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ORIGINAL ARTICLE

Differences in clinical outcomes between pre- and post-marketing clinical study following paclitaxel-coated balloon catheter treatment for coronary in-stent restenosis: from the Japanese regulatory viewpoint

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Abstract
In 2013, a drug-coated balloon catheter (DCB) (SeQuent Please) for the treatment of coronary in-stent restenosis (ISR) was approved in Japan. The pre-marketing Japan domestic NP001 study demonstrated better outcomes of the DCB ($n=138$) compared to plain balloon angioplasty ($n=72$). After the introduction to marketing, a post-marketing surveillance (PMS) ($n=396$) was conducted to evaluate the safety and efficacy of the DCB in Japanese routine clinical practice. The aim of this paper was to assess differences between the pre-marketing NP001 study and the PMS. Compared to the NP001 study, more complex lesions were treated in the PMS (type B2/C: 69.0% vs 20.4%, total occlusion: 11.2% vs 0%, $p<0.001$, respectively) and target lesion was more frequently ISR related to drug-eluting stent (DES) (79.5% vs 39.4%, $p<0.001$). Regarding clinical outcomes, the rate of target lesion revascularization (TLR) was higher in the PMS than in the NP001 study (TLR: 12.9% at 7 months and 17.6% at 12 months vs 2.8% at 6 months, $p=0.001$, $p<0.001$, respectively). Multivariable logistic regression analysis revealed that DES-ISR was a risk factor of TLR after DCB treatment for ISR (odds ratio: 5.77, 95% CI 1.75–18.95, $p=0.004$). Among representative published trials using DCB for ISR, clinical outcomes are often worse in DES-ISR trials than those in bare metal stent-ISR trials. The rates of TLR in previous DES-ISR trials are similar to that in the current PMS (TLR at 12 months: 22.1% for ISAR-DESIRE 3, 15.3% for PEPCAD-DES, and 13.0% for RIBS IV). The effectiveness and safety of DCB for coronary ISR have been confirmed in the Japanese real-world survey. PMS would be useful to evaluate the safety and effectiveness of medical products throughout their total life cycles.

Keywords Drug-coated balloon · Post-marketing surveillance · Percutaneous coronary intervention · Regulatory review

Abbreviations

BMS	Bare metal stents
BR	Binary restenosis
CABG	Coronary artery bypass grafting
CI	Confidence intervals
DAPT	Dual antiplatelet therapy
DCB	Drug-coated balloon
DES	Drug-eluting stents
DS	Diameter stenosis
GPSP	Good post-marketing surveillance practice
ISR	In-stent restenosis
LAD	Left anterior descending artery
LCX	Left circumflex artery
LMT	Left main trunk
LLL	Late lumen loss
MACE	Major adverse cardiac events
MI	Myocardial infarction
OR	Odds ratio
PCI	Percutaneous coronary intervention
PMDA	Pharmaceuticals and Medical Devices Agency
PMS	Post-marketing surveillance
POBA	Plain old balloon angioplasty

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QCA Quantitative coronary angiography
RCA Right coronary artery
RVD Reference vessel diameter
TLR Target lesion revascularization
TVF Target vessel failure
TVR Target vessel revascularization

Introduction

A clinical trial is the gold standard for evaluating the effectiveness and safety of new medical devices before marketing. Pre-marketing clinical trials are often conducted with a limited number of patients, with specific populations, and in specialized environments. On the other hand, in the real world of medical device use, several factors such as patient and disease characteristics different from those in pre-marketing clinical trials may affect both the effectiveness and safety of medical devices. In Japan, most new innovative medical devices need to be re-examined during a certain time period after their introduction into the market according to the post-marketing surveillance (PMS) system under the Pharmaceuticals and Medical Devices Act [1–3]. To ensure the effectiveness, safety, and quality of medical devices after their approval for marketing, PMS is conducted under the good post-marketing surveillance practice (GPSP), which is the Japanese system for ensuring the quality and reliability of the survey [4]. Following regulatory re-evaluation of the PMS, the results are classified into one of three approval categories: (1) approval refused (manufacturing and marketing suspended, approval revoked), (2) changes in approval (modifications in approved items as directed), and (3) approved (as per application for re-examination), and any additional required risk management measures are adopted [5].

