Circulation: Cardiovascular Interventions

ORIGINAL ARTICLE

Comparing the Efficacy of Sirolimus and Paclitaxel-Eluting Balloon Catheters in the Treatment of Coronary In-Stent Restenosis: A Prospective Randomized Study (TIS 2 Study)

Leos Pleva, MD, PhD; Pavel Kukla, MD; Tomas Kovarnik, MD, PhD; Jana Zapletalova, MSc, PhD

BACKGROUND: Current therapy for in-stent restenosis (ISR) is based on drug-eluting stents (DES) or drug-eluting balloon catheters. This prospective randomized study compared the efficacy of a novel sirolimus-eluting balloon (SEB) catheter to that of a paclitaxel-eluting balloon (PEB) catheter for the treatment of bare-metal stent (BMS-ISR) or DES-ISR.

METHODS: A total of 145 patients with 158 BMS or DES-ISR lesions were randomly assigned to the treatment with either SEB or PEB. The in-segment late lumen loss at 12 months, the 12-month incidence of binary ISR, and major adverse cardiac events (cardiac death, nonfatal acute myocardial infarction, or target lesion revascularization) were compared between groups.

RESULTS: The noninferiority of SEB compared with PEB in the treatment of BMS/DES-ISR with respect to late lumen loss was not demonstrated (Δlate lumen loss, −0.024 mm [95% CI, −0.277 to 0.229]; for a noninferiority margin of 0.20 mm), except in the post hoc subanalysis for the BMS-ISR group (−0.203 mm [95% CI, −0.584 to 0.178]). No significant differences in the incidence of repeated binary ISR (31.6% versus 30.4%, P=0.906) or 12-month major adverse cardiac events (31% for both; P>0.999) between the SEB and PEB groups were observed.

CONCLUSIONS: The noninferiority of SEB relative to PEB in the treatment of BMS/DES-ISR with respect to late lumen loss was not confirmed.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT03667313.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: angioplasty, balloon, coronary ■ coronary restenosis ■ paclitaxel ■ sirolimus

See Editorial by Paradies and Alfonso

Current therapy for in-stent restenosis (ISR) is based on drug-eluting stents (DESs) or drug-eluting balloon (DEB) catheters. To date, paclitaxel is the preferred drug for balloon coating (paclitaxel-eluting balloon [PEB] catheter) due to its irreversible binding to the microtubes, resulting in long persistence in the vascular cells.[1] Sirolimus and its analogues reversibly bind to the FK-506 binding protein 12, forming a complex with the mammalian target of rapamycin, thus blocking cell cycle progression at the juncture of the G1 and S phases.[2]

In contrast to paclitaxel, sirolimus must be continuously released for several weeks to effectively inhibit neointimal proliferation.[2,3] Moreover, in our previous TIS 1 study (Treatment of In-Stent Restenosis), we demonstrated that in BMS-ISR treatment, iopromide-coated PEB yielded significantly lower 12-month late lumen

Correspondence to: Leos Pleva, MD, PhD, Department of Internal Medicine and Cardiology, University Hospital Ostrava, Faculty of Medicine, University of Ostrava, 17 listopadu 1790, 708 52 Ostrava 8, Czech Republic. Email leos.pleva@volny.cz
For Sources of Funding and Disclosures, see page 401.

Circulation: Cardiovascular Interventions is available at www.ahajournals.org/journal/circinterventions

WHAT IS KNOWN

- Paclitaxel-eluting balloon has been used in the treatment of in-stent restenosis.
- However, the efficacy of sirolimus-eluting balloon in treating this condition remains unclear.

WHAT THE STUDY ADDS

- We evaluated the efficacy of sirolimus-eluting balloon and paclitaxel-eluting balloon in the treatment of bare-metal stent/drug-eluting stents-in-stent restenosis.
- The noninferiority of sirolimus-eluting balloon compared with paclitaxel-eluting balloon in treating in-stent restenosis with respect to 12-month late lumen loss was not demonstrated.
- The incidence of 12-month major adverse cardiac events and binary restenosis did not differ between the 2 groups.

