regression analysis to determine their correlation with angiographic restenosis. As shown in Table 3, there were 13 univariate predictors of restenosis that were entered into a multivariate logistic regression model for

**Table 1.** Clinical, Angiographic and Procedural Characteristics in the Restenosis and No Restenosis Groups

| | No Restenosis Group | Restenosis Group | p Value |
|---|---|---|---|
| No. of patients | 891 | 282 | |
| No. of lesions | 1,224 | 409 | |
| Age (years) | 58 ± 9 | 59 ± 10 | 0.02 |
| Male | 795 (89%) | 240 (85%) | NS |
| Risk factors | | | |
| Hypercholesterolemia | 490 (55%) | 176 (62%) | 0.038 |
| Active smoker | 308 (35%) | 74 (26%) | 0.008 |
| Diabetes | 100 (11%) | 52 (18%) | 0.002 |
| Hypertension | 366 (41%) | 118 (42%) | NS |
| Previous myocardial infarction | 489 (55%) | 147 (52%) | NS |
| Previous angioplasty | 86 (10%) | 33 (12%) | NS |
| Previous CABG | 83 (9%) | 41 (15%) | 0.017 |
| Unstable angina | 251 (29%) | 90 (32%) | NS |
| Follow-up duration (months) | 5.5 ± 2.4 | 5.3 ± 2.9 | NS |
| Treated vessels | | | |
| LAD | 611 (50%) | 185 (45%) | NS |
| LCx | 225 (18%) | 93 (23%) | NS |
| RCA | 339 (28%) | 106 (26%) | NS |
| LMCA | 20 (2%) | 3 (1%) | NS |
| SVG | 29 (2%) | 22 (5%) | 0.002 |
| Modified AHA/ACC lesion types | | | |
| A | 53 (4%) | 14 (4%) | NS |
| B1 | 382 (32%) | 97 (24%) | 0.004 |
| B2 | 515 (43%) | 169 (42%) | NS |
| C | 247 (21%) | 121 (30%) | < 0.0001 |
| Chronic occlusion | 114 (9%) | 43 (11%) | NS |
| Dissection | 63 (5%) | 39 (10%) | 0.002 |
| Ostial lesion | 85 (7%) | 34 (8%) | NS |
| Bifurcation | 272 (23%) | 107 (27%) | NS |
| Restenotic lesion | 68 (6%) | 25 (6%) | NS |
| No. of stents per lesion | 1.4 ± 0.8 | 1.6 ± 1.0 | < 0.0001 |
| 1 stent | 853 (70%) | 243 (60%) | 0.0001 |
| 2 stents | 252 (20%) | 99 (24%) | NS |
| ≥3 stents | 119 (10%) | 67 (16%) | 0.0002 |
| Total stent length (mm) | 24 ± 15 | 31 ± 19 | < 0.0001 |
| Maximal inflation pressure (atm) | 16 ± 3 | 16 ± 3 | NS |
| Palmaz-Schatz stent | 617 (54%) | 135 (38%) | < 0.0001 |
| IVUS guidance | 952 (78%) | 296 (72%) | 0.026 |

Data are presented as the mean value ± SD or number (%) of patients or lesions. CABG = coronary artery bypass graft surgery; IVUS = intravascular ultrasound; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LMCA = left main coronary artery; RCA = right coronary artery; SVG = saphenous vein graft.

the binomial variable of angiographic restenosis. In-stent restenosis was predicted independently by six variables (Table 3, right). Of these variables, a longer total stent length, previous bypass surgery, patient age and diabetes were variables that increased the risk of restenosis. A larger angiographic reference lumen diameter and a larger final MLD were variables that decreased the risk of restenosis. The best predictors of restenosis were total stent length and angiographic reference lumen diameter. The OR indicates that the predicted risk of restenosis increases 26% for every 10-mm increase in total stent length, and restenosis risk decreases 53% for ever 1-mm increase in reference lumen diameter. The use of IVUS guidance did not reach statistical significance in the multivariate model.

