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ORIGINAL ARTICLE

Comparison of clinical outcomes of two different types of paclitaxel-coated balloons for treatment of patients with coronary in-stent restenosis

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Abstract
Drug-coated balloon (DCB) angioplasty has been shown to be a promising option for the treatment of coronary in-stent restenosis (ISR). We compared the clinical outcomes of patients with ISR who were treated with two commonly used paclitaxel-containing DCBs, the Pantera Lux (PL) and SeQuent Please (SP). A total of 491 patients with 507 ISR lesions [PL-DCB in 127 (26%) patients and SP-DCB in 364 (74%) patients] underwent DCB angioplasty for ISR lesions. The major adverse cardiac events (MACEs), including cardiac death, target lesion-related myocardial infarction, and target lesion revascularization, were assessed. There were no significant differences in each occurrence of MACE and cardiac death: 16 MACEs (61 per 1000 person-years) in the PL-DCB group and 55 (60 per 1000 person-years) MACEs in the SP-DCB group, log-rank $p=0.895$, and three cardiac deaths (11 per 1000 person-years) in the PL-DCB group and ten cardiac deaths (11 per 1000 person-years) in the SP-DCB group, log-rank $p=0.849$. Diabetes mellitus under insulin treatment [hazard ratio (HR) 2.71; 95% confidence interval (CI) 1.31–5.60; $p=0.007$], chronic kidney disease (HR 1.99; 95% CI 1.01–3.92; $p=0.045$), early-onset ISR (HR 1.99; 95% CI 1.18–3.36; $p=0.010$), and recurrent ISR (HR 1.89; 95% CI 1.08–3.32; $p=0.026$) were associated with the occurrence of MACE after DCB angioplasty. There was no significant difference of MACE between PL-DCB and SP-DCB treatment in patients with ISR. Patients with insulin-treated diabetes, chronic kidney disease, early-onset ISR, and recurrent ISR were at a higher risk of MACE after DCB angioplasty.

Keywords Coronary artery disease · In-stent restenosis · Drug-coated balloon

Introduction

Although recent advances in the technology utilized in coronary revascularization strategies using percutaneous coronary intervention have been highly effective and safe in the treatment of patients with coronary artery disease, coronary in-stent restenosis (ISR) is still one of the major concerns in the field of current coronary intervention [1]. Although the drug-eluting stent (DES) is used as one of the most effective treatments, even for ISR lesions, multiple layers of stent struts may limit future therapeutic options in the subsequent occurrence of restenosis due to a higher burden of the remaining metallic cage. As an alternative therapeutic modality, drug-coated balloon (DCB), which does not leave an additional permanent metallic cage within prior ISR lesions and is widely used for the treatment of ISR lesions, has been another option for revascularization [2]. Two paclitaxel-eluting balloons, Pantera Lux (PL, Biotronik, Berlin, Germany) and SeQuent® Please (SP, B. Braun, Melsungen, Germany), have a different drug coating and releasing methods that may lead to heterogeneity in their pharmacokinetic profile and, thus, anti-restenotic efficacy [3, 4]. We aimed to compare the clinical effectiveness and safety of these two

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different paclitaxel-eluting balloons for treatment in patients with ISR lesions.

Methods

Study population

We retrospectively reviewed our institute's coronary intervention database, in which patients who underwent coronary intervention and consented to study enrollment were consecutively enrolled. Among them, patients who underwent coronary angioplasty with DCB for ISR lesions between July 2010 and December 2016 were included for the study, and those who had a target lesion with reference vessel diameter < 2.0 mm ($n = 3$), clinical presentation of stent thrombosis ($n = 1$), and missing data on time of admission were excluded ($n = 3$). Finally, 491 patients with 507 ISR lesions who underwent DCB angioplasty were selected for inclusion in this study. DCB angioplasty for ISR lesions was performed for documented myocardial ischemia with a significant stenosis (≥ 50% diameter stenosis by visual estimate) in a previously stented segment assessed by invasive coronary angiography. Our institution's institutional review board approved this study, and written consent was obtained from all enrolled patients.

