

Associations Between Target Lesion Restenosis and Drug-Eluting Balloon Use

An Observational Study

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Abstract: Percutaneous coronary interventions (PCIs) with drug-eluting balloons (DEBs) have emerged as an adjunctive treatment for in-stent restenosis (ISR) lesions. However, recurrent restenosis still occurs following DEB use. Our study aimed to identify the associations of target lesion restenosis following DEB use over a 1-year clinical follow-up.

Between November 2011 and May 2014, 246 patients were diagnosed with coronary artery ISR in our hospital. A total of 335 coronary ISR lesions were treated with DEBs. The 1-year patent coronary artery group was defined as those with negative noninvasive examinations and no clinical symptoms, or those with no angiographic restenosis. The 1-year current restenosis group was defined as those with angiographic restenosis. Clinical results were compared between 2 groups. Univariate and multivariate cox regression analyses were performed to identify the associations of target lesion restenosis following DEB use.

Patients' average age was 64.96 ± 10.68 years, and 77.2% were men. Non-ST segment elevation myocardial infarction was more frequent as the clinical presentation in the 1-year current restenosis group, whereas stable angina was more frequent in the 1-year patent coronary artery group. The 1-year current restenosis group exhibited higher percentages of comorbidities, including hypertension, diabetes, prior myocardial infarction, heart failure, prior coronary artery bypass grafting, and end-stage renal disease (ESRD). Regardless of ostial ISR or nonostial ISR, the results of drug-eluting stent ISR were worse than those for bare-metal stent ISR. Multivariate analysis revealed that ESRD, and coronary ostial lesion, and the severity of pre-PCI stenosis were independently associated with target lesion restenosis following DEB use ($P = 0.020$, $P = 0.009$, $P = 0.026$, respectively).

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Human rights statements and informed consent: all procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later revisions. Informed consent was obtained from all patients for being included in the study.

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ESRD, and coronary ostial lesion, and the severity of pre-PCI stenosis were independently associated with recurrent target lesion restenosis following DEB use.

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Abbreviations: BMS = bare-metal stent, CI = confidence interval, DEB = drug-eluting balloon, DES = drug-eluting stent, ESRD = end-stage renal disease, HR = hazard ratio, ISR = In-stent restenosis, IVUS = intravascular ultrasound, PCI = percutaneous intervention, TLR = target lesion restenosis.

INTRODUCTION

In-stent restenosis (ISR) has been an important issue following percutaneous coronary interventions (PCIs), and the rates of recurrent restenosis are high following conventional treatments for ISR lesions. Recently, drug-eluting balloons (DEBs) have emerged as a potential alternative to the current treatment of ISR.¹ Paclitaxel has been identified as the primary drug for use in DEBs because of its rapid uptake and prolonged retention. Paclitaxel is embedded in hydrophilic iopromide, which increases the solubility and the transfer of paclitaxel to the vessel wall.²

Compared to drug-eluting stents (DES), DEBs offer advantages that include immediate and homogeneous release of drug to the arterial wall and the absence of polymers, which can induce chronic inflammatory reactions. In randomized clinical trials, DEBs have been found to be superior to uncoated balloon angioplasty in the treatment of ISR with bare-metal stents (BMSs)³ and the treatment of DES ISR.^{4,5} However, recurrent restenosis still occurs following DEB use. Therefore, our study aimed to identify the associations between target lesion restenosis (TLR) following DEB use over a 1-year clinical follow-up.

METHODS

Patient Collection and Groups

Between November 2011 and May 2014, 246 patients were diagnosed with coronary artery ISR at our hospital. Three hundred and thirty-five coronary ISR lesions were treated with DEBs. The demographics, risk factors, lesion site, lesion severity, characteristics of coronary artery disease, previous stent, and intravascular ultrasound (IVUS) use were compared between the 1-year patent coronary artery group and the 1-year current restenosis group. The 1-year patent coronary artery group was defined as those with a negative noninvasive examination and no clinical symptoms or those with no angiographic restenosis. The 1-year current restenosis group was defined as those with angiographic restenosis.