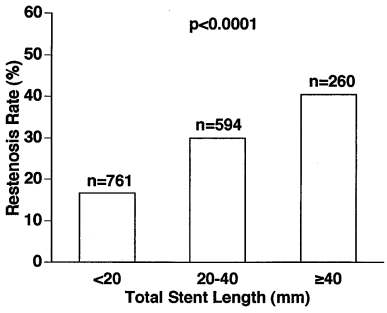



**Figure 1.** Effect of total stent length on in-stent restenosis rate ($p < 0.0001$). n = total number of patients at risk per category.

To assess the predictors of in-stent restenosis in lesions where IVUS measurements were obtained, stent lumen CSA by IVUS was entered into the multivariate model. As shown in Table 4,, IVUS stent lumen CSA and total stent length were the best predictors of in-stent restenosis in the patients in whom IVUS was performed. The OR indicates that the predicted risk of restenosis decreases 19% for ever 1-mm$^2$ increase in stent lumen CSA. When IVUS measurements were entered into the multivariate model, final MLD by angiography was no longer an independent predictor of restenosis.

Because the chance of restenosis of different stents within the same patient may not be independent, a separate logistic regression model was performed using the patient as the unit of analysis. In this model the independent predictors were the same as those in the per lesion analysis: total stent length (OR 1.34/10 mm), final MLD (OR 0.54/1 mm), diabetes (OR 1.33), reference diameter (OR 0.61/1 mm), previous bypass surgery (OR 1.32) and age (OR 1.17/10 years).

**Table 2.** Angiographic and Intravascular Ultrasound Measurements in the Restenosis or No Restenosis Groups

| | No Restenosis | Restenosis | p Value |
|---|---|---|---|
| Angiography | | | |
| No. of lesions | 1224 | 409 | |
| Lesion length (mm) | 11 ± 7 | 12 ± 8 | 0.0008 |
| Reference diameter (mm) | 3.1 ± 0.5 | 2.8 ± 0.5 | < 0.0001 |
| Pre MLD (mm) | 0.9 ± 0.6 | 0.8 ± 0.5 | 0.004 |
| Final MLD (mm) | 3.2 ± 0.6 | 2.9 ± 0.5 | < 0.0001 |
| Pre %DS | 70 ± 17 | 70 ± 17 | NS |
| Final %DS | 0.0 ± 13 | 3.1 ± 14 | < 0.0001 |
| Acute gain* (mm) | 2.2 ± 0.7 | 2.0 ± 0.7 | < 0.0001 |
| Intravascular ultrasound | | | |
| No. of lesions | 952 | 296 | |
| Proximal reference L-CSA (mm$^2$) | 9.4 ± 3.4 | 8.1 ± 2.7 | < 0.0001 |
| Distal reference L-CSA (mm$^2$) | 7.5 ± 3.2 | 6.1 ± 2.3 | < 0.0001 |
| Stent L-CSA (mm$^2$) | 8.0 ± 2.6 | 6.5 ± 2.1 | < 0.0001 |

*Acute gain = final MLD − beginning MLD. Data are presented as the mean value ± SD. %DS = percent diameter stenosis; L-CSA = lumen cross-sectional area; MLD = minimal lumen diameter.

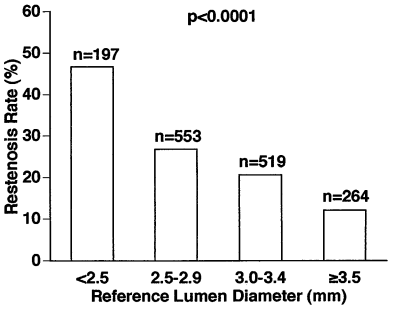



**Figure 2.** Effect of angiographic reference lumen diameter on in-stent restenosis rate ($p < 0.0001$). n = total number of patients at risk per category.

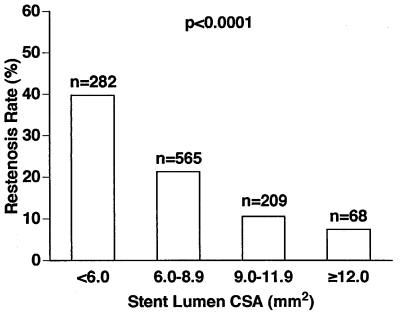


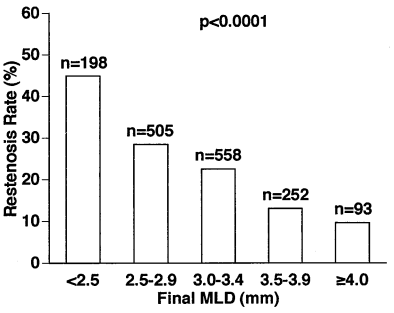

**Figure 4.** Effect of stent lumen CSA on in-stent restenosis rate ($p < 0.001$). n = total number of patients at risk per category.