Nonstandard Abbreviations and Acronyms

BMS	bare-metal stent
DEB	drug-eluting balloon
DES	drug-eluting stent
DS	diameter stenosis
ISR	in-stent restenosis
LLL	late lumen loss
MACE	major adverse cardiac events
MLD	minimum lumen diameter
PEB	paclitaxel-eluting balloon
TIS 1	Treatment of In-Stent Restenosis
TLR	target lesion revascularization

loss (LLL) compared with everolimus-eluting stents (*P*=0.0004). However, no differences in 12-month minimum lumen diameter (MLD; *P*=0.481), diameter stenosis (%DS; *P*=0.816) or repeated binary ISR (*P*=0.078) were found.[4]

In the case of DES, limus drugs are more effective in the inhibition of neointimal hyperplasia compared with paclitaxel.[1,2] However, paclitaxel is still used in DEB due to its easier binding to the balloon surface and better pharmacokinetics. Sirolimus-encapsulating technologies can be used for coating balloon catheters and provide sufficient drug transfer to the vessel wall. We hypothesized that a novel sirolimus-eluting DEB (with phospholipid-encapsulated nanoparticles) may be at least as effective as PEB.

The objective of our prospective randomized study, TIS 2 (Treatment of In-Stent Restenosis 2; URL: https://www.clinicaltrials.gov; Unique identifier: NCT03667313), was to compare (with statistical evidence of noninferiority) the efficacy of a novel DEB with sirolimus (MagicTouch; SEB with Nanoluté coating) with the standard iopromide-coated PEB (Sequent Please Neo) for the treatment of restenosis in bare-metal (BMS-ISR) or drug-eluting stents (DES-ISR).

METHODS

Data Availability

Anonymized data have been made publicly available at the LabArchives repository and can be accessed at: https://mynotebook.labarchives.com/share_attachment/TIS%25202%2520study/Ny44MDAwMDAwMDAwMDAwMDF8NT k2NzY5LzYtOC9UcmVlTm9kZS85NjAxODEzNjF8MTkuNzk5OTk5OTk5OTk3.

Patients

Between January 2019 and May 2022, a total of 145 patients with ISR were randomly assigned to the treatment with SEB or PEB at 2 sites in the Czech Republic (University Hospital Ostrava and General University Hospital in Prague).

The study included adult patients (≥18 years of age) with BMS-ISR or DES-ISR (≥70% DS by visual estimation or 50% to 69% DS with documented evidence of ischemia). Patients with acute coronary syndromes caused by ISR were also included. In the case of ST-segment–elevation myocardial infarction and complete stent occlusion, they were included only if significant residual ISR was evident following thrombus aspiration. To exclude mechanical causes of ISR, an X-ray postprocessing system (CLEARstent; Siemens, Forchheim, Germany) was used. The principal exclusion criteria were as follows: concomitant diseases carrying expected survival of <12 months or limiting the possibility of follow-up coronary angiography.

The in-segment LLL at 12 months, as measured by quantitative coronary angiography was the primary end point of the presented study. Secondary end points included the incidence of binary ISR (≥50% DS) and the overall incidence of 12-month major adverse cardiac events (MACE; cardiac death, nonfatal acute myocardial infarction, or target lesion revascularization [TLR]).

The study protocol complied with the Declaration of Helsinki and was approved by the Ethics Committee of University Hospital Ostrava, Czech Republic. The study was registered at ClinicalTrials.gov (URL: https://www.clinicaltrials.gov; Unique identifier: NCT03667313) on the November 23, 2018. Written informed consent was obtained from each patient before enrollment in the study.

Study Devices

The MagicTouch balloon catheter (Concept Medical, Miami, FL) is a SEB with phospholipid-encapsulated sirolimus nanoparticles (Nanoluté coating). The size of drug nanoparticles is about 100–300 nm, with a sirolimus concentration on the balloon surface of 1.27 mg/mm^2. The recommended inflation time is 60 seconds.

In the iopromide-coated PEB Sequent Please Neo (B. Braun, Melsungen, Germany), paclitaxel (3 µg/mm^2) is bound via the hydrophilic contrast agent iopromide (Paccocath),

increasing paclitaxel solubility and vascular wall penetration. The recommended inflation time is 30 seconds.

Randomization

Patients were randomized in a 1:1 manner to treatment with SEB or PEB. Randomization (using random permuted blocks) was stratified according to the type of original stent (BMS versus DES-ISR). The investigators and patients were not blinded to the treatment allocation. However, clinical events and angiographic measurements were recorded by an independent investigator who was blinded to avoid any bias.