Percutaneous coronary intervention

All patients received at least 75 mg of aspirin and a loading dose of 300 mg of clopidogrel at least 12 h before DCB angioplasty. During the intervention, unfractionated heparin was administered to maintain an activated clotting time of > 250 s. The procedures were performed according to the current standard techniques. The DCB was inflated inside the ISR lesion for at least 60 s after the lesion was predilated with a plain balloon. The DCB size was selected based on the length of the target ISR lesion and the diameter of the previously used stents. Patients were encouraged to continue dual anti-platelet therapy with aspirin (100 mg/day indefinitely) and clopidogrel (75 mg/day for at least 1 month) after the procedure.

Quantitative coronary angiography

Quantitative coronary angiography analysis was performed before and after DCB angioplasty by analysts at an independent core laboratory (Cardiovascular Research Center, Seoul, Korea) using an offline computerized quantitative coronary angiographic system (CASS system; Pie Medical Instruments, Maastricht, the Netherlands). Using the guiding catheter for magnification calibration, the minimal lumen diameters and reference vessel diameters of ISR lesions were measured from diastolic frames in a single, matched view showing the smallest minimal luminal diameter.

Definitions of clinical events

Major adverse cardiac events (MACEs) in this study were defined as cardiac death, target lesion-related myocardial infarction, and target lesion revascularization within 3 years after DCB angioplasty. All deaths were considered cardiac deaths unless a definite non-cardiac cause could be established [5, 6]. Target lesion revascularization was defined as repeated percutaneous coronary intervention or coronary artery bypass grafting involving the target ISR lesion [5, 6]. It was also driven by clinical findings, including the presence of ischemic symptoms and/or a positive functional ischemia study. Target lesion-related myocardial infarction was defined as the presence of clinical symptoms, an increase in cardiac enzymes (creatine kinase myocardial band fraction above the upper normal limits or troponin T or troponin I greater than the 99th percentile of the upper normal limits), and angiographic, echocardiographic, or electrocardiographic findings definitely suggestive of ischemic change in the corresponding territory supplied by the coronary artery containing the DCB-treated ISR lesion [5, 6]. Adverse events were initially recorded by prospective monitoring of original registry and further retrospective review of electric medical record of the study population. Study endpoints were adjudicated by independent analysts who blinded to patient's clinical and procedure-related variable. Patients were considered to keep follow-up if those regularly visited outpatient clinic, got admitted, or had a telephone interview within a month of a follow-up schedule.

Statistical analysis

Categorical data were expressed as number (%) and analyzed with Chi-square statistics or Fisher's exact test. After testing normality by the Kolmogorov–Smirnov test, continuous variables were expressed as mean ± SD or median (first quantile–third quantile) and were compared using the Student's *t* test or the Mann–Whitney test, respectively. Stabilized inverse probability of treatment weighting (IPTW) method was used for adjustment of unbalanced variables between two patient groups who were treated with either PL or SP-DCBs [7]. Stabilized IPTW estimator for each patient was calculated by using logistic regression model with clinical and procedure-related variables including those include missing values, which were imputed by using multiple imputation by chained equation for the calculation [8]. Estimators were truncated at both upper and lower 0.01 to reduce extreme weighting. Comparing groups were considered to be balanced if standardized mean difference of all covariates was within 0.1 after weighting. Time-to-event data are

shown as Kaplan–Meier curves and were compared using the log-rank test. Post hoc analysis of log-rank test was performed and adjusted by the Benjamini and Hochberg correction [9]. The type of DCB and clinical, angiographic, and procedural variables that showed a univariate relationship with a level of significance less than 0.1 for MACE were entered into multivariate Cox proportional-hazards regression models. The marginal Cox model was applied to adjust for patient effect in lesion-level multivariable analysis, and backward elimination with sequential deletion of the most nonsignificant correlation was performed to obtain a parsimonious final model [10]. Considering difference of introduction timing of DCBs in our institute, assessments were performed with and without patients enrolled before starting to use PL-DCB. Because the incidence of MACE rapidly increased after 7 months from DCB angioplasty, we conducted an additional landmark analysis, which included all patients without events beginning at 7 months and continuing to the last follow-up available. All reported p values are two-sided, and a p value < 0.05 was considered to be indicative of statistically significant differences. All statistical analyses were performed with R Statistical Software (version 3.3.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

