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Long-term outcomes after treatment of bare-metal stent restenosis with paclitaxel-coated balloon catheters or everolimus-eluting stents: 3-year follow-up of the TIS clinical study

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Abstract

Background: The efficacy of paclitaxel-eluting balloon catheters (PEB) and drug-eluting stents for treatment of bare-metal stent restenosis (BMS-ISR) have been demonstrated in several studies with follow-up times of 9 to 12 months; however, the long-term outcomes of ISR treatment are less defined.

Objectives: We aimed to compare the long-term efficacy of PEB and everolimus-eluting stents (EES) for the treatment of BMS-ISR.

Methods: We analyzed 3-year clinical follow-up data from patients included in the TIS randomized clinical study. A total of 136 patients with BMS-ISR were allocated to receive treatment with either PEB or EES (68 patients with 74 ISR lesions per group).

Results: The PEB and EES groups did not significantly differ in major adverse cardiac events-free survival (MACE; $P = .211$; including individual events: CV death: $P = .622$; myocardial infarction: $P = .650$ or target vessel revascularization: $P = .286$) at 3-year clinical follow-up. No event-free survival differences were found between the groups regarding overall mortality ($P = .818$), definite stent thrombosis ($P = .165$) or the second MACE ($P = .270$).

Conclusions: At the 3-year follow-up, no significant differences in clinical outcomes were found between iopromide-coated PEB and EES for the treatment of BMS-ISR. (ClinicalTrials.gov; https://clinicaltrials.gov; NCT01735825).

KEYWORDS
everolimus-eluting stent, in-stent restenosis, paclitaxel-eluting balloon

1 | INTRODUCTION

Coronary stent implantation has significantly improved outcomes of percutaneous coronary intervention (PCI). However, in-stent restenosis (ISR) remains a major limitation of this method [1,2].

Current ISR treatment is based on drug-eluting stents (DES) or drug-eluting balloon catheters (DEB). In the Treatment of In-Stent Restenosis (TIS) randomized clinical study, patients with bare-metal stent (BMS) ISR showed significantly lower 12-month late lumen loss (LLL) following treatment with iopromide-coated PEB compared to those with everolimus-eluting stents (EES) [3]. However, the long-term outcomes of ISR treatment remain uncertain.

In the present study, we sought to assess the long-term clinical efficacy of PEB versus EES with a 3-year follow-up of patients with BMS-ISR.

2 | MATERIALS AND METHODS

2.1 | Patients

The methods of the investigator-iniciated TIS study have been previously described in detail [3]. Briefly, this prospective randomized study

included adult patients (>18 years of age) having BMS-ISR with a ≥50% diameter stenosis (DS), who were treated in the Cathlab of University Hospital Ostrava between 2012 and 2014. The main exclusion criteria were concomitant diseases having an expected survival time of <12 months, or limiting the ability to undergo control coronary angiography.

The primary end-point was in-segment LLL at 12 months as measured by quantitative coronary angiography (QCA). Secondary endpoints were the incidence of binary ISR (≥50% DS) and the overall incidence of 12-month major adverse cardiac events (MACE), including cardiovascular death, nonfatal myocardial infarction (MI), or target vessel revascularization (TVR).

The patients were randomized 1:1 to receive treatment with either Sequent Please PEB (B. Braun AG, Melsungen, Germany) or implantation of platinum-chromium Promus Element EES (Boston Scientific, Marlborough, MA). All patients gave written informed consent before enrollment in the study. The study protocol was developed in compliance with the Declaration of Helsinki, and was approved by the Ethics Committee of University Hospital Ostrava, Czech Republic. This study was registered at ClinicalTrials.gov (NCT01735825).

2.2 | Interventions

The patients were pretreated with aspirin and clopidogrel (loading dose of 600 mg), and full anticoagulation was achieved by administering 100 IU/kg nonfractionated heparin with a target activated clotting time of 250–300 sec. The lesions were predilated using relatively shorter semi-compliant or scoring balloon catheters to prevent edge dissection. After predilation, the PEB was inflated for 30 sec, or the EES was implanted at the recommended pressure of 12–14 atm. When required for suboptimal angographic results, postdilatation was performed using a non-compliant balloon catheter, and an additional bailout stent was implanted in case of edge dissection. All patients received along with optimal medical therapy, aspirin 100 mg and clopidogrel 75 mg per day for 3 months after PEB application and for 6–12 months after EES implantation.