Interventions

PCI was performed under standard conditions. After lesion preparation (semi-compliant or scoring balloon predilation), the DEB was inflated for 60 seconds (SEB) or 30 seconds (PEB). The implantation of an additional bailout stent was allowed in cases of in-segment suboptimal results (>30%) or dissection (>type B).[5] The patients received dual antiplatelet therapy for 6 months.[5]

Follow-up

Clinical follow-up was performed at 6 and 12 months, and angiographic follow-up at 12 months (±2 months), unless required earlier. Any death that was not clearly due to noncardiac causes was considered cardiac-related. The fourth universal definition by the ESC[6] was used for the definition of myocardial infarction. Stent thrombosis, MACE, and target lesion failure (cardiovascular death, target vessel myocardial infarction, or ischemia-driven TLR) were defined according to the Academic Research Consortium criteria.[7]

Angiographic Follow-Up

The same imaging projections as in the periprocedural angiography were used for the follow-up coronary angiography. American College of Cardiology/American Heart Association criteria[8] and the Mehran classification were used to assess the lesion type and ISR.[9] Lesions were evaluated in the in-segment section (±5 mm from the proximal and distal edges of the stent), and the following parameters were measured: MLD, reference lumen diameter, acute gain, lesion length, %DS, and LLL ($LLL=MLD_{after\ intervention}-MLD_{control}$); binary restenosis was defined as repeated narrowing of the lumen ≥50% (DS ≥50%).[7]

Sample Size and Statistical Analysis

This noninferiority study was based on our previous TIS study,[4] with a 12-month LLL of 0.09 (±0.44) mm in the PEB arm. Using a noninferiority margin of 0.20 mm as the clinically significant difference between groups, an α error of 5%, and 90% power, the required sample size was 124. Accounting for a 15% dropout rate, the cohort size was set at 145 patients. The evaluation was performed on an intention-to-treat basis.

Continuous variables with normal distribution are presented as mean±SD and compared using the Student *t* test. Nonnormal variables are reported as median (range) and analyzed with the Mann-Whitney *U* test. Categorical variables are expressed as absolute and relative frequencies (%) and compared using the χ^2 test. Odds ratios are reported with 95% CIs, with $P<0.05$

Table 1. Baseline Characteristics

	SEB	PEB	*P* value
Patients, n	72	73	…
ISR lesions, n	79	79	…
Demographic and clinical parameters			
Male, n	56 (77.8%)	59 (80.8%)	0.651*
Female, n	16 (22.2%)	14 (19.2%)	
Age, y	69.7±9.6†	68.0±10.6†	0.319‡
Body mass index, kg/m²	27.8 (20.6–37.8)§	28.4 (20.6–38.6)§	0.523¶
EF LK, %	50.0 (25–68)§	50.0 (25–65)§	0.705¶
Ever smoked	34 (47.2%)	38 (52.1%)	0.505*
Diabetes	32 (44.4%)	26 (35.6%)	0.278*
Renal insufficiency	11 (15.3%)	6 (8.2%)	0.197*
CABG	10 (13.9%)	7 (9.6%)	0.421*
Previous MI	48 (66.7%)	50 (68.5%)	0.814*
Baseline PCI			
STEMI/NSTEMI	41 (56.9%)	47 (64.4%)	0.410*
2VD/3VD	53 (73.6%)	45 (61.6%)	0.177*
B2/C lesion	59 (74.7%)	60 (75.9%)	0.854*
Lesion localization			
LM	2 (2.5%)	2 (2.5%)	0.367*
LAD	25 (31.6%)	27 (34.2%)	
LCx/OM	14 (17.2%)	23 (29.1%)	
RCA	36 (45.6%)	25 (31.6%)	
SVG	2 (2.5%)	2 (2.5%)	
Previous stent diameter, mm	3.25 (2.25–5.0)§	3.25 (2.25–5.0)§	0.476¶
Previous stent length, mm	24.0 (12–66)§	24.0 (8–76)§	0.831¶
In-stent restenosis			
BMS-ISR	36 (45.6%)	39 (49.4%)	0.633*
DES-ISR	43 (54.4)	40 (50.6%)	
Time to ISR, d	1224 (64–6913)§	1069 (62–5765)§	0.612¶
UAP/NSTEMI	26 (36.1%)	24 (32.9%)	0.750*
STEMI	3 (4.2%)	2 (2.7%)	
Stable AP	40 (55.6%)	41 (56.2%)	
Silent	4 (5.6%)	6 (8.2%)	
Repeated ISR	10 (12.7%)	9 (11.4%)	0.807*
Thrombus	10 (12.7%)	12 (15.2%)	0.646*
Ostial ISR	4 (5.1%)	5 (6.3%)	1.000*
Bifurcation	9 (11.4%)	25 (31.6%)	0.002*
Type of ISR			
I (focal, all)	21 (26.6%)	37 (46.8%)	0.008*
II (diffuse)	43 (54.4%)	21 (26.6%)	0.0004*
III (proliferative)	5 (6.3%)	6 (7.6%)	0.755*
IV (occlusion)	10 (12.7%)	15 (19.0%)	0.276*
Nonfocal (II-IV)	58 (73.4%)	42 (53.2%)	0.008*
Periprocedural parameters			
Cutting predilation	66 (83.5%)	58 (73.4%)	0.121¶

