

One-year outcomes following drug-eluting balloon use for coronary ostial restenosis



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ABSTRACT

Aims: The management of ostial lesions is one of the challenges of percutaneous coronary intervention (PCI) in recent medicine. Although stent implantation has increased the accuracy of the results and improved long-term outcomes, in-stent restenosis (ISR) occurs more frequently following the treatment of ostial lesions than the treatment of non-ostial lesions. When additional stenting is not desirable, PCI with drug-eluting balloons (DEBs) has emerged as an adjunctive strategy. However, little data regarding the effects of DEBs in ostial ISR lesions are available. Our study aimed to assess the efficacy of the use of DEBs in coronary ostial in-stent restenotic lesions.

Methods and results: From November of 2011 to May of 2014, 85 patients were diagnosed with coronary ostial ISR in our hospital. A total of 93 coronary ostial ISR lesions were treated with DEBs. More than half of the study patients had comorbidities, including hypertension, diabetes, and hyperlipidemia, 77.6% of the study patients had triple vessel coronary artery disease, and 54.1% of the study patients had left main coronary artery disease. In our study, target lesion revascularization were performed in 19.2% in all groups; 11.5% were in the ostial left anterior descending artery, 29.0% were in the ostial left circumflex artery, and 21.4% were in the ostial right coronary artery. Across all of the groups, 24.4% of the patients experienced major adverse cardiac cerebral events.

Conclusion: Percutaneous coronary intervention with drug-eluting balloons is an alternative strategy for coronary ostial in-stent restenosis when additional stenting is not desirable.

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1. Introduction

Flow-limiting ostial coronary lesions are clinically important because they subtend a large myocardial territory and may induce extensive myocardial ischemia. The diagnosis and treatment of these lesions have been challenging aspects of percutaneous coronary intervention (PCI) in recent era. The procedural success and clinical of these lesions outcomes are inferior to those of non-ostial lesions. The majority of ostial lesions are due to atherosclerotic coronary artery disease [1]. Fibrocellular and sclerotic fragments are the major tissue components that are found on histological analyses of specimens removed from right coronary artery ostial lesions by directional atherectomy, and lipid-rich components are infrequent [2]. Although stent implantation has improved the accuracy of the results and the long-term outcomes, in-stent restenosis (ISR) occurs more frequently following the

treatment of ostial lesions than the treatment of non-ostial lesions. ISR is also related to poor clinical outcomes, particularly ostial restenosis. According to a previous study of the prevalence of coronary ostial in-stent restenosis following the use of CYPHER, TAXUS and BMS, the restenosis rates are 6%, 8%, and 33%, respectively [3]. ‘Stent in stent’ treatment causes lumen loss, and additional stenting may not be a desirable PCI for ostial ISR. The use of DEBs has emerged as an adjunctive strategy. Compared with DESs, the DEBs offer advantages, such as immediate and homogeneous drug release in the arterial wall and the absence of polymers that can induce chronic inflammatory reactions. To the best of my knowledge, no studies of strategies for coronary ostial ISR lesions have been published, and little data about the effect of DEBs in ostial ISR lesions are available. To address this gap in the published knowledge, our study aimed to assess the efficacy of the use of DEB for coronary ostial in-stent restenotic lesions.

2. Methods

2.1. Patient collection and groups

From November of 2011 to May of 2014, a total of 85 patients and 93 ostial ISR lesions were treated with DEBs in our hospital. A total of 28

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ostial left anterior descending artery (LAD) in-stent restenosis lesions, 32 ostial left circumflex artery (LCX) in-stent restenosis lesions and 33 ostial right coronary artery (RCA) in-stent restenosis lesions were included. The general demographics, clinical conditions, associated risk factors, characteristics of coronary artery disease, previous stents and characteristics of the DEBs were analyzed. Comprehensive inpatient and outpatient data from medical record abstractions and patient interviews were collected. The Institutional Review Committee on Human Research of our institution approved the study protocol.

2.2. Definitions

Ostial coronary lesions were defined as stenotic >50% of the lesion was within 3 mm of the orifices of the LAD, or LCX or RCA. Major adverse cerebral cardiac events (MACCEs) included myocardial infarction, target lesion revascularization, stroke and cardiovascular mortality.

