Predictors of Restenosis After Placement of Drug-Eluting Stents in One or More Coronary Arteries

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Although drug-eluting stents (DESs) have been increasingly used in a wide variety of clinical and anatomic situations, limited data are available regarding the predictors of DES failure in unselected lesions. We investigated the incidence and predictors of restenosis after implantation of DESs in routine clinical practice. A total of 1,795 consecutive patients underwent successful implantation of sirolimus-eluting (1,374 patients, 1,788 lesions) or paclitaxel-eluting (421 patients, 517 lesions) stents. Of the 1,743 eligible patients (2,221 lesions), follow-up angiography at 6 months was obtained for 1,228 patients (70.5%, 1,577 lesions). All data were prospectively recorded and analyzed to predict the occurrence of restenosis, defined as a diameter stenosis of ≥50%. Restenosis was documented in 125 patients with 138 lesions (8.8%), and target lesion revascularization was required in 70 patients with 82 lesions (5.2%). The pattern of restenosis was 85 focal (62%), 29 diffuse (21%), 11 diffuse proliferative (8%), and 13 total (9%). Lesion length, stent length, postintervention minimal lumen diameter, preintervention minimal lumen diameter, reference artery size, complex lesions, and use of a paclitaxel-eluting stent were univariate predictors of restenosis. Multivariate analysis showed that the use of a paclitaxel-eluting stent (odds ratio [OR] 4.37, 95% confidence interval [CI] 2.90 to 6.58, p <0.001), postintervention minimal lumen diameter (OR 0.32, 95% CI 0.20 to 0.50, p <0.001), and lesion length (OR 1.02, 95% CI 1.01 to 1.04, p <0.001) were independent predictors of restenosis.

In conclusion, the rate of restenosis after DES implantation in routine clinical practice was similar to the rate reported in clinical trials, confirming the efficacy of DES in routine clinical practice. © 2006 Elsevier Inc. All rights reserved. (Am J Cardiol 2006;97:506–511)

Drug-eluting stents (DESs) have been shown to reduce the risk of restenosis compared with bare metal stents.1–4 Recently, the use of DESs has grown exponentially in a wide variety of clinical and anatomic situations. Neointimal hyperplasia is strongly inhibited by DESs,5 but restenosis is still an important clinical problem. Several randomized trials have shown that diabetes, small vessel size, and long lesions may increase the risk of restenosis after DES implantation.2,3,6 These studies, however, enrolled only patients who fulfilled strict inclusion criteria. Thus, little information is available about the potential predictors of DES failure in unselected lesions.7,8 We, therefore, determined the incidence of restenosis after DES implantation in a large number of unselected patients in routine clinical practice and sought to identify the predictors of restenosis in this patient cohort.

Methods

Study patients: Between February 2003 and November 2004, a total of 1,795 consecutive patients underwent successful implantation of sirolimus-eluting (1,374 patients, 1,788 lesions) or paclitaxel-eluting (421 patients, 517 lesions) stents at our institution. Angiographic follow-up at 6 months (or earlier in the case of symptoms) was routine in all patients. Patients excluded from angiographic follow-up were those who experienced any major adverse cardiac event during the first 30 days after the procedure, including death, myocardial infarction, or repeat revascularization (4 patients); patients with medical conditions contraindicating angiographic follow-up, including those with severe stroke (2 patients), end-stage renal disease on hemodialysis (28 patients), severe allergic reactions to contrast (4 patients), and severe concomitant diseases (4 patients); and patients >85 years old (10 patients).

Stenting procedure: A Cypher stent (Cordis, Miami Lakes, Florida) or Taxus stent (Boston Scientific, Natick,
guiding catheter to calibrate magnification. Single matched views with the worst diameter stenosis were compared.

**Definitions:** All demographic, clinical, angiographic, and procedural characteristics were prospectively entered into the Asian Medical Center angiographic database. Restenosis was defined by a diameter stenosis of ≥50% occurring in the segment inside the stent or 5-mm segment proximal or distal to the stent at follow-up angiography. Restenotic lesions were classified as focal (type I, <10 mm), diffuse (type II), proliferative (type III), or total (type IV) occlusion.9 Late lumen loss was calculated as the difference between the minimal lumen diameter immediately after the procedure and that at 6 months.

**Statistical analysis:** Data are expressed as means ± SDs for continuous variables and as frequencies for the categor-
ical variables. Continuous variables were compared by unpaired Student’s t test and categorical variables by the chi-square test. Regression analysis was performed on all variables to identify the determinants of restenosis; variables that were significant on univariate analysis were entered into the multivariate analysis to determine their independent relation to restenosis. Statistical significance was defined as a 2-sided p value of <0.05.

Results

We were able to perform angiographic follow-up on 1,228 (1,577 lesions) of the 1,743 (2,221 lesions) eligible patients who constituted the study population (follow-up rate 70.5%). The groups with and without follow-up angiography did not differ significantly with regard to clinical, lesion, or procedural characteristics (data not shown). However, the 515 patients without follow-up angiography were older, had a higher percentage of women, and had a lower ejection fraction than the 1,228 patients in whom follow-up angiography was performed.