In July 2013, the first drug-coated balloon catheter (DCB) (SeQuent Please, B Braun, Melsungen, Germany, and Nipro Corporation, Osaka, Japan) for the treatment of coronary in-stent restenosis (ISR) was approved in Japan. In the pre-marketing stage, the Japan domestic randomized clinical trial (NP001 study) demonstrated that compared to plain old balloon angioplasty (POBA), the clinical outcome of the DCB for ISR was more favorable at 6 months follow-up [6]. At the time of approval of the DCB, the company that developed the device was required to conduct a PMS to evaluate the safety and efficacy of the DCB in Japanese routine clinical practice. In the regulatory review of the PMS results, the clinical outcome of the DCB in the PMS differed markedly from those reported in the NP001 study [7].

In this paper, we, the Pharmaceuticals and Medical Devices Agency (PMDA): the Japanese regulatory agency, compared baseline characteristics and clinical outcomes between the pre- and post-marketing clinical studies involving the use of the DCB for ISR and evaluated risk factors for worse clinical outcome after the DCB treatment for ISR lesions. In addition, we presented the Japanese regulatory view on the DCB PMS results.

All analyses were performed using data from application dossiers for the regulatory evaluation. This paper is not written for promotional purposes and the views expressed do not necessarily represent the views and findings of the PMDA. The protocol of the study was approved by the PMDA IRB (certification number: 2019-Z-10), and followed the Declaration of Helsinki and the ethical standards of the responsible committee on human experimentation.

Materials and methods

Outline of clinical studies

Pre-marketing clinical study for approval in Japan (NP001 study)

Between October 2009 and October 2011, 210 patients were enrolled from 13 centers across Japan and were randomized into the DCB group ($n=138$) and the POBA group ($n=72$). These patients underwent percutaneous coronary intervention (PCI) with DCB or POBA for ISR lesions. The main exclusion criteria were the occurrence of acute myocardial infarction (MI) within the preceding 72 h, the presence of severe renal insufficiency, and the presence of severe liver disease. Major angiographic exclusion criteria included the presence of lesions longer than 22 mm, vessels with diameters below 2.0 mm, the presence of total occlusion, unprotected left main stenosis, and a bifurcation lesion treated using the kissing balloon technique, vessels with previous paclitaxel-eluting stent implantation, and vessels treated with drug-eluting stent (DES) within 24 weeks. The primary endpoint was target vessel failure (TVF) at 6 months after PCI. TVF was defined as the occurrence of cardiac death, myocardial infarction, or target vessel revascularization (TVR). TVR or target lesion revascularization (TLR) was defined as either revascularization at the target lesion by PCI or coronary artery bypass grafting (CABG). Major adverse cardiac events (MACE) were defined as a composite of all-cause death, MI, and TVR. All patients provided written informed consent. During the follow-up, a patient was excluded due to the revocation of consent. This study was sponsored by the Nipro Corporation.

Post-marketing surveillance in Japan

The DCB PMS is a prospective, single arm, nationwide surveillance. Between January 2014 and July 2016, 396 patients were enrolled from 53 centers across Japan. These patients underwent PCI with DCB for ISR lesions. There were no

specific exclusion criteria. Patients were scheduled for an angiographic follow-up after 7 months and a 12-month clinical follow-up after PCI. The definitions of TVF, TVR, TLR, and MACE were the same as those used in the NP001 study. In 12 patients, both clinical and angiographic follow-up were not performed due to the intention of each patient. The PMS was funded and conducted by the Nipro Corporation under the GPSP Ordinance of the Japanese Ministry of Health, Labor, and Welfare. Informed consent from individual patients was waived, because post-marketing surveillance is legally obligated to marketing authorization holder under the provision of the Pharmaceuticals and Medical Devices Act in Japan.

Statistical analysis

Continuous variables are presented as the means with standard deviations. Differences in continuous parameters were evaluated using an unpaired *t* test. Categorical variables are presented as frequency counts and intergroup comparisons were made using Fisher's exact test or Chi-square test. To identify risk factors for TLR following DCB treatment for ISR, a multivariable logistic regression model was constructed using patient-level clinical data from the PMS. Independent variables were chosen as potentially significant independent factors with a p value level <0.10 by univariate analysis. The final model was obtained using a forward stepwise method with a threshold for exit set at a p value level >0.10. Factors in each comparison were expressed as odds ratios (ORs) and their 95% confidence intervals (CIs). Statistical analysis was performed using SPSS Statistics software (version 22.0, SPSS Inc., Chicago, IL). A p value <0.05 was considered statistically significant.