2.3. Procedure and protocol

The SeQuent Please (B Braun Melsungen AG, Melsungen, Germany) was the only DEB used in our hospital. B. Braun Melsungen AG (Berlin, Germany) has licensed this technology for use in its SeQuent Please DEB catheter, but the coating procedure and balloon technology have been improved. Paccocath coating is stable during ethylene oxide sterilization, and the balloon has a shelf life of >1 year. More than 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-second inflation. The DEBs were inflated at the ISR site for 30 to 60 s when the patients were able to tolerate this treatment.

2.4. Study end-points

The primary end-point of this study was target lesion revascularization. The secondary end-points of this study were myocardial infarction (ST elevation myocardial infarction and non-ST elevation myocardial infarction), stroke and cardiovascular mortality.

2.5. Statistical analysis

The data are expressed as percentages and the means \pm the standard deviations. The categorical variables were compared using chi-square tests. The continuous variables were compared using an analyses of variance (ANOVAs) test. The differences in the continuous variables between the two groups were analyzed using a one-way analyses of variance. A Kaplan–Meier survival curve was performed for the outcomes of target lesion revascularization at one-year follow-up duration. P values below 0.05 were considered statistically significant. All statistical analyses were performed using SPSS 22.0 software (SPSS, Inc., Chicago, Illinois).

3. Results

3.1. Baseline characteristics of the study patients (Table 1)

The average age of the patients was 66.76 ± 9.85 years with a range of 33 to 89 years, and 68.2% of the patients were male. The major clinical condition of the patients was unstable angina (56.5%). Other patients exhibited clinical problem, such as ST elevation myocardial infarction (STEMI, 1.2%), non-ST elevation myocardial infarction (NSTEMI, 24.7%) and stable angina (17.6%). The majority of patients had hypertension (90.6%), diabetes (61.2%) and hyperlipidemia (61.8%). Forty-one point two percent of the patients had medical histories of prior myocardial infarction, 30.6% had histories of heart failure, and 32.9% had ESRD. The average of serum creatinine level of the non-hemodialysis patients was 1.36 ± 1.32 mg/dL. The lesion-related arteries involved the LAD (30.1%), LCX (35.5%) and RCA (34.4%). The majority of patients had

Table 1
Baseline characteristics of study patients^a.

	Ostial lesion (N = 93)
Patient number	85
Lesion number	93
General demographics	
Age (year)	66.76 \pm 9.85
Male gender (%)	68.2
Clinical condition	
STEMI (%)	1.2
NSTEMI (%)	24.7
Unstable angina (%)	56.5
Stable angina (%)	17.6
Risk factors	
Hypertension (%)	90.6
Diabetes (%)	61.2
Current smoker (%)	37.6
Old myocardial infarction (%)	41.2
Old stroke (%)	4.7
PAOD (%)	8.2
Hyperlipidemia (%)	61.8
Heart failure (%)	30.6
Prior CABG (%)	9.4
ESRD on maintenance hemodialysis (%)	32.9
Laboratory examination	
Creatinine (mg/dL) (exclude ESRD)	1.36 \pm 1.32
Lesion-related artery (%)	
Left anterior descending artery	30.1
Left circumflex artery	35.5
Right coronary artery	34.4
Characteristics of coronary artery disease	
Single- or multiple-vessel disease (%)	
Single vessel disease	2.4
Double vessel disease	20
Triple vessel disease	77.6
Left main disease (%)	54.1
Previous stent	
Bare metal stent (%)	37.6
Drug eluting stent (%)	62.4
Pre-PCI angiography	
Pre-PCI stenosis (%)	77.26 \pm 13.43
Pre-PCI MLD (mm)	0.71 \pm 0.44
Pre-PCI RLD (mm)	3.10 \pm 0.54
Post-PCI angiography	
Post-PCI stenosis (%)	17.70 \pm 8.71
Post-PCI MLD (mm)	2.59 \pm 0.47
Post-PCI RLD (mm)	3.19 \pm 0.54
DEB	
Diameter (mm)	3.25 \pm 0.40
Length (mm)	25.98 \pm 4.34
IVUS use (%)	43
Complication of PCI (%)	0
F/U time (days)	601.13 \pm 291.06

Data are expressed as mean \pm SD or as number (percentage).

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

multiple vessel diseases (97.6%) and left main artery disease (54.1%). Among all patients, 77.6% had triple vessel coronary artery disease, 20% had double vessel coronary artery disease, and 2.4% had single vessel coronary artery disease. The previously used stents included bare-metal stents (BMSs, 37.6%) and drug-eluting stents (DESS, 62.4%).

