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Comparison of angiographic patterns of in-stent restenosis between sirolimus- and paclitaxel-eluting stent

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Abstract

Background: Angiographic pattern of in-stent restenosis (ISR) after drug-eluting stent (DES) implantation was known to be different to that after bare metal stent (BMS) implantation. But the different angiographic patterns of ISR and its prognosis between sirolimus-eluting stent (SES) and paclitaxel-eluting stent (PES) has not been properly addressed in large scale studies.
Objectives and methods: We evaluated the angiographic pattern of ISR and their subsequent clinical outcomes in 177 ISR lesions of 163 consecutive patients previously treated with SES (n=97) or PES (n=80) from February 2003 to April 2005.
Results: In angiographic ISR pattern, diffuse ISR was more common in PES implantation (SES vs PES; 23.7% vs 48.7%, p=0.001) mainly because of higher incidence of diffuse intrastent ISR (8.2% vs 33.8%, p<0.001, respectively) whereas focal ISR was more common in SES implantation (76.3% vs 51.3%, p=0.001, respectively) mainly because of higher incidence of focal margin ISR (27.8% vs 2.5%, p<0.001, respectively). Among 177 ISR lesions, clinically driven target lesion revascularization (TLR) was performed in 53.6% in SES implantation and 56.3% in PES implantation (p=0.725).
Conclusion: Angiographic pattern of ISR differed after SES and PES implantation, but their subsequent TLR rate was similar to both types of DES.

Keywords: Stents; Angioplasty; Coronary restenosis

1. Introduction

Routine stent implantation has been shown to have a better procedural success rate and clinical outcome than balloon angioplasty [1,2]. However, restenosis and repeat revascularization remain significant clinical problems limiting the long-term success of stent implantation [1–3]. The recent introduction of drug-eluting stent (DES) has reduced the incidence of stent-related restenosis to less than 10%, but did not eliminate it completely [4,5]. Previous reports [6,7] showed that the pattern of in-stent restenosis (ISR) has changed into a predominantly focal ISR after DES implantation but the number of patients was small and those results were restricted to sirolimus-eluting stents (SES). Furthermore, any difference of angiographic restenotic pattern and their subsequent clinical outcome between SES and paclitaxel-eluting stent (PES) were rarely known.

Therefore, we evaluated and compared the characteristics of angiographic pattern of ISR and their clinical outcomes after SES and PES implantation.

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2. Materials and methods

2.1. Patients

Between February 2003 and April 2005, 2317 consecutive patients underwent coronary DES implantation in 3329 lesions at Asan Medical Center. Follow-up angiography after coronary stenting was acquired in mean 6.6±1.7 months after procedure. Angiographic follow-up data were obtained in 2454 lesions of 1673 patients (follow-up rate, 72.2%), and overall angiographic restenotic rate was 7.9% (193 lesions). Of these patients, 177 ISR lesions in 163 patients were enrolled for this study. Patients were excluded from this study if the treatment site was in the left main coronary artery ($n=12$) or venous bypass graft ($n=4$). The study was approved by our institutional review board.

2.2. Stenting procedure

SES (Cypher™, Cordis Corporation, Miami, FL) or PES (Taxus™, Boston Scientific, Natric, MA) was used in all patients. Stent implantation was performed according to standard techniques [8], and stents were selected by the operator. Complete lesion coverage was recommended as well as angiographic optimization with <20% residual stenosis by visual estimate. During the procedure, patients received a bolus of 100 IU/kg of heparin, with repeated bolus of 2000 IU heparin to maintain the activated clotting time ≥300 s. All patients were treated with aspirin 100–200 mg a day indefinitely and clopidogrel 75 mg a day for at least 6 months.

Repeat revascularization was performed in patients with a symptomatic or restenotic diameter stenosis ≥70%. Asymptomatic patients with angiographically intermediate ISR lesion underwent a non-invasive functional test such as treadmill test or thallium SPECT. Patients with positive stress test underwent revascularization.

2.3. Angiographic analysis

Coronary angiograms were analyzed by two experienced investigators who were not aware of the study purpose. The reference vessel diameter, percent diameter stenosis, and the minimal luminal diameter using an on-line quantitative coronary angiographic system (Xelera Cath 1.1, Philips, Netherland) were determined at baseline, after the procedure, and at follow-up. Angiographic measurement was made during end diastole after intracoronary nitroglycerin administration. Lesion length was measured as the distance from the proximal shoulder to distal shoulder in the projection with least amount of foreshortening [15].

2.4. Definition

All demographic, clinical, angiographic and procedural characteristics were prospectively entered into the Asan Medical Center angiographic database. Angiographic restenosis was defined as 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. Patterns of restenosis were classified, according to what Mehran et al. [9] suggested, with an angiographic classification of ISR according to the geographic distribution of intimal hyperplasia; pattern I (focal ISR): 1A (gap), 1B (margin), 1C (focal body), 1D (multifocal), pattern II–IV (diffuse ISR): pattern II (intrastent ISR), pattern III (proliferative ISR) and pattern IV (totally occluded ISR). Clinically driven target lesion revascularization (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.