2.3 | Clinical and angiographic follow-up

With respect to the primary analysis, clinical follow-up was performed at 6 and 12 months and angiographic follow-up at 12 months (±2 months) unless needed earlier. 12-month QCA was performed in appropriate projections. The types of ISR lesions were evaluated using Mehran's classification [4]. An independent blinded investigator evaluated the angiographic parameters off-line using syngo Quantification software, version 2007 (Siemens AG, Forchheim, Germany). Lesions were quantified according to in-segment analyses (±5 mm from the proximal and distal edges of the stent) to assess the following parameters: minimum lumen diameter (MLD), reference lumen diameter (RefD), acute gain, lesion length, percentage diameter of the stenosis (%DS), and LLL. Binary ISR was defined as a ≥50% DS in the stented segment.

2.4 | Long-term clinical endpoints

After 1 year patients were followed per protocol every 12 month (±2 month) by phone call or office visit with the aim to assess very long-term outcomes. Final clinical follow-up was performed at 3 years (±0.5 year), including clinical evaluation and recording of all MACE. Adjudication of events were blinded and performed after centralized analysis by a Clinical Event Committee. All deaths were considered cardiac related if not clearly from noncardiac causes. MI was defined according to the third universal definition of myocardial infarction from the European Society of Cardiology (ESC) [5], and stent thrombosis (ST) according to the Academic Research Consortium (ARC) criteria [6].

2.5 | Statistical analysis

The TIS study was designed as a noninferiority study. Given the absence of high-quality data from randomized clinical trials on the performance of EES for the treatment of BMS-ISR at the time of protocol redaction and study initiation the required number of patients was statistically estimated based on data from the Spirit trials [7–9], showing achievement of LLL of 0.24 mm (±0.27 mm) after 12 months with an EES. Using a noninferiority margin of 0.12 (half of the average of 0.24 in the reference group of EES), an α type I error of 5%, and a β test power of 80%, it was determined that 128 patients were required (i.e., 64 per arm). Based on an expected loss of 5% of patients over the 12-month follow-up, a total of 136 patients (68 per arm) were included. Evaluation was based on intention to treat.

Continuous variable are presented as mean and standard deviation (SD) and compared by using the independent-sample Student's *t* test or as median and 25%-75% interquartile range and compared by using the Mann-Withney-Wilcoxon *U* test according to the results of the Shapiro-Wilk test. Categorical variables are presented as counts and percentages, and were compared using the χ^2 or Fisher's exact test as appropriate. A *P* value of <.05 was considered significant. Kaplan-Meier analysis with Log-rank test was used to analyse time-to-event data. Cox proportional hazard regression was performed to evaluate hazard ratio with or without adjustement for significantly different baseline variables. All statistical analyses were performed using IBM SPSS Statistics version 22.

3 | RESULTS

The course of the study is presented in the CONSORT study flow diagram (Figure 1). The study enrolled a total of 136 patients (68 patients with 74 ISR lesions per group). Table 1 presents the baseline characteristics of both cohorts [3].

Clinical data were obtained for all patients at the 3-year follow-up. Time to follow-up did not significantly differ between the groups: 1210 days (±168; median 1270) in the PEB group, and 1172 days (±178; median 1270) in the EES group (*P* = .289).

Table 2 shows the MACE incidence within 12 months, between 1–3 years, and for the entire follow-up period.

At 3-year clinical follow up, the PEB and EES groups did not significantly differ in MACE-free survival (*P* = .211; including individual