Angiography revealed a pre-PCI stenosis of $77.26 \pm 13.43\%$, a pre-PCI minimal luminal diameter (MLD) of 0.71 ± 0.44 mm and a pre-PCI reference luminal diameter (RLD) of 3.19 ± 0.54 mm. The post-PCI stenosis was $17.70 \pm 8.71\%$, the post-PCI MLD was 2.59 ± 0.47 mm, and the post-PCI RLD was 3.19 ± 0.54 mm. The average DEB length was 25.98 ± 4.34 mm, and the average DEB diameter was 3.25 ± 0.40 mm. Peri-procedure intravascular ultrasound was utilized

in 43% of the cases. No immediate complications related to PCI occurred. The mean follow-up duration was 601.13 ± 291.06 days.

3.2. One-year clinical outcomes of the study patients (Table 2)

During the one-year follow-up, 14 patients experienced myocardial infarction as NSTEMI, including 9% of all patients, 10.7% of the LAD patients, 7.7% of the LCX patients and 9.7% of the RCA patients. Among all patients, 19.2% underwent target lesion revascularization, including 11.5% of the LAD patients, 29.0% of the LCX patients and 21.4% of the RCA patients. Only one (1.2%) patient experienced ischemic stroke, and the patient had a LAD lesion. Only two (2.6%) patients experienced cardiovascular mortality. One of these patients had a LAD lesion, and the other had a RCA lesion. The incidence of MACCE was 24.4% across all patients, including 28.6% of the LAD patients, 15.4% of the LCX patients and 32.3% of the RCA patients. The incidence of all-cause mortality was 7.7% across all of the patients, including 10.7% of the LAD patients, 3.8% of the LCX patients and 6.5% of the RCA patients.

3.3. Comparison of the results of DEB use for BMS and DES ISR

In the previous BMS group, 17.1% of the patients experienced target lesion restenosis, and the rate of target lesion restenosis in the previous DES group was 20.6% (p = 0.539).

Kaplan–Meier survival curve for the outcomes of target lesion revascularization at one-year follow-up duration (Fig. 1)

Between LAD, LCX and RCA ISR groups, no significant difference (P = 0.526) was demonstrated. The ostial LAD ISR lesion had better result following DEB use.

4. Discussion

Ostial stenosis poses a unique challenge for interventionists. The interventions for ostial stenosis lesions are technically difficult even in cases of native lesions and especially in cases of restenotic lesions. The ostial lesions are also more prone to complications that include high rates of ISR [4]. Ostial ISR is also related to poor prognoses. Iakovou I. et al. reported that 6.3% patients in a CYPHER group and 28% patients in a BMS group underwent target vessel revascularizations within a 10-month follow-up [5]. In other study, I-Chang Hsieh et al. reported that the coronary ostial ISR rate following CYPHER, TAXUS and BMS use were 6, 8, and 33%, respectively [3]. However, no recent studies have been published regarding the strategy for the treatment of ostial ISR.

Additional stenting may be not a desirable PCI for ostial ISR. Repeated stenting suffers from the following limitations: 1) nonresorbable polymers trigger chronic inflammation and hypersensitivity reactions that might contribute to increased risks of late stent thrombosis and late restenosis [6,7]; 2) repeated stenting might lead to an uneven distribution of drug release and suboptimal stent geometry [8]; 3) repeated

Table 2
One-year clinical outcomes of study patients^a.

	All	LAD	LCX	RCA	P value
One-year clinical outcomes					
Myocardial infarction (%)	9	7.7	8.3	10.7	0.919
Target-vessel revascularization (%)	19.2	11.5	29.0	21.4	0.273
Stroke (%)	1.2	0	0	3.6	0.405
Cardiovascular mortality (%)	2.6	0	4.2	3.6	0.593
MACCE (%)	24.4	15.4	29.2	28.6	0.426
All-cause mortality (%)	7.7	3.8	8.3	10.7	0.633

Data are expressed as number (percentage).

^a Abbreviation: LAD: left anterior descending; LCX: left circumflex; RCA: right coronary artery; MACCE: major adverse cardiac cerebral event.