Of the eligible 491 patients, 127 (26%) and 364 (74%) patients were treated using PL-DCB and SP-DCB, respectively. Baseline clinical characteristics between the two groups were balanced, except a younger age in patients with PL-DCB (Table 1). More than 70% of the lesions in this study were previously treated with DES in each group. The median duration between stent implantation and DCB angioplasty was longer in patients treated with PL-DCB (6.8 years) than those treated with SP-DCB (4.7 years, $p = 0.006$). Lesions treated with PL-DCB (21 mm) were longer than those treated with SP-DCB (18 mm, $p = 0.018$). Predilation was performed in all lesions. Other angiographic and procedural characteristics did not significantly differ between the two groups (Table 2).

Clinical outcomes

Median follow-up duration was 25.7 (17.8–32.0) months in lesions treated with PL-DCB and 36.0 (27.1–36.0) months

Table 1 Baseline clinical characteristics

	Pantera Lux ($n = 127$)	SeQuent Please ($n = 364$)	p value
Age (years)	63 ± 10	65 ± 10	0.020
Male	97 (76%)	275 (76%)	0.946
Diabetes mellitus	45 (35%)	134 (37%)	0.864
Insulin dependent	4 (3.1%)	15 (4.1%)	0.825
Hypertension	82 (65%)	222 (61%)	0.543
Chronic kidney disease	12 (9.4%)	23 (6.3%)	0.327
Cigarette smoking	62 (49%)	179 (49%)	> 0.999
Dyslipidemia	83 (65%)	234 (64%)	0.913
Prior myocardial infarction	40 (31%)	117 (32%)	0.981
Coronary artery bypass graft surgery	8 (6.3%)	14 (3.8%)	0.367
Prior cerebrovascular attack	9 (7.1%)	25 (6.9%)	> 0.999
Clinical presentation at angioplasty with drug-coated balloon			0.519
Stable angina	79 (62%)	238 (65%)	
Unstable angina	48 (38%)	126 (35%)	
Discharge medication			
Aspirin	127 (100%)	353 (97%)	0.102
P2Y12 receptor antagonist	124 (97%)	353 (97%)	0.940
Oral anticoagulants	4 (3%)	5 (1%)	0.368
Statins	122 (96%)	344 (95%)	0.651
Beta-blockers	83 (65%)	243 (67%)	0.858
Calcium channel blockers	51 (40%)	158 (43%)	0.594
Renin–angiotensin system inhibitors	80 (63%)	239 (66%)	0.664

Data were expressed as mean ± standard deviation or number (%)

Table 2 Baseline angiographic and procedural characteristics

	Pantera Lux ($n=133$)	SeQuent Please ($n=374$)	p value
Time since stent implantation, years	6.8 (2.2–11.2)	4.7 (1.3–8.6)	0.006
≤ 1 year	18 (14%)	62 (17%)	0.491
Location of target lesion			0.953
Left main trunk	2 (2)	3 (1)	
Left anterior descending	71 (53)	199 (53)	
Left circumflex	28 (21)	76 (20)	
Right coronary	31 (23)	92 (25)	
Graft	1 (1)	4 (1)	
Type of stent			0.263
Bare-metal stent	24 (18%)	60 (16%)	
Drug-eluting stent	94 (71%)	287 (77%)	
Unknown	15 (11%)	27 (7%)	
Recurrent restenosis	13 (10%)	55 (15%)	0.199
Overlapping stents	6 (5%)	38 (10%)	0.071
Stent diameter[a]	3.0 (2.8–3.5)	3.0 (2.8–3.0)	0.542
Total stent length[a]	29 (23–41)	28 (18–38)	0.119
DCB angioplasty			
Predilation balloon diameter	2.5 (2.5–3.0)	2.5 (2.5–3.0)	0.124
Predilation balloon length	15 (15–15)	15 (15–15)	0.799
DCB diameter	3.0 (3.0–3.5)	3.0 (2.75–3.5)	0.124
DCB length	25 (20–30)	20 (15–25)	0.090
Quantitative coronary angiography			
Reference vessel diameter	2.7 (2.4–3.1)	2.8 (2.5–3.1)	0.106
Minimal lesion diameter	0.8 (0.4–1.1)	0.8 (0.5–1.1)	0.299
Lesions length	21 (15–25)	18 (14–24)	0.018
Acute gain	1.5 ± 0.6	1.5 ± 0.6	0.517