The Institutional Review Committee on Human Research at our institution approved the study protocol (104-7726B).

Study Procedure and Protocol

The SeQuent Please (B Braun Melsungen AG, Melsungen, Germany) was the only DEB used at our hospital. Paccocath coating is stable during ethylene oxide sterilization, and the balloon has a shelf life of >1 year. Also, >80% of the drug is retained during balloon delivery to the target lesion, and 10% to 15% of the initial dose is delivered to the vessel wall upon 60-s of inflation. The DEB was inflated at the ISR site for 30 to 60 s according to the patient's ability to tolerate this treatment.

During 1-year follow-up period following DEB treatment, we planned noninvasive examination including the treadmill test or thallium scan, for asymptomatic patients to detect recurrent restenosis, and we scheduled coronary angiography if the patient has typical angina symptoms.

Definitions

ISR can be defined clinically or angiographically. Clinically, ISR is defined as the presentation of recurrent angina or the objective evidence of myocardial ischemia, whereas angiographic ISR is defined by the presence of >50% diameter stenosis in the stented segment.⁶ Symptomatic restenosis was defined as angiographic ISR with clinical symptoms of angina.

Cardiovascular mortality was defined as death related to heart failure, cardiac arrhythmia, and myocardial infarction. All-cause mortality was defined as death from any cause.

Primary End-Points and Secondary End-Points

The primary end-point of this study was TLR. The secondary end-points of this study were cardiovascular mortality and all-cause mortality.

Statistical Analysis

The data are expressed as percentages and means \pm standard deviations. Categorical variables were compared using chi-square tests. Continuous variables were compared using the *t* test. Differences in the continuous variables between the 2 groups were analyzed using 2-way analyses of variance. Univariate and multivariate cox regression analyses were performed to identify the predictors of recurrent restenosis after DEB use. Each correlation between the variables is expressed as a hazard ratio with 95% confidence interval (CI). *P* values < 0.05 were considered statistically significant. All statistical analyses were performed using the SPSS 22.0 software (SPSS, Inc., Chicago, IL).

RESULTS

Baseline Characteristics of Study Patients

Patients' age was 64.96 ± 10.68 years (range 29–91 years), and 77.2% were men (Table 1). Overall, 41.2 % (138/335) of the lesions and 39.0 % (96/246) of the patients were received underwent follow-up angiography, and 38 lesions had restenosis by the 1-year follow-up.

The general demographics, including the average age and gender, were similar between the 2 groups. Non-ST segment elevation myocardial infarction (15.0% vs 42.3%) was more frequent as clinical presentation in the 1-year current restenosis group, whereas stable angina (23.2% vs 3.8%) was more frequent as a clinical presentation in the 1-year patent group.

Compared to the 1-year patent coronary artery group, the 1-year current restenosis group exhibited a higher percentage of comorbidities such as hypertension (78.2% vs 88.5%, *P* = 0.308), diabetes (50.5% vs 65.4%, *P* = 0.212), prior myocardial infarctions (40.5% vs 53.8%, *P* = 0.212), heart failure (20.0% vs 34.6%, *P* = 0.126), and end-stage renal disease (ESRD) on maintenance hemodialysis (18.2% vs 46.2%, *P* = 0.004). Other comorbidities such as being a current smoker (41.4% vs 46.2%, *P* = 0.678), prior stroke (6.4% vs 3.8%, *P* = 0.612), peripheral arterial occlusive disease (6.8% vs 3.8%, *P* = 0.561), hyperlipidemia (63.6% vs 61.5%, *P* = 0.834), and prior coronary artery bypass grafting (7.7% vs 11.5%, *P* = 0.501) were similar between the 2 groups. The serum creatinine levels of the patients without hemodialysis were similar between 2 groups (1.30 ± 1.00 vs 1.40 ± 0.95 , *P* = 0.701). More ostial lesions (30.5% vs 46.2%, *P* = 0.122) and more left main bifurcation lesions (19.1% vs 26.9%, *P* = 0.434) were observed in the 1-year current restenosis group than in the 1-year patent coronary artery group, but their findings were not significantly different.