Target lesion revascularization

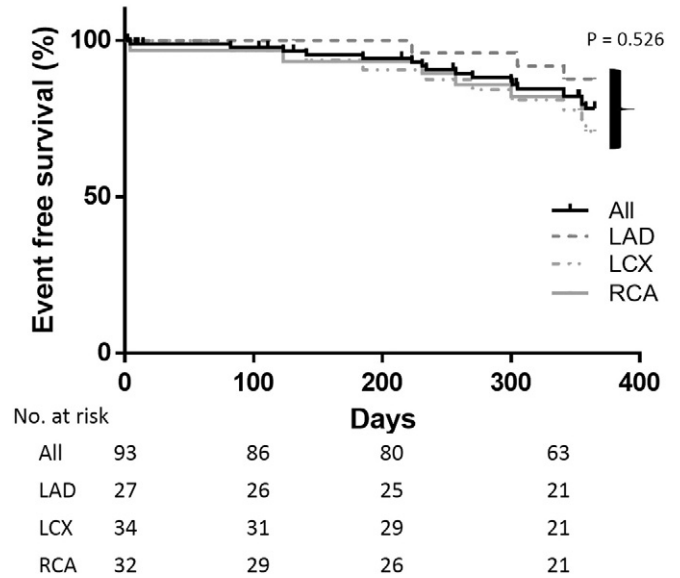


Fig. 1. Kaplan–Meier survival curve for the outcomes of target lesion revascularization at one-year follow-up duration: There were no significant difference (P = 0.526) between three groups. *Abbreviation: LAD: left anterior descending artery; LCX: left circumflex artery; RCA: right coronary artery; No: number.

stenting might cause insufficient stent expansion, which has been shown to be predictive of recurrent restenosis [9]; and 4) repeated stenting is problematic because the treatments for recurrent restenosis are limited due to the presence of multiple layers of metal in the coronary artery. DEBs allow for immediate and homogenous drug transfer to the vessel wall without any polymers or a sustained-release mechanism. The absence of a stent ensures that the original anatomies of the arteries are not altered. The advantage of DEB is that DEB use does to cause lumen loss because there is no stent structure. From this perspective, the use of a DEB might be the next preferred strategy for the treatment of ostial ISR. Paclitaxel has been identified as the primary drug for use in DEBs due to its rapid uptake and prolonged retention [10].

In a previous study, B. Scheller et al. reported a 4% restenosis rate following DEB at one year and a 6% rate of restenosis at two years [11]. Martin Unverdorben et al. stated that the treatment of coronary ISR with the paclitaxel-coated balloons is at least as efficacious and well-tolerated as the paclitaxel-eluting stents. DEB use has been shown to result in less lumen loss and to be related to the need for target lesion revascularization [12]. The outcome of DEB use for BMS ISR is better than that of DEB use for DES ISR [13]. In our study, the restenosis rate was still lower in the BMS ISR than the DES ISR patients following DEB use. We still found that restenosis occurred in a greater proportion of ostial ISR patients following DEB use. This result may be related to the problem of ostial lesions, which is atherosclerotic change.

In our study, all patients were diagnosed with ostial ISR and exhibited multiple risk factors. The majority of patients had hypertension (90.6%), diabetes (61.2%) and hyperlipidemia (61.8%). Moreover, 41.2% of the patients had medical histories of prior myocardial infarctions, 30.6% had histories of heart failure, and 32.9% had ESRD. Among all patients, 25.9% had experienced STEMI and NSTEMI. The majority of the patients had multiple vessel disease (97.6%) and left main artery disease (54.1%). DEBs with prolonged inflation for 1 min were used to treat ostial ISR according to the patients' abilities to tolerate this treatment. After one-year of follow-up, 19.2% of all patients, 11.5% of the LAD patients, 29.0% of the LCX patients and 21.4% of the RCA patients underwent target lesion revascularization. Cardiovascular mortalities were low at 2.6% of all patients, 3.6% of the LAD patients, 0% of the LCX patients and 3.2% of the RCA patients. To the best of my knowledge,

no study has reported the results of the use of balloon angioplasty and stenting for ostial ISR. We have described our experiences related to the results following the use of DEBs for ostial ISR. Although restenosis occurred in approximately one-fifth of the patients, we still consider DEB to be an alternative strategy for coronary ostial ISR when additional stenting is not desirable.

4.1. Limitation

This study was a retrospective report and included only one medical center. All of the patients did not receive follow-up coronary angiography to detect target lesion restenosis. We arranged for follow-up coronary angiographies and non-invasive examinations, such as treadmill tests and thallium scans, according to the patients' symptoms. We might have underestimated the occurrence of target lesion restenosis.

5. Conclusions

Percutaneous coronary interventions with drug-eluting balloons are an alternative strategy for coronary ostial in-stent restenosis when additional stenting is not desirable.

