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Incidence and Predictors of Recurrent Restenosis Following Implantation of Drug-Eluting Stents for In-Stent Restenosis

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Objectives: We investigated the incidence and predictors of recurrent restenosis after drug-eluting stent (DES) implantation for in-stent restenosis (ISR) in routine clinical practice. **Background:** Although DESs have been increasingly used for treatment of ISR, little is known about the predictors of DES failure. **Methods:** We determined the incidence of recurrent restenosis and major adverse cardiac events (MACE) in 224 consecutive patients with 239 lesions treated with sirolimus-eluting (n = 217 lesions) or paclitaxel-eluting (n = 22 lesions) stents for the first episode of ISR. **Results:** The procedural success rate was 99.2%, and in-hospital complications did not occur in any patient. Follow-up angiography at 6 months was obtained in 73.7% of patients. Angiographic re-restenosis rate was 12.6%, and target lesion revascularization was required in 7.6% of patients. Of the 22 incidents of re-restenosis, 15 were focal (68.2%), 5 were diffuse (22.7%), and 2 were total (9.1%) restenosis. Univariate analysis showed that lesion length, use of paclitaxel-eluting stent, and number of stents per lesion were significant predictors of re-restenosis. In multivariate analysis, however, lesion length and use of paclitaxel-eluting stent were independent predictors of re-restenosis. During the follow-up (mean, 18.3 ± 8.1 months), there were 4 deaths (1 cardiac, 3 noncardiac), but no nonfatal myocardial infarctions (MIs). MACE occurred in 18 patients. The cumulative probability of MACE-free survival was 92.9 ± 1.8% at 1 year and 90.5 ± 2.4% at 2 years. **Conclusions:** DESs are highly effective for treatment of ISR, with recurrent restenosis related to lesion length and type of DES.

Key words: drug-eluting stents; predictors; restenosis

INTRODUCTION

Despite advancements in coronary interventions, treatment of in-stent restenosis (ISR) still remains a challenging problem. Although coronary brachytherapy is effective, the incidence of recurrence approaches 20–30% [1–3]. Initial experiences with drug-eluting stents (DESs) have been very impressive, with low risk of restenosis [4–6], and effectiveness in ISR [7–9]. The increased use of DESs for ISR, however, also increases the risk of DES failure.

ISR can be focal ($<$10 mm in length) or diffuse ($\geq$10 mm in length). Prior to the use of DESs, diffuse ISR was regarded as a major risk factor for recurrent restenosis after repeat intervention [10,11]. Little is known, however, about the predictors of DES failure in the treatment of ISR. This information may be valuable in guiding clinical practice, and for diverting patients to alternative therapies. We therefore investigated clinical outcomes after DES implantation for treatment of unselected ISR lesions, to identify predictors of recurrent restenosis.

METHODS

Study Patients

The study population consisted of 224 consecutive patients successfully implanted with sirolimus-eluting (203 patients, 217 ISR lesions) or paclitaxel-eluting (21

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patients, 22 ISR lesions) stents for the first episode of ISR at Asan Medical Center between February 2003 and June 2005. All patients were asked to return for angiographic follow-up at 6 months (or earlier in cases of symptoms), except for 8 patients with medical conditions making angiographic follow-up difficult: 4 patients aged >80 years, and 1 patient each with amyotrophic lateral sclerosis, idiopathic pulmonary fibrosis, malignancy, and severe heart failure.

Stenting Procedure

Patients were implanted with Cypher™ stents (Cordis Corporation, Miami Lakes, FL) or Taxus™ stents (Boston Scientific Corporation, Natick, MA) according to standard techniques, and stent selection was left to the operator's discretion. Complete lesion coverage was recommended, as well as angiographic optimization with <20% residual stenosis by visual estimate. All patients were pretreated with aspirin and clopidogrel. During the procedure, each patient received an 8,000 U bolus of heparin, with a repeat bolus of 2,000 U to maintain the activated clotting time ≥300 sec. Aspirin (100–200 mg per day) was used indefinitely, and clopidogrel (75 mg per day) for at least 6 months.

TABLE I. Clinical and Angiographic Characteristics of the Original Lesions

Characteristics	
No. of patients	224
No. of lesions	239
Age (years)	59.7 ± 10.9
Men	168 (75.0%)
Current smoker	60 (26.8%)
Diabetes mellitus	63 (28.1%)
Hypercholesterolemia (≥200 mg/dl)	17 (7.6%)
Hypertension	113 (50.4%)
Left ventricular ejection fraction (%)	58.1 ± 9.2
Multivessel coronary disease	95 (42.4%)
Target coronary vessel	
Left anterior descending	128 (53.6%)
Left circumflex	18 (7.5%)
Right	67 (28.0%)
Left main	23 (9.0%)
Graft	3 (1.3%)
Infarct-related artery	40 (16.7%)
Lesion length (mm)	27.4 ± 15.8
Type B2/C	182 (76.2%)
Bare-metal stents	187 (78.2%)
Drug-eluting stents	52 (21.8%)
Sirolimus stent	27 (11.3%)
Paclitaxel stent	25 (10.5%)
Stents per lesion	1.16 ± 0.42