Restenosis patterns: Restenosis was angiographically documented in 125 patients with 138 lesions (8.8%, in-stent 7.5%, in-segment 8.8%). Target lesion revascularization was required in 70 patients with 82 lesions (5.7%). Focal restenosis occurred in 85 (62%), diffuse in 29 (21%), diffuse proliferative in 11 (8%), and total restenosis in 13 (9%) patients (Figure 1). The nonfocal restenosis group had a higher incidence of complex lesions (93% vs 81%, respectively, p = 0.036), lower incidence of the use of intravascular ultrasonography (59% vs 76%, p = 0.029), higher incidence of the use of Taxus stents (62% vs 39%, p = 0.007), and smaller postintervention minimal lumen diameter (2.46 ± 0.41 vs 2.68 ± 0.50, p = 0.006) compared with the focal restenosis group.

Univariate predictors: The baseline clinical characteristics were similar in the group in whom restenosis was documented and the group without restenosis (Table 1). Diabetes was also not a significant predictor of restenosis. When we compared the angiographic and procedural data (Table 2), the restenosis group had longer lesion and stent lengths, a smaller postintervention minimal lumen diameter, a smaller reference artery size, and more complex lesions than did the group with no restenosis. A significant correlation was found between the restenosis rate and lesion length, and a significant inverse correlation was found between the restenosis rate and postintervention minimal lumen diameter (Figure 2). Restenosis was more common in patients treated with Taxus stents than in those treated with Cypher stents (19.9% vs 5.8%, respectively; p <0.001). Late loss was also significantly higher in the Taxus stent group than in the Cypher stent group (0.70 ± 0.68 mm vs 0.28 ± 0.57 mm, respectively, p <0.001; Figure 3). No significant differences were found between the 2 DES groups in the baseline characteristics, except for age, lesion location, maximal inflation pressure, stents per lesion, and postintervention minimal lumen diameter (Table 3).

The univariate predictors of restenosis included complex lesions, lesion length, total stent length, number of stents per lesion, use of Taxus stents, reference vessel diameter, preintervention minimal lumen diameter, preintervention diameter stenosis, postintervention minimal lumen diameter, and acute gain (Table 4).

Multivariate analysis: On multivariate analysis, however, the use of Taxus stents, postintervention minimal lumen diameter, and lesion length were significant indepen-
Identification of independent predictors of restenosis. Of these, the postintervention minimal lumen diameter was a major predictor of restenosis after DES implantation, in that the predicted risk of restenosis decreased 68% for every 1-mm increase in postintervention minimal lumen diameter. In patients treated with Cypher stents, the lesion length (odds ratio [OR] 1.025, 95% confidence interval [CI] 1.005 to 1.046, p = 0.014) and postintervention minimal lumen diameter (OR 0.215, 95% CI 0.098 to 0.472, p = 0.001) were significant predictors of restenosis. In patients implanted with Taxus stents, the lesion length (OR 1.022, 95% CI 1.001 to 1.043, p = 0.001) and postintervention minimal lumen diameter (OR 0.213, 95% CI 0.104 to 0.437, p < 0.001) were also significant predictors of restenosis.

Discussion

We have demonstrated that the rate of restenosis after DES implantation in routine clinical practice is similar to the restenosis rate reported in clinical trials. Our results have also indicated that sirolimus-eluting stents may be superior to paclitaxel-eluting stents for the treatment of unselected lesions and that the postintervention final lumen size is a major determinant of restenosis even in patients implanted with DESs. These results suggest that routine DES implantation is highly effective in routine clinical practice, providing a rationale for its use.

Restenosis has been the major limiting factor in coronary angioplasty. Many studies that sought to define factors predictive of restenosis have shown that the postintervention final lumen diameter is the most powerful predictor of restenosis after bare metal stenting.10–12 In patients implanted with bare metal stents, an increased restenotic risk has been associated with smaller stent area. With DES, however, the relation between the postintervention final lumen size and restenosis in unselected patients has not been well defined. We have shown that, in patients receiving DES implants, the postintervention final lumen size continues to be the most important determinant of restenosis, suggesting that a larger stent area contributes to a decreased rate of restenosis, even in patients implanted with DESs.13,14 Lesion length and stent length also correlated weakly with restenosis, but stent length was not an independent predictor of restenosis. These results indicate that, for DESs, stent length has less influence on restenosis than it does with bare metal stents, supporting the current strategy of complete lesion coverage. Coronary artery disease is more
aggressive in diabetic than in nondiabetic patients, and coronary revascularization procedures are associated with less favorable outcomes in diabetic patients. In randomized trials, sirolimus- and paclitaxel-eluting stents were shown to demonstrate durable clinical and angiographic benefits for diabetic patients, but it was unclear whether diabetes increased the risk of restenosis after DES implantation. Our results have demonstrated that diabetes is not a predictor of restenosis after DES implantation, indicating that DESs significantly improve on the major limitations of bare metal stenting in diabetic patients. In-stent restenosis, which is secondary to neointimal hyperplasia, presents in different patterns. Focal in-stent restenosis was the most favorable pattern with respect to late outcome after sirolimus-eluting stent implantation in complex patients: a rush to judgment? N Engl J Med 2002;346:1773–1780.


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