The involved vessels exhibited mild differences; the 1-year patent coronary artery group had more lesions that included left anterior descending artery and right coronary artery, and the 1-year current restenosis involved more lesions that included the left circumflex artery. Lesion type C (65.7%) was dominant in 1-year patent coronary artery group. Lesion type B2 (36.8%) and type C (52.6%) were dominant in 1-year current restenosis group. However, these findings were not significant (*P* = 0.060). There were more lesion of target vessel were more in the 1-year patent coronary artery group than in the 1-year current restenosis group (1.51 ± 0.79 vs 1.39 ± 0.68 ; *P* = 0.385). There were more multiple lesions of the target vessel in the 1-year patent coronary artery group than in the 1-year current restenosis group (36.4 % vs 28.9 %; *P* = 0.472). The characteristics of coronary artery disease were similar between the 2 groups, and many patients had multiple vessel disease (*P* = 0.798). Angiography revealed more severe stenosis in the 1-year current restenosis group than in the 1-year patent coronary artery group ($78.67 \pm 12.82\%$ vs 82.99 ± 13.24 , *P* = 0.052), and the average post-PCI minimal luminal diameter was smaller in the 1-year-patent coronary artery group than in the 1-year current restenosis group (2.39 ± 0.48 mm vs 2.61 ± 0.69 mm, *P* = 0.013).

Previous BMS use was dominant in the 1-year patent coronary artery group (55%), and previous DES use was dominant in the 1-year current restenosis group (65.4%) (*P* = 0.049). IVUS use was higher in the 1-year patent coronary artery group than in the 1-year patent coronary artery group. Only 1 case, which was in the 1-year current restenosis group, had a PCI-related complication, that is, a balloon-jailed side branch vessel.

The incidence of cardiovascular mortality was 2.4 % (5/207) in the 1-year patent coronary artery group and 11.5 % (3/26) in the 1-year current restenosis group. The incidence of all-cause mortality was 5.8 % (12/207) in the 1-year patent group and 15.4 % (4/26) in the 1-year current restenosis group.

Involved Coronary Artery Segments

Thirty-eight lesions exhibited recurrent symptomatic restenosis, and the TLR rate was 11.9 % (Tables 2 and 3). During a 1-year follow-up, the TLR rates were 19.4% in the ostial ISR group and 8.3% in the nonostial ISR group (*P* = 0.004). More proximal left circumflex artery lesions were involved in the 1-year current restenosis group.