Data were expressed as mean ± standard deviation, median (interquartile range) if skewed, or number (%)

[a]Stent diameter and length were calculated excluding missing values in 61 and 59 lesions, respectively. *DCB* drug-coated balloon

in those with SP-DCB ($p<0.001$). More than 80% patients with both PL-DCB (115, 87%) and SP-DCB (312, 83%) were followed for more than 1 year. Among overall patients, there were no significant differences in each occurrence of MACE: 16 MACEs (61 per 1000 person-years) in the PL-DCB group and 55 (60 per 1000 person-years) MACEs in the SP-DCB group, log-rank $p=0.895$. After IPTW, comparing groups were balanced. Analysis with weighting also revealed no significant difference in the occurrence of MACE between two groups (log-rank $p=0.798$). Further analysis excluding 98 patients who were enrolled before PL-DCB began to be available in the institute also showed no association between types of DCB and MACE (log-rank $p=0.824$, Fig. 1). Each component of study endpoint did not differ in two groups as well. Cardiac death occurred in three patients (11 per 1000 person-years) treated with PL-DCB and ten patients (11 per 1000 person-years, log-rank $p=0.849$) treated with SP-DCB. Type of DCB did not impact on the target lesion-related myocardial infarction and revascularization (Fig. 2). There were also no significant differences in the occurrence of MACE between two DCBs among each subset, including lesions with a DES or a bare-metal stent (Fig. 3). Landmark analysis at 7 months also demonstrated no difference in the occurrence of MACEs between the two groups (Fig. 4a).

Predictors for MACEs

Diabetes mellitus (DM) treated with insulin, chronic kidney disease, early-onset ISR, and recurrent ISR were significant predictors for MACE during the study period in univariate analysis. After adjustment, insulin-treated DM [hazard ratio (HR) 2.71, 95% confidence interval (CI) 1.31–5.60, $p=0.007$], chronic kidney disease [HR 1.99, 95% CI 1.01–3.93, $p=0.045$], early-onset ISR [HR 1.99, 95% CI 1.18–3.36, $p=0.010$], and recurrent ISR [HR 1.89, 95% CI 1.08–3.32, $p=0.026$] were associated with MACE after DCB angioplasty (Table 3). At landmark analysis at 7 months, the same predictors for overall events were