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None.

Disclosures

None.

Conflict of interest

The authors declare that they have no conflict of interest.

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.

References

- [1] V. Rissanen, Occurrence of coronary ostial stenosis in a necropsy series of myocardial infarction, sudden death, and violent death, *Br. Heart J.* 37 (1975) 182–191.
- [2] J.J. Popma, R.J. Dick, C.C. Haudenschild, E.J. Topol, S.G. Ellis, Atherectomy of right coronary ostial stenoses: initial and long-term results, technical features and histologic findings, *Am. J. Cardiol.* 67 (1991) 431–433.
- [3] I.-C. Hsieh, M.-J. Hsieh, S.-H. Chang, C.-Y. Wang, C.-H. Lee, F.-C. Lin, C.-C. Chen, Acute and long-term outcomes of ostial stentings among bare-metal stents, sirolimus-eluting stents, and paclitaxel-eluting stents, *Coron. Artery Dis.* 24 (2013) 224–230.
- [4] P. Zampieri, A. Colombo, Y. Almagor, L. Maiello, L. Finci, Results of coronary stenting of ostial lesions, *Am. J. Cardiol.* 73 (1994) 901–903.
- [5] I. Iakovou, L. Ge, I. Michev, G.M. Sangiorgi, M. Montorfano, F. Airolidi, A. Chieffo, G. Stankovic, G. Vitrella, M. Carlino, N. Corvaja, C. Briguori, A. Colombo, Clinical and angiographic outcome after sirolimus-eluting stent implantation in aorto-ostial lesions, *J. Am. Coll. Cardiol.* 44 (2004) 967–971.
- [6] R. Virmani, G. Guagliumi, A. Farb, G. Musumeci, N. Grieco, T. Motta, L. Mihalcsik, M. Tsepili, O. Valsecchi, F.D. Kolodgie, Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? *Circulation* 109 (2004) 701–705.
- [7] M. Joner, A.V. Finn, A. Farb, E.K. Mont, F.D. Kolodgie, E. Ladich, R. Kutys, K. Skorija, H.K. Gold, R. Virmani, Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk, *J. Am. Coll. Cardiol.* 48 (2006) 193–202.
- [8] H. Takebayashi, G.S. Mintz, S.G. Carlier, Y. Kobayashi, K. Fujii, T. Yasuda, R.A. Costa, I. Moussa, G.D. Dangas, R. Mehran, A.J. Lansky, E. Kreps, M.B. Collins, A. Colombo, G.W. Stone, M.B. Leon, J.W. Moses, Nonuniform strut distribution correlates with more neointimal hyperplasia after sirolimus-eluting stent implantation, *Circulation* 110 (2004) 3430–3434.
- [9] A. Kastrati, A. Dibra, J. Mehilli, S. Mayer, S. Piniel, J. Pache, J. Dirschinger, A. Schömig, Predictive factors of restenosis after coronary implantation of sirolimus- or paclitaxel-eluting stents, *Circulation* 113 (2006) 2293–2300.
- [10] R. Waksman, R. Pakala, Drug-eluting balloon the comeback kid? *Circ. Cardiovasc. Interv.* 2 (2009) 352–358.
- [11] B. Scheller, C. Hehrlein, W. Bocksch, W. Rutsch, D. Haghi, U. Dietz, M. Böhm, U. Speck, Two year follow-up after treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter, *Clin. Res. Cardiol.* 97 (2008) 773–781.
- [12] M. Unverdorben, C. Vallbracht, B. Cremers, H. Heuer, C. Hengstenberg, C. Maikowski, G.S. Werner, D. Antoni, F.X. Kleber, W. Bocksch, M. Leschke, H. Ackermann, M. Boxberger, U. Speck, R. Degenhardt, B. Scheller, Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis, *Circulation* 119 (2009) 2986–2994.
- [13] S. Habara, M. Iwabuchi, N. Inoue, S. Nakamura, R. Asano, S. Nanto, Y. Hayashi, N. Shioda, S. Saito, Y. Ikari, T. Kimura, J. Hosokawa, M. Nakamura, J. Kotani, K. Kozuma, K. Mitsudo, A multicenter randomized comparison of paclitaxel-coated balloon catheter with conventional balloon angioplasty in patients with bare-metal stent restenosis and drug-eluting stent restenosis, *Am. Heart J.* 166 (2013) 527–533.