(*Continued*)

Table 1. Continued

	SEB	PEB	*P* value
ISR; DEB diameter	3.5 (2.5–4.0)§	3.5 (2.25–4.0)§	0.651¶
ISR; DEB length	20.0 (15–70)§	20.0 (10–65)§	0.265¶
Dilation pressure, atm	12 (12–26)§	12 (12–28)§	0.865¶
Second DEB	13 (16.5%)	12 (15.2%)	0.827*
DEB per lesion	1.23±0.55†	1.15±0.46†	0.445‡
Bailout stent implantation	18 (22.8%)	18 (22.8%)	1.000*
Duration of DAPT, mo	6 (2–8)§	6 (2–9)§	0.752¶

Qualitative data are given as n (%). 2VD indicates 2 vessel disease; 3VD, 3 vessel disease; AP, angina pectoris; atm, atmosphere; BMS, bare-metal stent; CABG, coronary artery bypass grafting; DAPT, dual antiplatelet therapy; DEB, drug-eluting balloon; DES, drug-eluting stent; EF LK, ejection fraction of left ventricle; ISR, in-stent restenosis; LAD, left anterior descending; LCx, left circumflex artery; LM, left main; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; OM, obtuse marginal; PCI, percutaneous coronary intervention; PEB, paclitaxel-eluting balloon; RCA, right coronary artery; SEB, sirolimus-eluting balloon; STEMI, ST-segment–elevation myocardial infarction; SVG, saphenous vein graft; and UAP, unstable angina pectoris.

**P* value: significance of χ^2 test.

†Quantitative data are given as mean (±SD).

‡*P* value: significance of Student 2-sample *t* test.

§Quantitative data are given as median (range: min-max).

¶*P* value: significance of Mann-Whitney *U* test.

considered significant. The 95% CI for the difference in LLL between study arms was compared with the noninferiority margin. Time-to-event data were analyzed with Kaplan-Meier curves and the log-rank test. The cumulative frequency distribution of LLL was assessed using the Kolmogorov-Smirnov test.

RESULTS

A total of 145 patients with 158 ISR lesions were included in the study. Basic demographic, clinical and angiographic data are presented in Table 1.

The representation of BMS- and DES-ISR was the same in both treatment arms (*P*=0.633). The SEB group had a significantly higher frequency of nonfocal (diffuse+proliferative+occlusive) ISR than focal ISR (*P*=0.008). Bifurcation ISR lesions were more common in the PEB group (*P*=0.002). Periprocedurally, patients treated with SEB achieved significantly lower residual stenosis (post-PCI %DS) compared with PEB (*P*=0.025).

A 12-month angiographic follow-up was performed in 91.7% of patients in the SEB group and 89.0% of patients in the PEB group (*P*=0.592). After 12 months, no statistically significant difference in the measured angiographic parameters between the 2 groups was observed (Table 2). However, the primary end point of our study was to evaluate whether SEB is noninferior to PEB. The difference in ΔLLL between the SEB and PEB groups was −0.024 mm (95% CI, −0.277 to 0.229). The upper bound of the 2-sided 95% CI of LLL difference exceeded the noninferiority margin (0.20 mm); in effect, the noninferiority of SEB was not demonstrated (Table 3; Figure 1).

Nonetheless, there were no significant differences in the incidence of repeated binary ISR (*P*=0.906) or 12-month MACE (*P*>0.999) between the groups (Table 3). The 2 groups did not differ in clinical event-free survival either (Figure 2).

A post hoc subanalysis separately evaluating the treatment of BMS and DES-ISR with SEB and PEB was performed. Data for both subgroups are shown in Table 4.

The noninferiority of SEB versus PEB treatment was demonstrated only in the BMS-ISR subgroup (ΔLLL −0.203 mm; 95% CI, −0.584 to 0.178); but not in the DES-ISR subgroup (ΔLLL 0.110 mm; 95% CI, −0.233 to 0.453; Table 3; Figure 1).

In terms of secondary end points, no difference was observed in the incidence of recurrent binary restenosis (*P*=0.949 and >0.999) or 12-month MACE (*P*=0.884 and 0.926) in the 2 subgroups (Table 5).