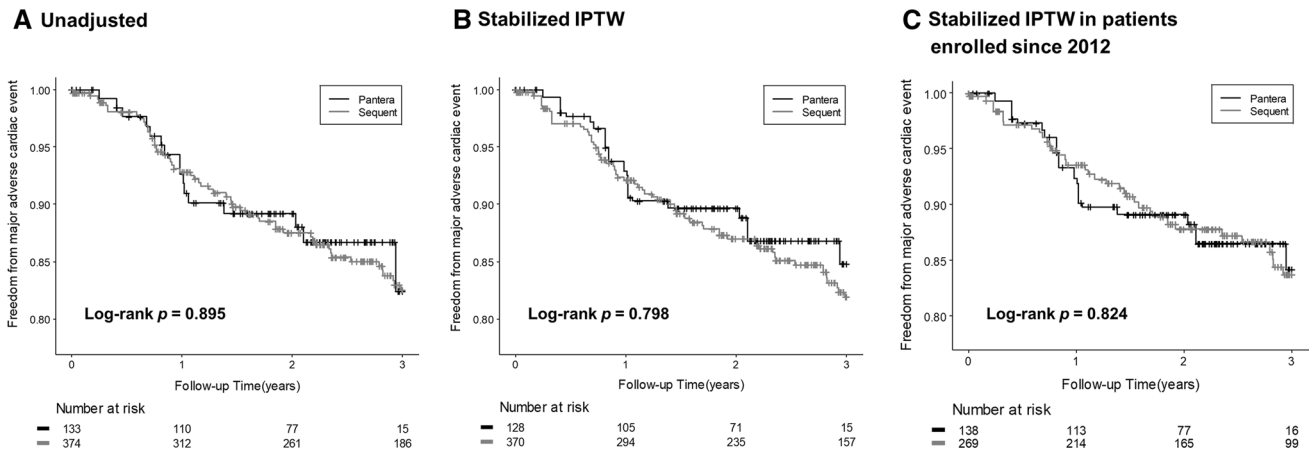

Fig. 1 Kaplan–Meier survival plots of major adverse cardiac events. Unadjusted (**a**), stabilized inverse probability of treatment weighting (IPTW) analyses was performed for comparison between two drug-coated balloons in overall patients (**b**) and in those enrolled since 2012 when both DCBs were available (**c**)

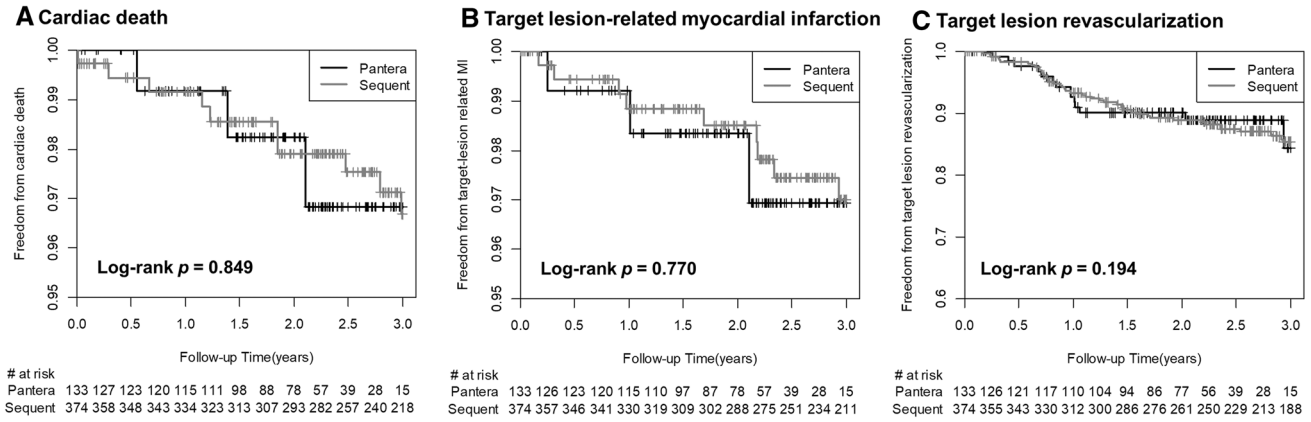

Fig. 2 Kaplan–Meier survival plots of each adverse event comparing two drug-coated balloons

included as independent predictors for MACEs. Insulin-treated DM was associated with a higher incidence of MACEs after DCB angioplasty during both the early ($p=0.015$) and late periods ($p=0.003$; Fig. 4b). The incidence of MACEs did not differ between early-onset and late-onset ISR, but it was substantially increased in early-onset ISR lesions after 7 months ($p=0.004$; Fig. 4c).

Discussion

This study showed that there was no significant difference in the occurrence of MACE between the two DCB treatment groups. In ISR lesions treated with DCB, the risk of MACE may be more affected by clinical factors, including insulin-treated DM, chronic kidney disease, early-onset ISR and recurrent ISR, rather than the type of DCB.