## Discussion

**Comparison with other studies.** Klugherz et al. (15) reported that predictors of clinical events 3 years after Palmaz-Schatz stenting included diabetes, higher angina score at follow-up, smaller stent deployment balloon size and greater number of stents implanted. Haude et al. (16) and Ellis et al. (17) reported that multiple stents were an important predictor of angiographic restenosis. Carrozza et al. (18) reported that diabetes, small postprocedure lumen diameter and stenting of the left anterior descending coronary artery were associated with higher rates of restenosis by multivariable logistic regression analysis. The numbers of patients in these studies (50 to 227 patients) were smaller and the patients were more selected as compared with the patients in our study. Recently, Kastrati et al. (19) reported that the strong predictors of in-stent restenosis after Palmaz-Schatz stent implantation in 1,399 lesions were diabetes, multiple stents and smaller final MLD; however, they did not analyze IVUS measurements or total stent length.

**Length of stents.** A frequent finding in these previous studies is that in-stent restenosis is more common with multiple stents (16,17). Because we used a variety of stents with different lengths, we analyzed total stent length as well as the number of stents per lesion. By univariate logistic regression analysis, both total stent length and the number of stents per lesion were significant variables. By multiple logistic regression analysis, total stent length was the strongest predictor of restenosis, but the number of stents per lesion or lesion length was not an independent predictor. These results suggest that achieving an optimal result with a minimal total stent length during the procedure may reduce in-stent restenosis.

**Figure 3.** Effect of final MLD on in-stent restenosis rate ($p < 0.0001$). n = total number of patients at risk per catetory.




**Role of angiography and IVUS.** Several studies have demonstrated that the incidence of restenosis is decreased when a larger final lumen is achieved for balloon angioplasty, directed atherectomy or stent insertion (10,17,18,20). This prospective analysis extends these observations. Both larger final MLD and larger reference lumen diameter are inversely correlated with restenosis. This combination is understandable because it is easier to obtain a larger stented lumen area in bigger vessels. In arteries with a reference lumen diameter ≥3.5 mm, the incidence of angiographic restenosis was only 12% (Fig. 2). A persistent problem is how to optimize the results for smaller arteries (17,21,22) and diffuse disease.

Although angiographic guidance has been the traditional method to assess stent deployment, we have reported that 40% of stents with an acceptable angiographic result still required additional dilation with larger balloon to achieve an optimal result by IVUS (13). IVUS provided critical information regarding the adequacy of stent deployment and reference vessel dimensions. This information was used for determining balloon size and whether to use a stent and for maximizing stent expansion. The lesions with IVUS guidance had a larger final MLD and a lower final %DS than the lesions without IVUS guidance. These results indicate that IVUS guidance may be useful for optimizing stent implantation. In addition, the restenosis rate in the lesions where IVUS guidance was used was significantly lower than in the lesions without IVUS guidance. Because this study was not a randomized comparison between angiography and IVUS guidance of coronary stenting, no definitive conclusions can be made from this analysis. Although the binominal variable of IVUS guidance was not an independent predictor of restenosis by multivariate logistic regression analysis, this does not necessarily imply that IVUS guidance does not help decrease restenosis. Because IVUS guidance was associated with a larger final MLD, these two variables parallel each other, and therefore IVUS guidance may not appear in the model as an independent predictor of restenosis. In lesions with IVUS guidance, stent lumen CSA by IVUS was a better predictor of restenosis than angiographic