Angiographic Analysis

Angiographic analysis was performed by two experienced angiographers unaware of the study goal. Percent diameter stenosis, minimal lumen diameter, and reference diameter using an on-line quantitative angiographic analysis system (Xcelera Cath 1.1, Philips, Netherlands) were measured before predilation, after the stenting procedure and at follow-up. Angiographic measurements were made during diastole after intracoronary nitroglycerin administration using the guiding catheter for magnification calibration. Single matched views with the worst diameter stenosis were compared.

Definitions

All demographic, clinical, angiographic, and procedural characteristics were prospectively entered into a dedicated database. Restenosis at follow-up was defined by a stenosis diameter ≥50% in the segment inside the stent or 5 mm proximal or distal to the stent. Restenotic lesions were classified according to the Mehran classification as I, focal (<10 mm); II, diffuse; III, proliferative; or IV, total occlusion. Late lumen loss was calculated as the difference between the minimal lumen diameter immediately after the procedure and at 6 months. Major adverse cardiac events (MACE) were defined as cardiac death, nonfatal myocardial infarction (MI), or repeat target lesion revascularization (TLR). MI was diagnosed when CK-MB was elevated >3-fold with chest pain ≥30 min or with the appearance of new electrocardiographic changes. TLR was defined as either surgical or percutaneous reintervention driven by significant (≥50%) luminal narrowing, within or 5 mm proximal or distal to the stent, together with angina symptoms or objective evidence of ischemia.

Statistical Analysis

Data were expressed as mean ± SD for continuous variables, and frequencies for categorical variables. Continuous variables were compared by unpaired Student's t test and categorical variables by chi-square test. Regression analysis was performed on all variables to identify determinants of recurrent restenosis, and variables found to be significant by univariate analysis were entered into multivariate analysis. The cumulative incidence of MACE was estimated according to the Kaplan–Meier method. A two-sided P-value < 0.05 was required for statistical significance.

RESULTS

Original Stenting Procedure

Initial clinical and angiographic data are summarized in Table I. Most lesions (78.2%) were implanted with bare-metal stents, with the remainder (21.8%) receiving drug-eluting stents (Cypher 11.3%, Taxus 10.5%).

TABLE II. Clinical and Angiographic Characteristics of In-Stent Restenosis

Characteristics	
No. of patients	224
No. of in-stent restenotic lesions	239
Clinical presentation	
Stable angina pectoris	109 (48.7%)
Unstable angina pectoris	40 (17.9%)
Acute myocardial infarction	8 (3.6%)
Asymptomatic	67 (29.9%)
In-stent restenosis pattern	
Focal	70 (29.3%)
Diffuse	128 (53.6%)
Proliferative	20 (8.4%)
Total	21 (8.8%)
Procedural characteristics	
Balloon to artery ratio	1.25 ± 0.19
Maximal inflation pressure (atm)	17.0 ± 3.4
Stents per lesion	1.42 ± 0.62
Stent length per lesion (mm)	34.6 ± 18.9
Drug-eluting stents	
Cypher stent	217 (90.8%)
Taxus stent	22 (9.2%)
IVUS guidance	188 (78.7%)

IVUS, intravascular ultrasound; NSTEMI, non-ST segment elevation myocardial infarction; STEMI, ST segment elevation myocardial infarction.

TABLE III. Quantitative Coronary Angiography

Characteristics	$N = 239$
Lesion length (mm)	27.3 ± 15.8
Reference vessel diameter (mm)	2.91 ± 0.56
Pre-intervention	
Minimal lumen diameter (mm)	0.94 ± 0.69
Diameter stenosis (%)	67.2 ± 20.7
Post-intervention	
Minimal lumen diameter (mm)	2.91 ± 0.49
Diameter stenosis (%)	−0.43 ± 16.01
Follow-up	
Minimal lumen diameter (mm)	2.46 ± 0.74
Diameter stenosis (%)	15.3 ± 26.9
Acute gain (mm)	1.94 ± 0.63
Late loss (mm)	0.48 ± 0.62
Re-restenosis	12.6% (22/174)

Repeat Intervention

Clinical and angiographic characteristics of ISR are shown in Table II, and quantitative angiographic analysis in Table III. Before DES implantation, predilation was performed with cutting balloon angioplasty ($n = 142$ lesions), directional atherectomy ($n = 8$ lesions), or conventional balloon angioplasty ($n = 89$ lesions). DES implantation was performed with high-pressure balloon inflation, and multiple contiguous overlapping stents were deployed in 93 lesions (35.1%). The procedural success rate (<30% residual diameter stenosis and the absence of in-hospital complications) was 99.2%. In-hospital complications, including stent thrombosis, MI, emergency bypass surgery, or death, did not occur in any patient.