2.5. 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. Statistical significance was defined as a two-sided value of $p<0.05$.

3. Results

ISR after PES and SES implantation occurred in 80 and 97 lesions, respectively. Clinical, angiographic, and procedural variables were analyzed and summarized in Tables 1 and 2. There was no significant difference of clinical variables in both types of DES except for tendency of higher incidence of prior coronary intervention in SES group. But in angiographic variables, SES group showed significantly a longer lesion length (SES vs PES; 41.0±21.6 mm vs 33.4±17.9 mm, $p=0.013$), more mean number of implanted stent

Table 1
Clinical characteristics of sirolimus- and paclitaxel-eluting stents

	SES ($n=90$)	PES ($n=73$)	p value
Age, years	58.4±10.3	60.4±10.9	0.242
Sex, male	67 (74.4%)	50 (68.5%)	0.401
Diabetes mellitus	25 (27.8%)	16 (21.9%)	0.391
Hypertension	45 (50%)	34 (46.6%)	0.664
Current smoking	27 (30.0%)	25 (34.2%)	0.563
Hypercholesterolemia (≥200 mg/dL)	25 (27.8%)	20 (27.4%)	0.445
Prior PCI	25 (27.8%)	12 (16.4%)	0.086
Prior CABG	1 (1.1%)	0 (0%)	1.000
Clinical presentation			0.604
Stable angina	53 (58.9%)	42 (57.5%)	
Unstable angina	20 (22.2%)	15 (20.5%)	
Acute myocardial infarction	17 (18.9%)	16 (21.9%)	
Use of statin	58 (64.4%)	44 (60.3%)	0.584
LVEF (%)	59.4±8.5	58.1±8.7	0.370
Multivessel disease	43 (47.8%)	37 (50.7%)	0.712

Abbreviations: SES, sirolimus-eluting stent, PES, paclitaxel-eluting stent, PCI, percutaneous coronary intervention, CABG, coronary artery bypass surgery, LVEF, left ventricular ejection fraction.

Table 2
Angiographic and procedural characteristics of sirolimus-and paclitaxel-eluting stent

	SES (*n*=97)	PES (*n*=80)	*p* value
Lesion characteristics			
Target coronary vessel			0.098
Left anterior descending	50 (51.5%)	53 (66.3%)	
Left circumflex	15 (15.5%)	6 (7.5%)	
Right coronary	32 (33.1%)	21 (26.3%)	
Type B2/C lesions	92 (94.8%)	72 (90.0%)	0.219
Chronic total occlusion	13 (13.4%)	6 (7.5%)	0.207
Restenotic lesion	14 (14.4%)	5 (6.3%)	0.080
Ostial lesion	10 (10.3%)	3 (3.8%)	0.096
Bifurcation	13 (13.4%)	12 (15.0%)	0.761
Procedural characteristics			
Balloon/artery ratio	1.27±0.20	1.27±0.16	0.968
Stent per lesion	1.79±0.82	1.60±0.72	0.011
Stent length per lesion, mm	48.2±25.4	39.1±21.4	0.099
Quantitative coronary angiography			
Lesion length, mm	41.0±21.6	33.4±17.9	0.013
Reference vessel diameter, mm	2.74±0.41	2.76±0.53	0.853
Pre-intervention			
Minimal luminal diameter, mm	0.69±0.52	0.86±0.53	0.034
Diameter stenosis, %	72.9±19.1	68.7±18.0	0.147
Post-intervention			
Minimal luminal diameter, mm	2.61±0.40	2.62±0.49	0.886
Diameter stenosis, %	2.66±14.89	3.54±15.19	0.704
Postprocedural TIMI 3 flow	95 (97.9%)	78 (97.5%)	1.000
Acute gain	1.91±0.58	1.76±0.56	0.078
IVUS guidance	67 (69.1%)	53 (66.3%)	0.689

Abbreviations: SES, sirolimus-eluting stent, PES, paclitaxel-eluting stent, IVUS, intravascular ultrasound.

(SES vs PES; 1.79±0.82 mm vs 1.60±0.72 mm, $p=0.011$), and smaller pre-stenting minimal luminal diameter (SES vs PES; 0.69±0.52 mm vs 0.86±0.53 mm, $p=0.034$). Of the 177 lesions analyzed (Table 3), PES was more common in diffuse ISR than SES (SES vs PES; 23.7% vs 48.7%, $p=0.001$) mainly due to higher incidence of diffuse intrastent ISR (SES vs PES; 8.2% vs 33.8%, $p<0.001$) whereas SES was more common in focal ISR mainly due to higher incidence of focal margin ISR (SES vs PES; 27.8% vs 2.5%, $p<0.001$). Focal margin ISR after SES was shorter than diffuse intrastent ISR after PES (SES; 5.42±1.93 mm, PES; 20.66±8.31 mm, $p<0.001$) but two groups did not show any difference in terms of stenotic severity (SES; 59.4±9.0%, PES; 62.3±9.3%, $p=0.282$).