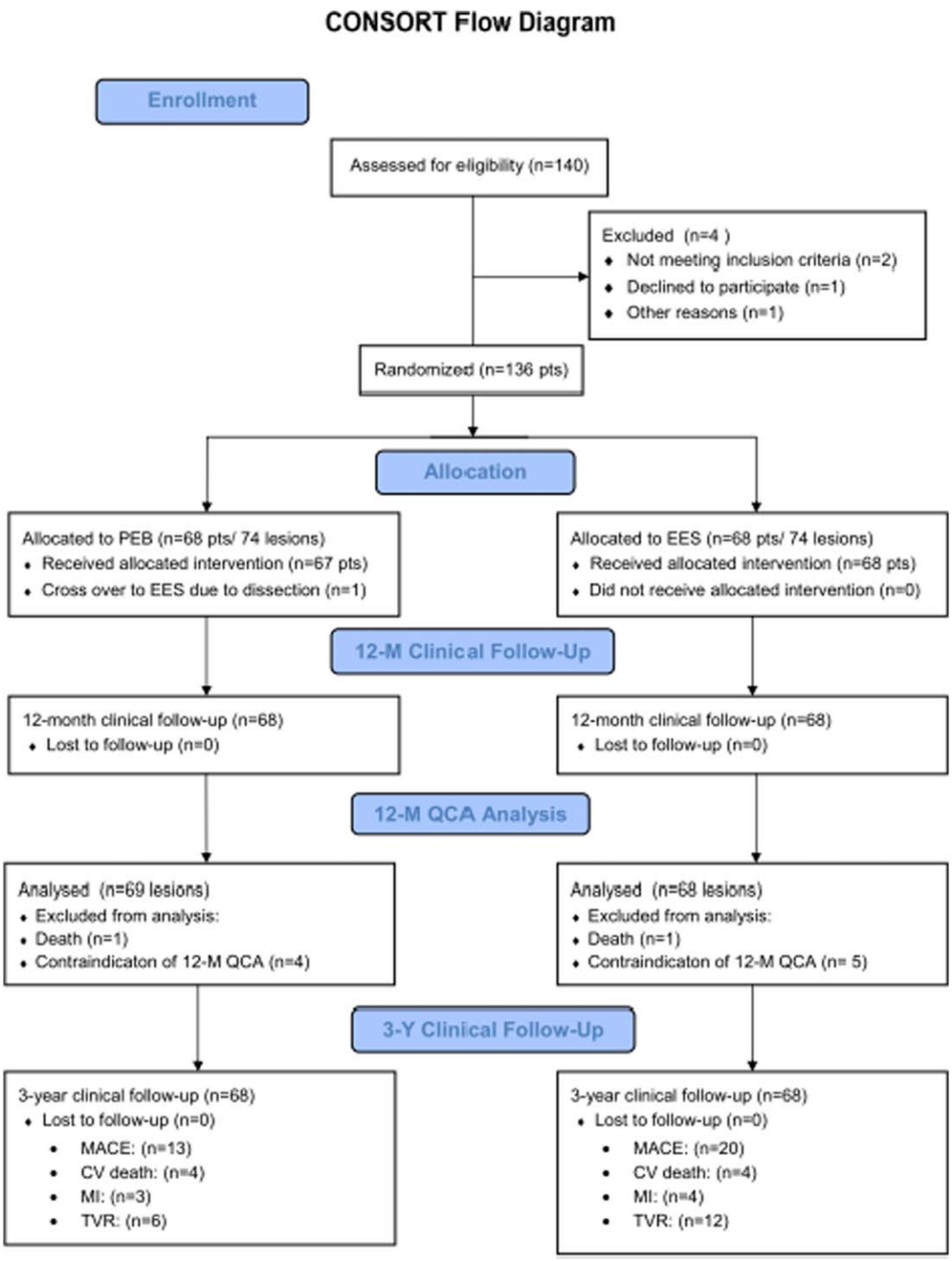

FIGURE 1 CONSORT study flow diagram [Color figure can be viewed at wileyonlinelibrary.com]

events: CV death: $P = .622$, MI: $P = .650$ or TVR: $P = .286$). No event-free survival differences were found between the groups regarding overall mortality ($P = .818$), definite ST ($P = .165$) or the second MACE ($P = .270$) (Table 3).

The incidences of MACE in either groups were not affected by scoring or cutting balloon predilatation ($P > .999$ for PEB and EES groups, respectively) (Table 4).

In subanalysis, there were no significant differences in the individual end-points of TVR between the groups (Table 5).

Cox proportional hazards regression analysis did not reveal any significant differences in the risk of MACE (including individual events) between the groups, even after the adjustment for significantly different baseline variables (time to ISR, scoring/cutting predilatation, PEB/EES treatment) (Table 6).

Figure 2 presents estimates of event-free survival (EFS). Average EFS was 1160 ± 37 days in the PEB group, and 1076 ± 50 days in the EES group. The Log-rank test revealed no significant difference in EFS (time to MACE) between the PEB and EES groups ($P = .298$).