Results

Differences between the pre- and post-marketing clinical studies

Baseline characteristics

The comparison of baseline characteristics between the NP001 study and the PMS is shown in Table 1. At baseline, more patients in the PMS had heart failure, peripheral artery disease, and chronic kidney disease compared to the NP001 study, whereas the prevalence of prior MI, prior stroke and hyperlipidemia was higher in the NP001 study. In the PMS, 13.4% of patients received hemodialysis that was one of the exclusion criteria in the NP001 study. Regarding lesion characteristics, more complex lesions were treated with DCB in the PMS (type B2/C lesion: 69.0% vs 20.4%, $p<0.001$, Mehran ISR classification [8] type IV: total occlusion lesion: 11.2% vs 0%, $p<0.001$). In addition, approximately 80% of all lesions in the PMS were ISR lesions that occurred after DES implantation, whereas the proportion of DES-ISR was around 40% in the NP001 study (the proportion of DES-ISR: 79.5% vs 39.4%, $p<0.001$).

Clinical and angiographic outcomes

Clinical and angiographic outcomes of the two studies are summarized in Table 2. The rate of MACE, TVF, TVR and TLR was significantly higher in the PMS than in the NP001 study, respectively, (PMS: MACE 16.9% at 7 months and 27.1% at 12 months, TVF 16.1% at 7 months and 24.7% at 12 months, TVR 14.9% at 7 months and 22.1% at 12 months, TLR 12.9% at 7 months and 17.6% at 12 months; NP001 study: MACE 6.6% at 6 months, TVF: 6.6% at 6 months, TVR 6.4% at 6 months, TLR: 2.8% at 6 months).

Quantitative coronary angiography (QCA) analysis revealed that the diameter stenosis (DS), binary restenosis (BR) rate, and late lumen loss (LLL) during the follow-up period was significantly higher in the PMS than in the NP001 study (DS: 41.6% vs 28.1%, BR: 27.2% vs 4.4%, and LLL: 0.41 mm vs 0.11 mm, respectively).

Risk factors for TLR following DCB treatment for ISR

Multivariate logistic regression analysis revealed that DES-ISR was a risk factor for TLR at 12 months after PCI using DCB for ISR (OR: 5.77, 95% CI 1.75–18.95, $p=0.004$) (Table 3).

Discussion

The current main findings were: (1) patient background and lesion characteristics in the PMS differed from those in the pre-marketing NP001 study, (2) the rate of TLR in the PMS was markedly higher than in the NP001 study and (3) multivariate analysis revealed that DES-ISR was a risk factor for TLR after PCI using DCB for ISR.

In the NP001 study, the study protocol described that vessels with previous paclitaxel-eluting stent implantation and vessels treated with other DES within 24 weeks were excluded due to safety concern such as drug overdose at that time. Consequently, the proportion of DES-ISR in the NP001 study was much smaller than in the PMS. Some reports have shown that DES-ISR is different from bare metal stents (BMS)-ISR in terms of its mechanism of action, morphological patterns, tissue composition, and response to treatment [9–12]. Clinical outcomes in representative published trials that used DCB for ISR are summarized in Table 4. Among these trials, TLR and MACE occurred more often in the trials that involved DES-ISR [13–15] than in

Table 1 Comparison of baseline patient and lesion characteristics between the PMS and the NP001 study

	PMS *N* = 396	Pre-marketing NP001 study DCB group *N* = 137	*p* value
Female (%)	18.9% (75)	19.0% (26)	1.000
Age (years)	70.0 ± 9.7	68.3 ± 10.3	0.120
More than 75 years	34.6% (137)	32.1% (44)	0.672
Prior MI	32.6% (129)	51.8% (71)	< 0.001
Diabetes mellitus	53.0% (210)	46.0% (63)	0.186
Hyperlipidemia	67.7% (268)	83.2% (114)	< 0.001
Hypertension	79.0% (313)	84.7% (116)	0.175
Prior stroke	3.0% (12)	10.9% (15)	< 0.001
Chronic kidney disease	19.9% (79)	3.6% (5)	< 0.001
Hemodialysis	13.4% (53)	0	< 0.001
Peripheral artery disease	10.9% (43)	2.2% (3)	0.003
Heart failure	9.3% (37)	2.2% (3)	0.011
Clinical presentation			0.008
Stable angina	80.3% (318)	93.4% (128)	
Unstable angina	14.6% (58)	3.6% (5)	
Recent MI	4.3% (17)	2.9% (4)	
AMI	0.8% (3)	0	
	L = 439	*L* = 142	
Lesion characteristics			
Target vessel			0.478
LMT	0.9% (4)	0	
LAD	41.2% (181)	49.3% (70)	
LCX	21.2% (93)	18.3% (26)	
RCA	36.7% (161)	32.4% (46)	
Lesion type; AHA classification			< 0.001
Type A/B1	31.0% (136)	79.6% (113)	
Type B2/C	69.0% (303)	20.4% (29)	
Restenosis morphology; Mehran classification [8]			< 0.001
Type I (focal)	40.0% (171/428)	54.2% (77/142)	
Type II (> 10 mm within the stent)	40.2% (172/428)	39.4% (56/142)	
Type III (> 10 mm extending outside the stent)	8.6% (37/428)	6.3% (9/142)	
Type IV (total occlusion)	11.2% (48/428)	0% (0)	
Stent type related to ISR			< 0.001
DES	79.5% (349)	39.4% (56)	
BMS	15.7% (69)	60.6% (86)	
Unknown	4.8% (21)	0% (0)	