**Table 3.** Predictors of In-stent Restenosis by Logistic Regression Analysis (n = 1,501)

| | Univariate Analysis | | | Multivariate Analysis ($r^2$ = 0.1) | | |
|---|---|---|---|---|---|---|
| Variables | Odds Ratio | 95% CI | p Value | Odds Ratio | 95% CI | p Value |
| Total stent length | 1.26/10 mm | 1.17–1.34 | < 0.0001 | 1.26/10 mm | 1.17–1.35 | < 0.0001 |
| Reference diameter | 0.32/1 mm | 0.25–0.42 | < 0.0001 | 0.47/1 mm | 0.34–0.65 | < 0.0001 |
| Final MLD | 0.37/1 mm | 0.29–0.47 | < 0.0001 | 0.55/1 mm | 0.41–0.75 | 0.0001 |
| Previous CABG | 1.58 | 1.14–2.19 | 0.024 | 1.33 | 1.11–1.60 | 0.0024 |
| Age | 1.14/10 years | 1.02–1.29 | 0.025 | 1.17/10 years | 1.03–1.33 | 0.018 |
| Diabetes | 1.45 | 1.06–1.97 | 0.020 | 1.20 | 1.01–1.43 | 0.038 |
| Lesion length | 1.30/10 mm | 1.11–1.52 | 0.0009 | | | |
| Active smoker | 0.76 | 0.59–0.97 | 0.032 | | | |
| Dissection | 1.94 | 1.27–2.93 | 0.0018 | | | |
| Palmaz-Schatz stent | 0.51 | 0.40–0.65 | < 0.0001 | | | |
| Single stent | 0.64 | 0.51–0.80 | 0.0001 | | | |
| Type C lesion | 1.66 | 1.29–2.14 | 0.0001 | | | |
| IVUS guidance | 0.75 | 0.58–0.97 | 0.026 | | | |

CABG = coronary artery bypass graft surgery; CI = confidence interval; IVUS = intravascular ultrasound; MLD = minimal lumen diameter.

measurements. If the lumen CSA was ≥12 $mm^2$, the angiographic restenosis rate was only 7% (Fig. 4). Our interpretation is that IVUS guidance is helpful in achieving an optimal result, which in turn may reduce in-stent restenosis.

**Study limitations.** Angiographic follow-up was obtained in 70% of the lesions studied during this period. Comparing the two groups with and without follow-up angiography, the group of patients without follow-up angiography were slightly older (59 ± 10 vs. 58 ± 10 years, $p < 0.01$) than the group with follow-up angiography. However, between the two groups, there were no differences in total stent length, angiographic reference lumen diameter, final MLD and IVUS stent lumen CSA, which were major independent predictors of in-stent restenosis. This suggests that the study group does not represent a biased population.

Although this was an unselected case analysis, there was no randomized protocol for the use of different stents or IVUS guidance. In the multivariate model, $r^2 = 0.1$, which means that only 10% of the variance for restenosis is predicted by these clinical or quantitative variables. The majority of restenosis is not accounted for in this analysis (or by other investigators' studies). One alternative explanation may be that there are biologic predictors that are not measurable at the present time (23). Despite these limitations, this study is based on one of the largest data bases available of coronary stents with angiographic follow-up. Therefore, these observations may be useful guidelines as predictors of in-stent restenosis, because it is unlikely that many of these individual variables will be studied in prospective, randomized trials.

**Table 4.** Predictors of In-stent Restenosis in Lesions With Intravascular Ultrasound Guidance by Multivariate Logistic Regression Analsyis (n = 1,054)

| Variables | Odds Ratio | 95% CI | p Value |
|---|---|---|---|
| IVUS stent L-CSA | 0.81/1 $mm^2$ | 0.74–0.88 | < 0.0001 |
| Total stent length | 1.21/10 mm | 1.11–1.33 | < 0.0001 |
| Reference diameter | 0.60/1 mm | 0.40–0.89 | 0.012 |
| Dissection | 1.47 | 1.08–1.99 | 0.014 |
| Age | 1.19/10 years | 1.02–1.39 | 0.03 |
| Previous CABG | 1.27 | 1.00–1.60 | 0.046 |

L-CSA = lumen cross-sectional area; other abbreviations as in Table 3.

**Conclusions.** This study has identified several factors that predispose to in-stent restenosis: 1) total stent length; 2) angiographic reference lumen diameter; 3) angiographic final MLD; 4) previous bypass surgery; and 6) diabetes. In addition, when IVUS guidance was used, the most important inverse predictor of restenosis was stent lumen CSA. Achieving an optimal stent lumen CSA with the use of IVUS guidance, with a minimal total stent length, may reduce in-stent restenosis.

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