TABLE 1 Baseline characteristics

	PEB	EES	*P*-value
Demographic parameters			
Patients/ISR lesions, *n*	68/74	68/74	
Male/female	43 (63.2%)/25 (36.7%)	46 (67.6%)/22 (32.4%)	.589
Age, years	65.6 ± 10.9†	65.5 ± 10.6†	.930
Body mass index, kg/m^2	28.7 ± 4.0†	29.3 ± 4.2†	.365
Ejection fraction, %	50.0 (40.0–60.0)‡	50.0 (43.0–60.0)‡	.956
Diabetes mellitus	17 (25.0%)	18 (26.5%)	.844
Renal insufficiency	2 (2.9%)	7 (10.3%)	.165
CABG	3 (4.4%)	6 (8.8%)	.493
Ever smoked	31 (45.6%)	29 (42.6%)	.730
stp. MI	43 (63.2%)	41 (60.3%)	.724
2VD/3VD	38 (55.9%)	41 (60.3%)	.602
Multi ISR	4 (5.9%)	5 (7.4%)	>.999
Baseline PCI			
ACSy (STEMI/NSTEMI)	45 (66.2%)	50 (73.5%)	.350
stable AP	23 (33.8%)	18 (26.5%)	
Type of lesion			
B2/C	51 (68.9%)	47 (63.5%)	.487
Lesion localization			
LAD/RD	35 (47.3%)	40 (54.0%)	.576
RCx/OM	16 (21.6%)	10 (13.5%)	
RCA	22 (29.7%)	22 (29.7%)	
SVG	1 (1.4%)	2 (2.7%)	
Diameter of the previous stent, mm	3.0 (3.0–3.5)‡	3.0 (3.0–3.5)‡	.609
Length of the previous stent, mm	19.0 (16.0–27.0)‡	16.0 (13.0–23.0)‡	.077
In-stent restenosis			
ACSy, STEMI/NSTEMI	24 (35.3%)	25 (36.8%)	.098
Stable AP	41 (60.3%)	33 (48.5%)	
Other, silent ischemia	3 (4.4%)	10 (14.7%)	
Time to ISR, months	9.0 (4.0–24.0)‡	24.0 (5.0–25.0)‡	.009
Type of ISR			
I (focal; all)	30 (40.5%)	21 (28.4%)	.266
II (diffuse)	34 (46.0%)	35 (47.3%)	
III (proliferative)	5 (6.8%)	8 (10.8%)	
IV (occlusion)	5 (6.8%)	10 (13.5%)	
Periprocedural parameters			
Scoring/cutting predilatation	16 (21.6%)	5 (6.8%)	.010
ISR; PEB/EES diameter, mm	3.5 (3.0–3.5)‡	3.5 (3.0–3.5)‡	.989
ISR; PEB/EES length, mm	20.0 (17.0–26.0)‡	24.0 (20.0–32.0)‡	.001
Postdilatation, atm	16.0 (12.0–16.0)‡	12.0 (12.0–16.0)‡	.093
Second stent implantation	11 (14.9%)	11 (14.9%)	>.999

Qualitative data are given as n (%). Quantitative data are given as †mean (± standard deviation) or ‡median (the 25th to 75th quartiles).

In the PEB group, the MACE incidence was almost the same up to 12 months and after 12 months (10.3% vs. 8.8%; $P>0.999$). On the other hand, in the EES group, over 2/3 of MACE occurred earlier, during the first 12 months (19.1% vs. 8.8%; $P = .136$).

4 | DISCUSSION

Current ISR treatment is based on DES or DEB [10,11]. In contrast to DES, DEB allow short-term passage of the active substance into the vascular wall, preventing hyperproliferation of smooth muscle cells in the vascular wall and leading to a shorter influence on stent neoendothelialization [12]. Several studies have demonstrated the efficacy of PEB for treatment of BMS-ISR with follow-up times of 9 to 12 months, and the long-term results of these studies are also now available.

In the PACCOCATH I and II trials, the PEB groups showed significantly less 6-month LLL ($P = .002$), lower incidence of recurrent restenosis ($P = .002$), and 12-month MACE ($P = .01$) compared to the POBA group [10]. The reduction of MACE also persisted during the long-term follow-up ($P = .009$) [13].