TABLE IV. Univariate Predictors of Recurrent Restenosis After Repeat Intervention

	Univariate analysis		
Variables	OR	95% CI	*P*-Value
Use of Taxus stent	5.952	1.876–18.868	0.002
Restenotic lesion length	1.041	1.016–1.066	0.001
Stent per lesion	2.331	1.183–4.587	0.014
Diffuse restenosis ≥20mm	3.312	1.078–10.174	0.036
In-stent restenosis pattern	1.198	0.708–2.028	0.501
Total stent length	1.020	0.998–1.044	0.068
Stent length ≥40mm	1.724	0.657–4.522	0.269
Reference artery diameter	0.726	0.303–1.739	0.472
Pre-intervention MLD	0.815	0.377–1.764	0.604
Post-intervention MLD	0.508	0.202–1.277	0.150
Diabetes	1.299	0.450–3.745	0.629

CI, confidence interval; MLD, minimal lumen diameter; OR, odds ratio.

Recurrent Restenosis

We were able to perform angiographic follow-up on 165 (174 lesions) of the 224 eligible patients (follow-up rate, 73.7%). Patients who did and did not receive follow-up angiography did not differ significantly in clinical, lesional, and procedural characteristics (data not shown). Recurrent restenosis was angiographically documented in 22 patients with 22 lesions (in-stent, 9.0%; in-segment, 12.6%). There were 15 incidents of focal re-restenosis (68.2%: unifocal 13, multifocal 2), 5 of diffuse (22.7%), and 2 of total (9.1%) re-restenosis. The recurrent restenosis rate was higher in patients treated with Taxus stents than in those treated with Cypher stents (10.1% vs. 40%, $P = 0.005$). Univariate predictors of re-restenosis included use of Taxus stents, lesion length, and number of stents per lesion (Table IV). Diabetes was not a significant predictor of re-restenosis. In addition, there were no differences between post-DES ISR and post-bare stent ISR in terms of late loss (0.47 ± 0.62 mm vs. 0.48 ± 0.63 mm, respectively, $P = 0.974$) or re-restenosis rate (11.2% vs. 13.0%, respectively, $P = 0.733$). In multivariate regression analysis, use of paclitaxel-eluting stents (odds ratio [OR], 4.425; 95% confidence interval [CI], 1.156–16.949; $P = 0.03$), and lesion length (OR, 1.046; 95% CI, 1.003–1.091; $P = 0.036$) were significant independent predictors of recurrent restenosis.

Clinical Outcomes

We were able to perform clinical follow-up on all patients, and their clinical events are summarized in Table V. Over a mean follow-up time of 18.3 ± 8.1 months, there were 4 deaths (1 cardiac, 3 noncardiac) but no incidents of nonfatal MI or stent thrombosis.

TABLE V. Clinical Outcomes During Follow-Up ($n = 224$)

Mean follow-up (months)	18.3 ± 8.1
Any events (cardiac death, MI, and TLR)	18 (8.0%)
Death	1 (0.4%)
Myocardial infarction	0
Target lesion revascularization	17 (7.6%)
Angioplasty	15 (6.7%)
Bypass surgery	2 (0.9%)

MI, myocardial infarction; TLR, target lesion revascularization.

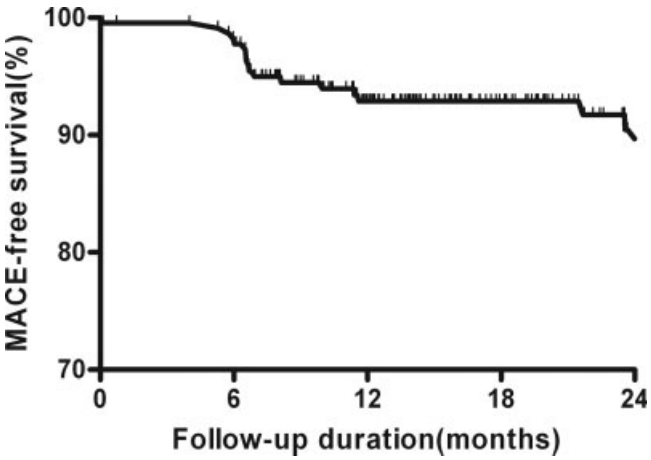

Fig. 1. Kaplan–Meier curves of cumulative event (cardiac death, myocardial infarction, and target lesion revascularization)—free survival.

Repeat revascularization was required in 17 patients (7.6%), with repeat intervention required in 15 patients (6.7%) and a bypass graft in 2 patients (0.9%). MACE occurred in 18 patients. The cumulative probability of MACE-free survival was 92.9 ± 1.8% at 1 year and 90.5 ± 2.4% at 2 years (Fig. 1).