Table 3
Patterns of in-stent restenosis after sirolimus-and paclitaxel-eluting stent

	SES (*n*=97)	PES (*n*=80)	*p* value
Focal-type	74 (76.3%)	41 (51.3%)	0.001
1A (gap)	0 (0%)	0 (0%)	–
1B (margin)	27 (27.8%)	2 (2.5%)	<0.001
1C (focal body)	34 (35.1%)	33 (41.3%)	0.397
1D (multifocal)	13 (13.4%)	6 (7.5%)	0.207
Diffuse-type	23 (23.7%)	39 (48.7%)	0.001
II (intrastent)	8 (8.2%)	27 (33.8%)	<0.001
III (proliferative)	5 (5.2%)	8 (10.0%)	0.219
IV (total occlusion)	10 (10.3%)	4 (5.0%)	0.193

Abbreviations: SES, sirolimus-eluting stent, PES, paclitaxel-eluting stent.

Table 4
Predictors of clinically driven target lesion revascularization by logistic regression analysis

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	*p* value
Bifurcation	2.581	1.072–6.212	0.034	2.748	1.012–7.460	0.047
Stent number.	1.556	1.033–2.345	0.035	1.716	0.679–4.332	0.253
Stent length	1.014	1.000–1.027	0.047	1.006	0.964–1.012	0.775
Lesion length	1.018	1.002–1.034	0.031	1.007	0.967–1.049	0.730

Abbreviations: OR, odds ratio, CI, confidence interval.

Over a mean follow-up time of 7.5±8.4 months after initial stenting procedure, clinically driven TLR was required in 97 lesions, with repeat intervention using DES implantation or brachytherapy in 86 lesions (47 lesions in SES, 39 lesions in PES) and bypass graft surgery in 11 lesions (5 lesions in SES, 6 lesions in PES). Overall subsequent TLR rate after initial stenting procedure did not differ between two DES groups (SES vs PES; 53.6% vs 56.3%; $p=0.725$). Of the patients who did not undergo TLR due to asymptomatic and no evidence of ischemia at the 6 month angiographic follow-up, 1 lesion was required to retreat the ISR because of further lesion progression at 24 month follow-up.

Univariate analysis showed that bifurcation lesion, number of stent, stent length and lesion length were significantly related with clinically driven TLR. But multivariate analysis showed that bifurcation lesion was only significantly related with an independent factor related with clinically driven TLR (OR 2.748, 95% CI, 1.012–7.460, $p=0.047$) (Table 4).

4. Discussion

The major findings of this study were that angiographic pattern of ISR was different between SES and PES implantation, but no significant difference of subsequent TLR rate existed despite the different angiographic patterns of ISR.

Stenting has become a standard therapy for coronary artery disease because of the simplicity of the procedure and its favorable outcomes. Recent randomized trials [4,5] showed that DES dramatically reduced restenosis. However, restenosis still affects a significant number of patients with more complex lesion, requiring more effective strategies. Recently, several clinical trials have evaluated SES and PES related to angiographic restenotic rate and late luminal loss [10,11], but they did not evaluate ISR patterns according to each type of DES. Previous studies [6,7] showed that angiographic ISR pattern after SES implantation was mainly focal ISR with the incidence of 86–100% and the site of restenosis was at the edge or focal body. Our results showed a similar pattern of ISR after SES implantation and incidence of focal ISR was somewhat low. In contrary, the other reports [12,13] related to ISR pattern after PES implantation showed that incidence of focal ISR was 50–54%, and diffuse proliferative and total occlusion were main subtypes of diffuse ISR. Our results showed a relatively higher incidence of diffuse ISR similar to previous reports, but diffuse intrastent ISR was the most common subtype of diffuse ISR. Interestingly, when we compared with angiographic pattern of ISR between SES and PES, focal ISR was more common in SES group, mainly due to focal margin ISR in SES, while diffuse ISR was more common in PES group, mainly due to diffuse intrastent ISR. The reason why angiographic ISR patterns in two types of DES were so different, especially the site of ISR and length of angiographic narrowing, was not known at present. We speculate that a better performance of SES platform compared with PES regarding the prevention of neointimal hyperplasia and less late in-stent luminal loss might be related to these observations. However, ISR site according to type of DES could not explain. Therefore, more studies are required to clarify this discrepancy.

Our study showed that clinically driven TLR rate after initial stenting procedure was 53.6–56.3% and did not differ in both types of DES irrespective of incidence of diffuse ISR. Previous study [14] related to BMS implantation showed a similar clinically driven TLR rate but rare data available to DES. Therefore, we infer from our results that clinically driven TLR rate of DES did not change as compared with BMS and both types of DES would have similar clinically driven TLR rates. However, more related studies would be needed for these observational results to be confirmed.

In conclusion, our results showed that angiographic pattern of ISR after PES and SES implantation was different, but their clinically driven TLR rate was similar to both types of DES.

4.1. Study limitation

There were several limitations to our study. First, the choice of drug-eluting stents was left to the physician, leading to possible selection bias. Second, this study was retrospective, single center experience. Despite these limitations, this study was demonstrating different patterns of ISR in both type of DES.

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