The PEPCAD II study compared the effects of PEB versus PES for treatment of BMS-ISR, finding that the PEB group showed significantly less 6-month LLL ($P = .03$), and a trend toward reduced the incidence of binary restenosis ($P = .06$) and 12-month MACE ($P = .08$) [11]. These data were also previously suggested in a Bayesian network meta-analysis comparing existing strategies for the treatment of ISR where PEB emerged as

TABLE 2 Incidence of MACE within 12 months, 1 to 3 years and for the entire follow-up period

	PEB *n* (%)	EES *n* (%)	*P*-value
Patients, *n*	68	68	
0–12 month			
MACE all	7 (10.3%)	13 (19.1%)	.213
CV death	1 (1.5%)	1 (1.5%)	>.999
MI	1 (1.5%)	1 (1.5%)	>.999
TVR	5 (7.4%)	11 (16.2%)	.110
Definite ST	1 (1.4%)	0 (0%)	>.999
1–3 years			
MACE all	6 (8.8%)	6 (8.8%)	>.999
CV death	3 (4.4%)	3 (4.4%)	>.999
MI	2 (2.9%)	2 (3.2%)	>.999
TVR	3 (4.8%)	3 (4.8%)	>.999
Definite ST	1 (1.5%)	0 (0%)	>.999
2nd MACE/TVR	1 (1.5%)	2 (2.9%)	>.999
non CV death	2 (2.9%)	2 (2.9%)	>.999
all cause of death	5 (7.4%)	5 (7.4%)	>.999
0–3 years			
MACE all	13 (19.1%)	20 (29.4%)	.230
CV death	4 (5.9%)	4 (5.9%)	>.999
MI	3 (4.4%)	3 (4.8%)	>.999
TVR	8 (12.9%)	14 (22.2%)	.205
Definite ST	2 (2.9%)	0 (0%)	.496
2nd MACE/TVR	1 (1.5%)	3 (4.8%)	.619
non CV death	2 (2.9%)	2 (2.9%)	>.999
all cause of death	6 (8.8%)	6 (8.8%)	>.999
Event-free survivals	57 (83.2%)	51 (75%)	.203

effective as DES [14]. In long-term follow-up of the PEPCAD II study, the between-group differences in the 3-year incidences of MACE ($P = .14$) and TVR ($P = .10$) did not reach statistical significance [15].

In the RIBS V study, patients with BMS-ISR were treated with PEB or EES (Xience, cobalt-chromium metallic platform). The EES group showed significantly higher 9-month MLD ($P < .001$) and lower %DS ($P < .001$). However, the two groups did not significantly differ in LLL ($P = .14$), in the incidence of binary restenosis ($P = .22$), 12-month MACE ($P = .6$), or TVR ($P = .22$) [16]. Long-term follow-up of the RIBS V study revealed that the EES group showed significantly lower target lesion revascularization (TLR; $P = .04$). However, the groups did not significantly differ with regards to TVR ($P = .24$) or overall 3-year incidence of MACE ($P = .64$). The two groups showed low and comparable incidence of definite/probable ST ($P = .61$) or "late" TLR (>1 year; $P = .54$) [17].

Contrary to the RIBS V study, our present TIS study comparing PEB with EES having a platinum-chromium metallic platform revealed significantly less 12-month LLL in the PEB group ($P = .0004$) [3]. However, we did not find significant between-group differences in the incidence of MACE within one year ($P = .213$) and three years ($P = .230$).

The patients were followed-up clinically, stress tests were not routinely performed. TVR was considered to be ischemia-driven in case of a) acute coronary syndromes (ST changes, troponin +) or b) recurrence of exertional angina in case of significant restenosis (> 70%) and absence of other vessels narrowing.

We found one late (after 8 months) and one very late (after 2 years) ST in the PEB arm, both of them after termination of dual antiplatelet therapy (DAPT). There was no case of ST in the EES arm, however, this difference was not signifficant. In our study, duration of DAPT was based on the treatment regimen (3 month after PEB and for 6–12 month after EES implantation). According to the German consensus group, DAPT was necessary for at least 1 month even after DEB use for ISR treatment [18]. However, DAPT durations varied from 3 to 6 months in most clinical studies [15,17] and in the recently published (2017) ESC recommendations, the 6-month DAPT regimen in patients treated with DEB should be considered [19].

Although the RIBS V and TIS studies found different 12-month angiographic results, both studies showed no significant differences in the occurrence of composite MACE in the long term follow-up. In contrast to RIBS V, that revealed significantly lower incidence of TLR in the EES group, the TIS results did not show differences in the occurrence of individual clinical events (CV death, MI, or TVR). Despite the different early angiographic results, both PEB and EES lead to similar clinical outcomes (MACE) in the long-term follow-up. Although both approaches to BMS-ISR are reasonable, it might be preferred a first-line strategy by DEB to avoid a permanent additional metallic layer.