Certain types of DCBs have been suggested to have different mechanisms of effective and sustainable drug delivery to the vessel wall [11, 12]. Although both PL-DCB and SP-DCB contain a similar concentration of paclitaxel (3.0 mg/mm^2) on the balloon surface, PL-DCB and SP-DCB use different excipients (*n*-butyryl-tri-*n*-hexyl citrate and iopromide, respectively) which may alter efficacy in drug delivery. The excipients used in the coatings are as important as the anti-proliferative drug applied, as they play the central role in influencing DCB pharmacokinetic profiles. For instance, the excipients counteract the high hydrophobicity of paclitaxel, which causes it to stick to the balloon surface, through increasing drug transfer capability [11]. Iopromide is a contrast medium that has been used as an excipient to facilitate the transfer of paclitacxel from the DEB to the vessel wall. On the other hand, n-butyryl-tri-*n*-hexyl citrate can be rapidly metabolized, is biocompatible, and has been approved in blood-contacting medical devices, such as blood

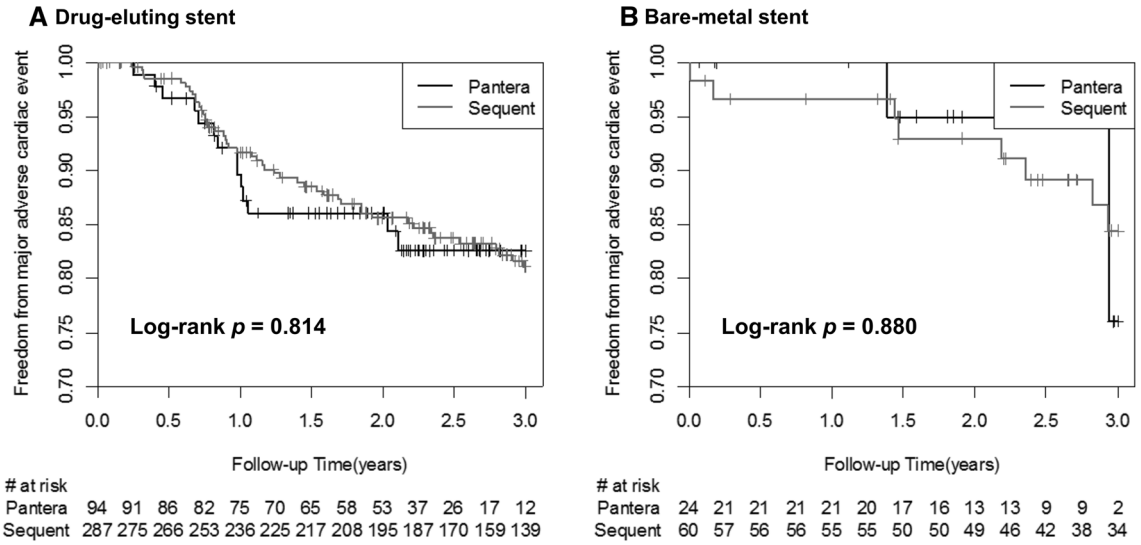

Fig. 3 Kaplan–Meier survival plots of major adverse cardiac events comparing two drug-coated balloons in lesions with drug-eluting stents (**a**) and bare-metal stents (**b**)