DISCUSSION

The major findings of this study are that the re-restenosis rate after DES implantation was very low in both diffuse and focal restenotic lesions; that sirolimus-eluting stents were superior to paclitaxel-eluting stents for treatment of ISR; and that restenotic lesion length was a major predictor of DES failure. Taken together, these findings indicate that DESs are very effective in the treatment of unselected ISR.

Coronary stenting has become a standard therapy for coronary artery disease, both because of the simplicity of the procedure and its favorable long-term outcomes. DESs dramatically reduce restenosis in selected patients, and its adoption by interventional cardiologists is widespread. However, restenosis, which affects a number of patients with more complex lesions, remains a therapeutic challenge. Conventional treatments of ISR are usually unsatisfactory, with high rates of recurrence. Balloon angioplasty is a simple and effective method for revascularization of focal ISR, but has high recurrence rates for diffuse ISR [11]. Various catheter-based strategies, including debulking atherectomy, cutting balloon angioplasty, and additional stent implantation have been tested in patients with diffuse ISR, but none of these was more effective than simple balloon angioplasty [12]. Coronary brachytherapy, the first treatment shown to be effective for ISR, is both safe and effective and remains the standard therapy for ISR. This procedure, however, requires additional equipment, and there are concerns about late occlusion and durability. Several small studies suggested that DES implantation is at least as effective as coronary brachytherapy in the treatment of ISR [7,9]. More recently, a randomized controlled trial (ISAR-DESIRE) comparing sirolimus-eluting and paclitaxel-eluting stents with conventional angioplasty in 300 patients with ISR found that the re-restenosis rates for patients implanted with sirolimus- and paclitaxel-eluting stents were 14% and 22%, respectively, whereas the re-restenosis rate in patients treated by balloon angioplasty was 45%, demonstrating significant advantages of DESs over balloon angioplasty [8]. Despite the rapid adoption of DESs for treatment of ISR, randomized clinical trials may not reflect clinical practice, and the risk of DES failure may be higher in real-world patients. In our study, the overall angiographic re-restenosis rate was 12.6%, and the TLR rate was 7.6%, confirming the efficacy of DESs for treatment of unselected ISR. These results may provide a further rationale for the use of DESs as the primary treatment of these lesions.

Over the past several years, prediction of DES failure has been an important issue in clinical research. Diabetes, small vessel size, and long lesions have been shown to increase the risk of restenosis following DES implantation [5,6,13]. Since these trials included only selected patients with de novo coronary lesions, it may not be possible to extrapolate these results to patients with ISR. In general, diffuse ISR has a higher recurrence rate after repeat interventions. Mehran et al. [10] developed an angiographic classification of ISR according to the geographic distribution of intimal hyperplasia, demonstrating that repeat revascularization increases with increasing ISR class, with pattern I indicative of focal ISR (19%), pattern II of diffuse ISR within the stent (35%), pattern III of diffuse ISR outside the stent (50%), and pattern IV of totally occluded ISR (83%). We have shown here that lesion length was significantly related to recurrent restenosis after DES implantation, suggesting that the response to implantation is in part determined by the angiographic patterns of ISR. In addition, a meta-analysis found that

the postprocedural diameter stenosis is the strongest predictor of the rate of MACE in patients undergoing conventional treatment for ISR [12]. We found, however, that postintervention final lumen size failed to predict recurrent restenosis after DES implantation for ISR, which may have been due to the small number of patients included.

Several head-to-head comparison trials of sirolimus and paclitaxel-eluting stents have found that the former may have significant advantages [14,15]. In one study [14], sirolimus-eluting Cypher stents were superior to paclitaxel-eluting Taxus stents in angiographic re-restenosis rate (6.9% vs. 16.5%, $P = 0.03$) and in late luminal loss (0.43 vs. 0.67 mm, $P = 0.001$). Furthermore, the recurrence rates after treatment of ISR were 12–14% with sirolimus stents and 18–20% with paclitaxel stents [16,17]. We also found that the angiographic re-restenosis rate was significantly higher in patients implanted with Taxus stents than in those implanted with Cypher stents, suggesting that Cypher stents may be better for treatment of ISR.

There were several potential limitations to this study. First, the choice of DESs was left to the physician, leading to possible selection biases. Furthermore, the number of paclitaxel-eluting stents used was small, making it difficult to conclude the superiority of sirolimus-eluting stent, and suggesting that our results require confirmation in larger patient populations. Finally, our study was limited by incomplete angiographic follow-up, which could potentially cause errors in the true restenosis rate. Nevertheless, our findings reflect "real world" conditions for the use of DESs for ISR, showing that these stents are effective in routine clinical practice, and identifying predictors of recurrent restenosis.

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