In the PEB group of our study, MACE incidence was almost the same both up to and after 12 months, thus the "late catch-up" phenomenon described by Habara et al. after DES-ISR treatment was not observed after BMS-ISR treatment [20]. Conversely, the outcomes of the EES group appear to be stabilized after the first year. This may suggest that the EES used for BMS-ISR treatment do not appear to be more vulnerable in the long term follow-up. However, further long-term studies are needed.

The long-term efficacy of the PEB use for DES-ISR treatment has also been studied. The PEPCAD-DES study compared the treatment of SES/PES-ISR using iopromide-coated PEB vs. POBA, and found that PEB was associated with significantly lower 6-month LLL ($P < .001$), repetitive binary restenosis ($P < .001$), and clinical end-points (MACE and ST; $P < .001$) [21]. Moreover, the PEB group showed significantly lower 36-month rates of MACE ($P = .001$) and TLR ($P = .046$) [22].

The ISAR-DESIRE III study compared PES vs. PEB or POBA for treatment of SES-ISR. With regards to follow-up %DS, PEB was noninferior to PES ($P_{\text{non-inferiority}} = .007$), and the use of either PEB or PES was superior to POBA alone ($P_{\text{superiority}} < .0001$ for both) [23]. Over the 3-year follow-up, the risk of TVR was comparable between PEB and PES ($P = .11$), and was lower with PEB compared to with POBA ($P < .001$). The risk of death/MI tended to be lower with PEB compared to with PES ($P = .08$), but was similar between PEB and POBA treatment ($P = .91$) [24].

The PEPCAD ISR China study demonstrated that iopromide-coated PEB was at least as effective as PES (9-month LLL: $P_{\text{non-inferiority}} = .0005$) for the treatment of DES-ISR, and the two groups showed no differences in 12-month target lesion failure (TLF; CV death, target-lesion MI or TLR: $P = .69$) [25]. Over the 2-year follow-up, the combined rate of all-cause mortality and MI was significantly lower in the PEB group compared to the PES group ($P = .03$) [26].

Recently published DARE trial, comparing iopromide-coated PEB vs. EES in the treatment of BMS/DES-ISR, confirmed the noninferiority of

TABLE 3 Kaplan-Meier analysis

Event	Time	Group	Cumulative Proportion Surviving at the Time	1-Cumulative Proportion Surviving at the Time	N of Cumulative Events	N of Remaining Cases	Log-rank test *P*
MACE all	12 months	PEB	0.956	0.044	3	65	.211
		EES	0.868	0.132	9	59	
	3 years	PEB	0.852	0.148	10	53	
		EES	0.779	0.221	15	53	
CV death	12 months	PEB	0.985	0.015	1	67	.622
		EES	0.985	0.015	1	67	
	3 years	PEB	0.971	0.029	2	66	
		EES	0.985	0.015	1	67	
MI	12 months	PEB	0.958	0.042	1	66	.650
		EES	0.985	0.015	1	67	
	3 years	PEB	0.970	0.030	2	64	
		EES	0.955	0.045	2	65	
TVR	12 months	PEB	0.970	0.030	2	65	.286
		EES	0.897	0.103	7	61	
	3 years	PEB	0.894	0.106	8	53	
		EES	0.837	0.163	14	53	
All course of death	12 months	PEB	0.985	0.015	1	67	.818
		EES	0.985	0.015	1	66	
	3 years	PEB	0.971	0.029	2	66	
		EES	0.970	0.030	2	65	
Definite ST	12 months	PEB	0.985	0.015	1	65	.165
		EES	1.000	0.000	0	68	
	3 years	PEB	0.985	0.015	1	65	
		EES	1.000	0.000	0	68	
2nd MACE	12 months	PEB	1.000	0.000	0	68	.270
		EES	0.985	0.015	1	66	
	3 years	PEB	1.000	0.000	0	68	
		EES	0.969	0.031	2	59	

PEB with respect to 6-month in-segment MLD ($P_{\text{non-inferiority}} < .0001$). TVR at 12-month follow-up was also similar in both groups ($P = .65$) [27].

Lower efficacy of DEB in patients with DES failure may be explained by a resistance to the previous anti-proliferative drug. A pooled analysis of the RIBS IV and V studies compared the outcomes of iopromide-coated PEB treatment for BMS-ISR or DES-ISR. Compared to BMS-ISR, the DES-ISR group displayed a significantly lower 9-month MLD ($P = .001$), a higher repeated restenosis rate ($P < .05$), 12-month MACE ($P = .03$), and TVR ($P = .02$) [28].