All values are % (*N*) or mean ± standard deviation

AHA American Heart Association, *AMI* acute myocardial infarction, *BMS* bare-metal stent, *DCB* drug-coated balloon, *DES* drug-eluting stent, *ISR* in-stent restenosis, *LAD* left anterior descending artery, *LCX* left circumflex artery, *LMT* left main trunk, *MI* myocardial infarction, *PMS* post-marketing surveillance, *RCA* right coronary artery

the trials that involved BMS-ISR [16–18]. The results of the DES-ISR trials were similar to the result of the current PMS (TLR at 12 months: 22.1% for ISAR-DESIRE 3 [13], 15.3% for PEPCAD-DES [14], and 13.0% for RIBS IV [15]). Therefore, the marked differences in clinical outcomes between the NP001 study and the PMS could be mainly attributed to the difference in the proportion of DES-ISR lesions in each study.

There are several treatment options for ISR including DCB, repeat stenting with DES, and POBA. Recent guidelines in Japan and the European Union recommend both DCB and DES treatments for ISR as class I [19, 20].

Table 2 Comparison of clinical and angiographic outcomes between the PMS and the NP001 study

	PMS ($N=384$)		NP001 study DCB group ($N=136$)	*p* value	
	12 months	7 months	6 months	†	‡
MACE	27.1% (104)	16.9% (65)	6.6% (9)	0.005	< 0.001
Cardiac death	1.8% (7)	1.0% (4)	0% (0)	0.533	0.249
Non-cardiac death	1.8% (7)	0.8% (3)	0% (0)	0.708	0.249
Unknown cause death	0.3% (1)	0.3% (1)	0% (0)	1	1
TVF	24.7% (95)	16.1% (62)	6.6% (9)	0.008	< 0.001
Q wave MI	0.5% (2)	0.5% (2)	0% (0)	0.970	0.970
Non Q wave MI	1.0% (4)	0.8% (3)	0% (0)	0.708	0.533
TVR	22.1% (89/403)	14.9% (60/403)	6.4% (9/141)	0.014	< 0.001
TLR	17.6% (71/403)	12.9% (52/403)	2.8% (4/141)	0.001	< 0.001
		$L=363$	$L=141$		
QCA analysis					
Pre					
Lesion length (mm)		14.8 ± 10.1	12.8 ± 6.5	0.042	
RVD (mm)		2.52 ± 0.61	2.52 ± 0.49	0.960	
DS (%)		70.2 ± 15.0	66.3 ± 11.2	0.003	
Post					
DS (%)		24.9 ± 10.6	22.3 ± 7.4	0.010	
F/U					
DS (%)		41.6 ± 20.8	28.1 ± 11.1	< 0.001	
BR (%)		27.3% (99)	4.3% (6)	< 0.001	
LLL (mm)		0.41 ± 0.49	0.11 ± 0.33	< 0.001	

All values are % (*N*) or mean ± standard deviation

BR binary restenosis, *DCB* drug-coated balloon, *DS* diameter stenosis, *F/U* follow-up, *LLL* late lumen loss, *MACE* major adverse cardiac events, *MI* myocardial infarction, *PMS* post-marketing surveillance, *QCA* quantitative coronary angiography, *RVD* reference vessel diameter, *TLR* target lesion revascularization, *TVF* target vessel failure, *TVR* target vessel revascularization

†PMS 7 months vs NP001 study 6 months

‡PMS 12 months vs NP001 study 6 months

Table 3 Univariate and multivariate analyses investigating relationship between baseline variables and TLR after PCI for ISR using DCB

Independent variables	TLR			
	Univariate analysis		Multivariable analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
DES-ISR	6.14 (1.87–20.14)	0.003	5.77 (1.75–18.95)	0.004
Mehran classification type IV [7]	2.20 (1.08–4.49)	0.030	–	
Hemodialysis	1.95 (1.04–3.65)	0.037	–	
Hyperlipidemia	1.83 (1.04–3.24)	0.037	–	
Unstable angina	1.88 (1.02–3.46)	0.043	–	
Female	1.72 (0.97–3.05)	0.064	–	
More than 75 years old	0.62 (0.36–1.08)	0.089	–	
LAD	0.64 (0.38–1.07)	0.089	–	