TABLE 1. Baseline Characteristics of Study Patients

	1-Year Patent Group (N = 297)	1-Year Current Restenosis Group (N = 38)	P Value
Patient number	220	26	
Lesion number	297	38	
General demographics			
Age (year)	65.09 ± 10.66	63.88 ± 10.92	0.751
Male (%)	77.7	73.1	0.622
Clinical condition			0.002
STEMI (%)	1.8	3.8	
NSTEMI (%)	15.0	42.3	
Unstable angina (%)	60.0	50.0	
Stable angina (%)	23.2	3.8	
Risk factors			
Hypertension (%)	78.2	88.5	0.308
Diabetes (%)	50.5	65.4	0.212
Current smoker (%)	41.4	46.2	0.678
Old myocardial infarction (%)	40.5	53.8	0.212
Old stroke (%)	6.4	3.8	0.612
PAOD (%)	6.8	3.8	0.561
Hyperlipidemia (%)	63.6	61.5	0.834
Heart failure (%)	20.0	34.6	0.126
Prior CABG (%)	7.7	11.5	0.501
ESRD on maintenance hemodialysis (%)	18.2	46.2	0.004
Laboratory examination			
Creatinine (mg/dL) (exclude ESRD)	1.30 ± 1.00	1.40 ± 0.95	0.701
Lesion site (%)			
Ostial lesion (%)	30.5	46.2	0.122
Left main bifurcation (%)	19.1	26.9	0.434
Involved coronary artery			0.081
Left anterior descending artery	38.5	29.7	
Left circumflex artery	19.3	35.1	
Right coronary artery	42.2	35.1	
Lesion type			0.060
A	5.1	5.3	
B1	10.8	5.3	
B2	18.5	36.8	
C	65.7	52.6	
Numbers of lesions of the target vessel			
Average	1.51 ± 0.79	1.39 ± 0.68	0.385
Multiple (%)	36.4	28.9	0.472
Characteristics of coronary artery disease			
Single- or multiple-vessel disease (%)			0.798
Single vessel disease	7.7	11.5	
Double vessel disease	24.1	23.1	
Triple vessel disease	68.2	65.4	
Left main disease (%)	28.2	30.8	0.782
Previous stent			0.049
Bare metal stent (%)	55.0	34.6	
Drug-eluting stent (%)	45.0	65.4	
Pre-PCI angiography			
Pre-PCI stenosis (%)	78.67 ± 12.82	82.99 ± 13.24	0.052
Pre-PCI MLD (mm)	1.00 ± 0.72	0.54 ± 0.43	0.693
Pre-PCI RLD (mm)	2.83 ± 0.56	2.98 ± 0.58	0.115
Post-PCI angiography			
Post-PCI stenosis (%)	16.56 ± 8.70	15.82 ± 8.17	0.621
Post-PCI MLD (mm)	2.39 ± 0.48	2.61 ± 0.69	0.013
Post-PCI RLD (mm)	2.92 ± 0.57	3.11 ± 0.65	0.062
DEB			
Diameter (mm)	3.08 ± 0.40	3.26 ± 0.40	0.014
Length (mm)	27.39 ± 3.97	26.84 ± 3.96	0.426

	1-Year Patent Group (N = 297)	1-Year Current Restenosis Group (N = 38)	P Value
IVUS use (%)	33.3	23.7	0.272
Complication of PCI (%)	0.3	0	0.887
Cardiovascular mortality (%)	2.4	11.5	0.047
All-cause mortality (%)	5.8	15.4	0.087

Data are expressed as mean ± SD or as percentage.

CABG = coronary artery bypass grafting, ESRD = end-stage renal disease, F/U = follow-up, IVUS = intravascular ultrasound, MLD = minimal luminal diameter, NSTEMI = non-ST segment elevation myocardial infarction, PAOD = peripheral arterial occlusive disease, PCI = percutaneous intervention, RLD = reference luminal diameter, STEMI = ST segment elevation myocardial infarction.

The recurrent TLR rate of different previous stents for ostial and nonostial lesion is presented at Table 3. Regardless of ostial ISR or nonostial ISR, the results of DES ISR were worse than those of BMS ISR following DEB use. The recurrent TLR rate of ostial DES ISR was 20.7%, and the recurrent TLR rate of nonostial DES ISR was 10.2% following DEB use ($P = 0.059$). The recurrent TLR rate of ostial BMS ISR was 17.1%, and the recurrent TLR rate of nonostial BMS ISR was 6.9% following DEB use ($P = 0.065$).

Univariate and Multivariate Cox Regression Analyses of 1-year Current Restenosis

Univariate cox regression analyses identified diabetes (hazard ratio (HR): 2.251 (95% CI: 1.136–4.462, $P = 0.020$), heart failure (HR: 2.156, 95% CI: 1.103–4.217, $P = 0.025$), ESRD on maintenance hemodialysis (HR: 2.738, 95% CI:

1.427–5.254, $P = 0.002$), ostial lesion (HR: 2.516, 95% CI: 1.330–4.756, $P = 0.005$), left main bifurcation lesion (HR: 2.142, 95% CI: 1.081–4.246, $P = 0.029$), and the severity of pre-PCI stenosis (HR: 1.029, 95% CI: 1.003–1.055, $P = 0.030$) as factors with significant predictive values (Table 4). Hypertension was also associated with the predictive values (HR: 3.228, 95% CI: 0.993–10.495, $P = 0.051$). Other variables as age, gender, current smoker, prior myocardial infarction, numbers of lesions of the target vessel, a previous DES, and IVUS use were not significantly different.