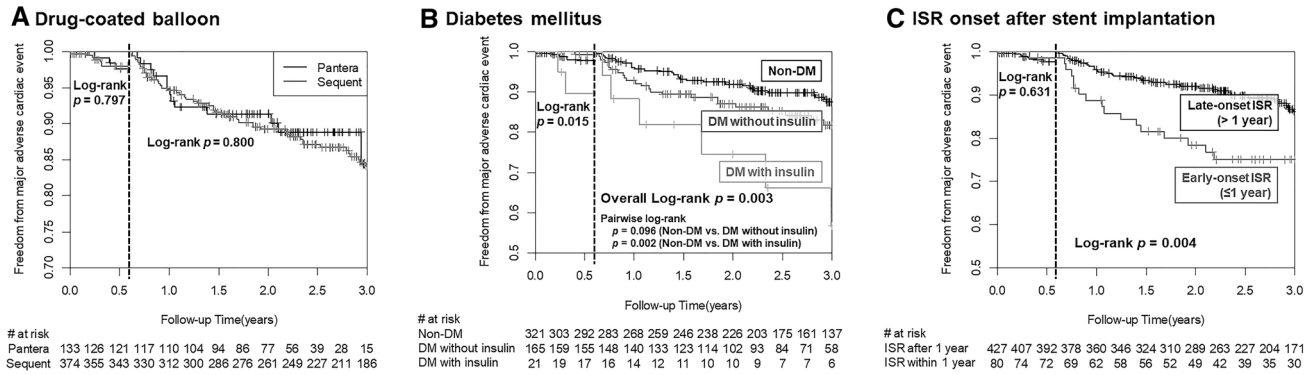

Fig. 4 Landmark analysis for major adverse cardiac events beginning at 7 months comparing patients with different drug-coated balloons (**a**), status of diabetes mellitus (**b**), and early-onset (≤ 1 year) vs. late-onset (> 1 year) ISR (**c**). *DM* diabetes mellitus, which denotes in-stent restenosis

Table 3 Predictors for major adverse cardiac events after drug-coated balloon angioplasty

Predictors	Univariable model		Adjusted model	
	HR (95% CI)	*p*	HR (95% CI)	*p*
SeQuent Please balloon	1.04 (0.58–1.84)	0.898	1.04 (0.59–1.86)	0.884
Diabetes mellitus				
Treated without insulin	1.32 (0.78–2.24)	0.301	1.24 (0.73–2.11)	0.429
Treated with insulin	4.17 (2.01–8.67)	< 0.001	2.71 (1.31–5.60)	0.007
Chronic kidney disease	3.03 (1.59–5.75)	0.001	1.99 (1.01–3.92)	0.045
Early-onset ISR (≤ 1 year)	1.94 (1.14–3.33)	0.015	1.99 (1.18–3.36)	0.010
Recurrent ISR	2.15 (1.27–3.65)	0.005	1.89 (1.08–3.32)	0.026

The marginal Cox model was used to determine the predictors for MACE

CI confidence interval, *HR* hazard ratio, *ISR* in-stent restenosis, *MACE* major adverse cardiac events

bags. Unlike the iopromide coating, *n*-butyryl-tri-*n*-hexyl citrate has a hydrophobic nature and is expected to be less soluble than hydrophilic excipients. This hydrophobicity improves both the coating integrity and the resistance of the coating as the balloon goes through the path from catheter to lesion, ensuring that more drug is available at the target lesion site. As opposed to the hydrophilic excipients in which paclitaxel is poorly soluble, *n*-butyryl-tri-*n*-hexyl citrate's lipophilic characteristic helps to facilitate solvation of paclitacxel to microcrystalline forms, resulting in better drug retention at the target lesion site and improved endothelial penetration of the drug [13]. Increased tissue uptake of paclitaxel may lead to a more potent anti-proliferative effect on neointimal growth after DCB angioplasty [3, 14, 15]. A pharmacokinetic study revealed that tissue concentrations of paclitaxel in patients with different DCBs differed only within the first hour and decreased to undetectable or less than 1% of the level from the first hour [16]. Considering that similar effects on clinical outcomes have been presented by different types of recently developed DES using various stent designs, strut thickness, polymers, and drugs [17], it may be difficult to show significant differences in clinical outcomes by using different types of DCBs. Furthermore, recent meta-analyses revealed that both DES and DCB had similar clinical outcomes in the treatment of ISR lesions, and both drug-containing devices were superior (80% reduction in MACE for 1 year) to plain balloon angioplasty [18, 19].