CI confidence interval, *DCB* drug-coated balloon, *DES* drug-eluting stent, *ISR* in-stent restenosis, *LAD* left anterior descending artery, *OR* odds ratio, *PCI* percutaneous coronary intervention, *TLR* target lesion revascularization

Previous trials have shown that repeat stenting with DES is effective and safe in patients with ISR [13, 15, 17, 18, 21, 22]. However, in repeat DES stenting, there is a concern about prolonged dual antiplatelet therapy (DAPT) duration

Table 4 Clinical outcomes of representative clinical trials using DCB for ISR

Trial	Trial design	Number of subjects	Stent type related to ISR	DCB at 12 months		Control at 12 months	
				TLR (%)	MACE (%)	TLR	MACE
PACCOCATH-ISR I/II [16]	DCB vs POBA	54 vs 54	BMS	3.7	9.3	POBA: 37.0%	POBA: 44.4%
PEPCAD II ISR [17]	DCB vs DES	66 vs 65	BMS	6.1	7.6	DES: 15.4%	DES: 16.9%
RIBS V [18]	DCB vs DES	95 vs 94	BMS	6.3	8.4	DES: 1.1%	DES: 6.4%
ISAR-DESIRE 3 [13]	DCB vs DES vs POBA	137 vs 131 vs 134	DES	22.1	23.5	DES: 13.5% POBA: 43.5%	DES: 23.5% POBA: 46.2%
PEPCAD-DES [14]	DCB vs POBA	72 vs 38	DES	15.3	16.8	POBA: 36.8%	POBA: 52.6%
RIBS IV [15]	DCB vs DES	154 vs 155	DES	13.0	15.6	DES: 4.5%	DES: 6.5%

BMS bare-metal stent, *DCB* drug-coated balloon, *DES* drug-eluting stent, *ISR* in-stent restenosis, *MACE* major adverse cardiovascular event, *POBA* plain old balloon angioplasty, *TLR* target lesion revascularization

due to the additional metal layers in the coronary vessel. In this respect, DCB treatment can offer the benefit of drug delivery to the ISR site without additional metal layers [23, 24], which could lead to minimization of the DAPT duration.

Considering all the above, the PMDA concluded that the benefit of DCB treatment for ISR outweighs its risk and that DCB could be an effective and safe option for the treatment of coronary ISR lesions. Finally, the DCB-PMS result was classified as "approved (as per application for re-examination)".

Pre-marketing clinical trials are often conducted with specific populations and in specialized environments because of control variability, data quality and cost. However, the populations enrolled in the trials may differed from those seen in routine practice. In the regulatory approval review of medical products, generalizability is always be discussed. Consequently, the indication and/or target patients of products is not always the same as in the pre-marketing trials. Regarding this point, PMS would be very useful and effective system to determine effectiveness and safety of medical products in the real-world practice. As the target population or the proportion of specific lesions such as complex lesions are sometimes largely different between pre-marketing clinical trials and PMS, unexpected results could be obtained in the PMS. In such a situation, a cause analysis is often performed. A cause analysis is very useful in optimizing the benefit–risk balance of medical devices. However, there are some limitations in the analysis of PMS, such as the unavailability of an active control, limited follow-up period, and data resource limitations. In the current case, some published data are supportive of the PMS result. Although PMS have some limitations compared to controlled pre-marketing clinical trials, PMS could be useful to evaluate the safety and effectiveness of medical devices throughout their total life cycles.

Limitations

Some limitations should be noted. First, there was limited information concerning the results of laboratory investigations, echocardiographic findings and medications in the PMS. Second, 12-month follow-up data of the NP001 study are unavailable because the follow-up period ends 6 months. Third, the current PMS was a single arm surveillance.

Therefore, significant advantages of DCB treatment over repeat DES stenting in patients with DES-ISR remain unknown. A large-scale randomized trial comparing DCB and repeat DES stenting for DES-ISR in Japanese routine clinical practice, would be warranted.

Conclusions

The effectiveness and safety of DCB for coronary ISR have been confirmed in the Japanese real-world survey. In the real-world, the target population and/or lesions of medical products is not always the same as in the pre-marketing trials. Regarding this point, PMS would be useful to evaluate the safety and effectiveness of medical products throughout their total life cycles.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest. This paper was written with no external funding.

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