In the SeQuent Please World Wide Registry, PEB was associated with significantly lower 9-month TLR ($P<0.001$) and MACE rates ($P < .001$) in patients with BMS-ISR than in those with DES-ISR [29].

Novel DEBs that release limus drugs are developed. In contrast to paclitaxel, sirolimus must be released for a period of several weeks to inhibit neointimal proliferation effectively. Clinical trials for testing DEB

TABLE 4 Scoring or cutting balloon predilatation and the occurrence of MACE in the PEB and EES groups

	Scoring/cutting predilatation	Noncutting	*P*-value
PEB	16 (21.6%)	52 (78.4%)	.010
EES	5 (6.8%)	63 (93.2%)	
PEB group			
pts	16	52	
MACE	2 (12.5%)	9 (17.3%)	>.999
EES group			
pts	5	63	
MACE	1 (20%)	15 (23.8%)	>.999

TABLE 5 TVR subanalysis

	PEB *n* (%)	EES *n* (%)	*P*-value
Patients, n	68	68	
TVR, all	8 (12.9%)	14 (22.2%)	.205
Clinical reasons			
MI	3 (4.4%)	3 (4.8%)	>.999
Recurrence of sAP	3 (4.4%)	8 (11.8%)	.116
Pathophysiology			
Re-ISR	4 (5.9%)	11 (16.2%)	.055
Definite ST	2 (2.9%)	0 (0%)	.496

TABLE 6 Cox proportional hazards regression analysis

		Unadjusted estimates				Adjusted estimates			
				95%CI for HR				95%CI for HR	
Event	Predictor	Sig.	HR	Lower	Upper	Sig.	HR	Lower	Upper
MACE	Group (1=EES)	0.302	1.463	0.710	3.014	0.350	1.454	0.663	3.187
CV	Group (1=EES)	0.959	0.964	0.235	3.957	0.747	0.784	0.179	3.439
MI	Group (1=EES)	0.652	1.509	0.252	9.033	0.486	1.993	0.286	13.909
TVR	Group (1=EES)	0.292	1.665	0.645	4.295	0.221	1.874	0.685	5.129
All course of death	Group (1=EES)	0.818	0.868	0.260	2.901	0.515	0.655	0.183	2.343
Definite ST	Group (1=EES)	0.475	0.016	0.000	1381	0.967	-	-	-
2nd MACE	Group (1=EES)	0.299	3.323	0.345	32.02	0.259	4.518	0.329	61.96

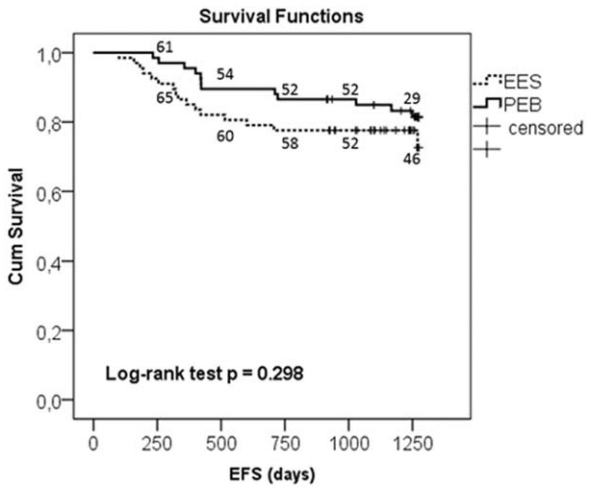

FIGURE 2 Event-Free Survival

coated with sirolimus (encapsulated in phospholipid nanoparticles) in the ISR treatment are ongoing.

5 | LIMITATIONS

One limitation of this study is that the patients and investigators were not blinded to the assigned treatment method. However, clinical events were blinded and evaluated by an independent Clinical Event Committee. Additionally, this study lacked sufficient statistical power to detect significant differences in the clinical end-points (i.e., MACE).

6 | CONCLUSIONS

At the 3-year follow-up, no significant differences in clinical outcomes were found between iopromide-coated PEB and EES for the treatment of BMS-ISR.

DISCLOSURE STATEMENT

We hereby declare that there is no conflict of interest concerning the work published in our study.

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