Multivariate cox analysis revealed that ESRD (HR: 2.192, 95% CI: 1.129–4.254, $P = 0.020$), coronary ostial lesions (HR: 2.383, 95% CI: 1.242–4.573, $P = 0.009$), and the severity of pre-PCI stenosis (HR: 1.030, 95% CI: 1.003–1.056, $P = 0.026$) were independently associated with recurrent TLR following DEB use.

DISCUSSION

ISR has become an important issue after PCI. Recurrent restenosis rates are high following conventional treatments for ISR lesions. The treatment of ISR remains a technical challenge, and the long-term clinical outcomes of these patients may be complicated by recurrent restenosis. BMS is still widely used during coronary interventions, and the treatment of patients with BMS-ISR continues to represent a frequent problem in everyday clinical practice. Additionally, DES is also not immune to ISR. Overall, the annual number of patients who present with DES ISR approaches 200,000 in the United States alone.⁷ In a previous study of the application of DES for ISR, the restenosis rate ranged from 14% to 24%, and the mean late lumen loss was 0.32 to 0.55 mm in the repeat stenting group.^{8,9} In a previous study on the application of DEB for ISR, the angiographic restenosis rate ranged 1% to 9%, and the mean late lumen loss was 0.05 to 0.18 mm. DEB was superior to DES in terms of the diameters of the stenosis.¹⁰ Therefore, DEB has

TABLE 2. Coronary Artery Segments of Study Patients

	1-Year Patent Group (N = 297)	1-Year Current Restenosis Group (N = 38)
Patient number	220	26
Lesion number	297	38
Lesion segment (%)		
Left main		
5	0	2.6
Left anterior descending artery		
6	22.6	18.4
7	12.8	7.9
8	2.7	2.6
9	0.3	0
10	0	0
Left circumflex artery		
11	12.8	31.6
12	2.4	0
13	3.4	0
14	0.7	2.6
Right coronary artery		
1	16.9	18.4
2	13.2	10.5
3	8.4	5.3
4	1.4	0
16	2.4	0

Data are expressed as percentage.

TABLE 3. Current Restenosis Rate of Differently Previous Stent at Ostial Lesion and Nonostial Lesion

	DES	BMS	P Value
Restenosis rate of ostial lesion	20.7	17.1	0.447
Restenosis rate of nonostial lesion	10.2	6.9	0.251
P value	0.059	0.065	

Data are expressed as percentage.

BMS = bare-metal stent, DES = drug-eluting stent.

TABLE 4. Univariate and Multivariate Cox Regression Analyses About 1-Year Current Restenosis

Variables	Univariate Analyses			Multivariate Analyses		
	Hazard Ratio	95% CI	P Value	Hazard Ratio	95% CI	P Value
General demographics						
Age	1.003	0.972–1.034	0.875			
Male	0.714	0.347–1.470	0.360			
Risk factors						
Hypertension	3.228	0.993–10.495	0.051			
Diabetes	2.251	1.136–4.462	0.020			
Current smoker	1.186	0.627–2.242	0.599			
Prior myocardial infarction	1.356	0.717–2.563	0.349			
Heart failure	2.156	1.103–4.217	0.025			
ESRD on maintenance hemodialysis	2.738	1.427–5.254	0.002	2.192	1.129–4.254	0.020
Lesion site						
Ostial lesion	2.516	1.330–4.756	0.005	2.383	1.242–4.573	0.009
Left main bifurcation	2.142	1.081–4.246	0.029			
Lesion type B2 and C	1.663	0.590–4.686	0.336			
Numbers of lesions of the target vessel	0.722	0.358–1.455	0.362			
Previous drug-eluting stent	1.541	0.809–2.935	0.188			
The severity of pre-PCI stenosis	1.029	1.003–1.055	0.030	1.030	1.003–1.056	0.026
IVUS use	0.662	0.313–1.398	0.280			