There have been a limited number of studies comparing clinical effectiveness of different types of DCBs. Recently published study including two consecutive trials included 164 patients and assessed angiographic and clinical outcomes. Although patients with PL-DCB underwent more frequent balloon predilation but had higher postprocedural stenosis, there were no significant differences in mean diameter stenosis at follow-up angiography at 6–8 months and 1-year MACE between PL-DCB and SP-DCB [20]. However, another registry study noted that PL-DCB was superior to SP-DCB with lower risk of MACE (HR 0.65, 95% CI 0.43–0.98). Among 434 patients who were included for comparison of follow-up events, only 47 patients (11%) were remained until 1 year in the study. Considering that the difference between two DCBs was mainly driven by the events occurred after 1 year, the number of patients in the analysis might be too small to exclude the possibility of findings by chance or bias [21]. Similar to our finding, previous studies with DCB [20–24] displayed that the incidence of recurrent events abruptly increases after early period since DCB angioplasty for treatment of ISR. Considering that late restenosis after DCB angioplasty is more frequent in DES-ISR than in BMS-ISR [25], it should be important to assess clinical outcomes occurred during long-term period with sufficient number of subjects in further studies. Our analysis, in which more than half of patients with follow-up of more than 2 years were included in each group, did not show any differences in long-term effect between two DCBs until 3 years.

Our study adds to the current literature by pointing out some predictors for the occurrence of MACEs including DM, chronic kidney disease, early-onset ISR, and recurrent ISR. DM is known to cause further neointimal proliferation in stented or non-stented coronary lesions. Previous investigations described the association of insulin resistance or hyperinsulinemia with neointimal hyperplasia after coronary stenting [26–28]. Although insulin has a growth-promoting effect on vascular biology, it has been suggested to have mainly protective roles after arterial injury [29–31]. It may be reasonable to assume that DM requiring more intensive treatment (poorly controlled by oral medication due to hyperglycemia or high insulin resistance) was correlated with worse outcomes after DCB angioplasty. Further study is warranted to determine the pathophysiologic mechanism of DM on outcomes after repeat revascularization. Early study using plain balloon angioplasty for ISR [32] reported that clinical predictors for recurrent events in ISR lesions included DM and short interval from stent implantation to ISR within 4 months, which are similar to our results using DCB. However, the literature exploring the association between stent age (time from stent implantation to restenosis) and clinical outcomes after repeat revascularization is scarce in recent stent era. Early-onset ISR may be triggered by instantaneous resistance to mechanical (stenting) or pharmacological barriers (anti-proliferative drug) against restenosis. Compared with late-onset ISR, it may have different mechanisms of restenosis such as neoatherosclerosis, which is more frequently found in stents with longer duration or DES [33]. It is also important to be determined in further studies.

Study limitations

As we included eligible patients in a retrospective manner, differences between the groups might lead to biased results even using adjusted analysis. Clinical endpoints were recorded by reviewing the medical report of the last visit or contacted by phone; however, we might have accounted for the rather modest rate of follow-up beyond 1 year or more. Given that the results of recently published trials comparing PL-DCB versus SP-DCB treatment showed comparable clinical outcomes until 12 months, our results may reinforce the comparable clinical implications of these two DCBs within or after 1 year of follow-up. Our study did not assess angiographic or intravascular imaging data at follow-up, which may provide more information about neointimal growth or re-progression of neoatherosclerosis affecting long-term outcomes. Although we included nearly 500 patients treated with DCBs for ISR lesions which are

greater than the number of participants in previous studies, it might be not sufficiently powered to compare the difference of adverse events. Our findings may not be appropriate for conclusion to declare null effect of certain DCB compared with the other, but it should be hypothesis-generating considering unmeasured confounding. Further studies are required for the comparisons of vascular responses between different DCBs for ISR lesions.

Conclusions

We found no significant differences of MACE after angioplasty using PL-DCB and SP-DCB in ISR lesions. Some predictors have a significant influence on the occurrence of MACEs for the overall follow-up period, including insulin-treated DM, chronic kidney disease, early-onset ISR, and recurrent ISR.

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Compliance with ethical standards

Conflict of interest The author declares that they have no conflict of interest.

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