CI = confidence interval, ESRD = end-stage renal disease, IVUS = intravascular ultrasound, PCI = percutaneous intervention.

emerged as a potential alternative to the current treatment of ISR. When DES-ISR compared to BMS-ISR, DES-ISR were associated with poorer outcomes following treatment with DEB.¹⁰

DEBs are the balloons that contain antineoplastic agents that are coated on the target lesion during the expansion of the balloon. The active substance on the DEB should be lipophilic so that they have a high absorption rate in the vessel wall¹¹ to compensate for the short period of contact between the inflated balloon and the vessel wall itself, and to maintain a sustained effect once released.¹² Paclitaxel inhibits cell replication in the smooth-muscle cells and thereby reduces neointimal hyperplasia.¹³ Paclitaxel has been identified as the primary drug for DEBs because of its pharmacological characteristics such as its highly lipophilic properties and its ability to remain in the vessel wall for nearly a week.¹⁴

In our study, the 1-year current restenosis group exhibited a more severe clinical condition and worse comorbidity than the 1-year patent coronary artery group. Nearly half (46.2%) of the patients in the 1-year current restenosis group had ESRD and were receiving maintenance hemodialysis, and a significant difference between the 2 groups was observed. Greater numbers of ostial lesions and more left main bifurcation lesions were observed in the 1-year current restenosis group than in the 1-year patent group, but these differences were not significant. Angiography revealed more severe stenosis in the 1-year recurrent restenosis group, which was related to recurrent restenosis. The average post-PCI minimal luminal diameters were smaller in the 1-year patent group, which was related to decreased numbers of ostial lesions. In addition, the diameters of DEB were also smaller in the 1-year patent coronary artery group. Thirty-eight lesions exhibited recurrent restenosis, and the TLR rate was 11.9%. Recurrent TLR were 19.4% in the ostial ISR group and 8.3% in the nonostial ISR group ($P = 0.004$). Recurrent TLR occurred more often after the use of DEBs for ostial

lesions than nonostial lesions. Additionally, regardless of ostial ISR or nonostial ISR, the results of DES ISR were worse than those of BMS ISR following DEB use.

Univariate Cox regression analyses identified the diabetes, heart failure, ESRD, ostial lesion, left main bifurcation lesion, and the severity of pre-PCI stenosis as factors with significant predictive values. Multivariate Cox analysis revealed that ESRD, coronary ostial lesion, and the severity of pre-PCI stenosis were independently associated with recurrent TLR after DEB use. This result may be related to the problems related to restenosis of ostial lesions and ESRD in those with atherosclerotic change. We also hypothesized that DEB may not provide a good response to atherosclerotic change, but it may provide a better responses to lipid-rich components according to our results. The lesion type and multiple lesions of the target vessel did not influence the result following DEB use. Only the severity of pre-PCI stenosis can affect TLR.

Our study had some limitations. First, this study was a retrospective report conducted at only a single medical center. Second, not all of the patients underwent follow-up coronary angiography to detect TLR. We scheduled follow-up coronary angiography and noninvasive examinations (ie, treadmill tests or thallium scans) according to the patient's symptoms. During the 1-year follow-up period following DEB treatment, we scheduled noninvasive examination such as the treadmill test or thallium scan for asymptomatic patients to detect recurrent restenosis, and planned coronary angiography if the patient have typical angina symptoms. We may have underestimated the occurrence of TLR due to pseudo-negative expression of non-invasive examinations. Third, only 1 brand of DEB was used at our hospital, which might have caused some bias.

To the best of my knowledge, only a few studies have focused on current restenosis following DEB use. We have discussed our experiences and determined the associations between DEB use and recurrent target lesion restenosis.

CONCLUSIONS

ESRD, and coronary ostial lesion, and the severity of pre-PCI stenosis were independently associated with recurrent target lesion restenosis following DEB use.

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