After recruitment, the significantly higher incidence of nonfocal ISR in the SEB group (*P*=0.008) led to an additional post hoc subanalysis. The noninferiority of SEB compared with PEB in LLL was not demonstrated in either the focal or nonfocal ISR subgroups (Table 3).

Table 2. Baseline, Postprocedural, and 12-Month Follow-Up Quantitative Control Angiography Parameters

	SEB	PEB	*P* value
Preprocedural parameters; ISR			
RefD, mm	2.68 (1.87–3.63)*	2.69 (1.78–3.85)*	0.918†
MLD, mm	0.53 (0–1.61)*	0.70 (0–2.10)*	0.664†
%DS	77 (51–100)*	76 (35–100)*	0.708†
ISR length	12.6 (4.7–54.5)*	10.9 (3.7–51.3)*	0.130†
Postprocedural parameters; post re-PCI			
RefD, mm	2.90 (2.15–3.87)*	2.92 (1.98–3.79)*	0.663†
MLD, mm	2.34 (1.57–3.19)*	2.22 (1.36–3.20)*	0.079†
Acute gain, mm	1.76 (0.63–2.87)*	1.48 (0.40–3.20)*	0.078†
%DS	21 (1–40)*	24 (6–41)*	0.025†
12 months follow-up parameters			
RefD, mm	2.83 (1.89–3.90)*	2.86 (1.86–4.30)*	0.922†
MLD, mm	1.85 (0–3.58)*	1.63 (0–2.89)*	0.463†
%DS	32 (0–100)*	36 (8–100)*	0.270†
Binary re-ISR	25 (31.6%)	24 (30.4%)	0.906‡

Qualitative data are given as n (%). DS indicates diameter stenosis; ISR, in-stent restenosis; MLD, minimal lumen diameter; PCI, percutaneous coronary intervention; PEB, paclitaxel-eluting balloon; RefD, reference lumen diameter; and SEB, sirolimus-eluting balloon.

*Quantitative data are given as median (range: min-max).

†*P* value: significance of Mann-Whitney *U* test.

‡*P* value: significance of χ^2 test.

Table 3. Late Lumen Loss Difference

	SEB	PEB	Delta	95% CI	Noninferiority margin (0–20 mm)
LLL, mm					
All ISR	0.596±0.83	0.62±0.781	−0.024	−0.227 to 0.229	>0.20
BMS-ISR	0.411±0.856	0.614±0.802	−0.203	−0.584 to 0.178	<0.20
DES-ISR	0.736±0.799	0.626±0.771	0.110	−0.233 to 0.453	>0.20
Focal ISR	0.451±0.776	0.500±0.560	−0.049	−0.415 to 0.317	>0.20
Nonfocal ISR	0.694±0.853	0.738±0.901	−0.044	−0.416 to 0.328	>0.20

Quantitative data are given as mean (±SD). BMS indicates bare metal stent; DES, drug eluting stent; ISR, in-stent restenosis; LLL, late lumen loss; PEB, paclitaxel-eluting balloon; and SEB, sirolimus-eluting balloon.

DISCUSSION

Our prospective randomized study compared the efficacy of a novel SEB with sirolimus encapsulated in phospholipid nanoparticles to iopromide-coated PEB in the therapy of BMS or DES-ISR.

Sirolimus delivery to the balloon surface is challenging due to limited tissue uptake and short retention of limus drugs. Drug-encapsulation technologies, such as phospholipid-encapsulated sirolimus nanoparticles (Nanoluté coating), have shown promise for efficient vessel wall transfer with high tissue concentration and minimal systemic leakage. Lemos et al[3] reported that 56% of sirolimus is released within 40 to 60 seconds of balloon inflation, with persistence in the vessel wall for 15 to 30 days. There are also other ways of applying sirolimus to the surface of the balloon catheter: the Selution SLR balloon catheter (Med Alliance, Nyon, Switzerland) uses micro-reservoirs in a biodegradable polymer as a carrier of sirolimus, while the SeQuent Please SCB (B. Braun) uses crystalline sirolimus (4 μg/mm^2) bound by butylated hydroxytoluene.[10]

Due to different pharmacokinetics, sirolimus requires a longer balloon insufflation time (60 seconds) compared with paclitaxel (30 seconds), potentially contributing to a significantly lower postprocedural %DS in the SEB arm (*P*=0.025), although the acute gain was similar.

Several registries evaluated the efficacy of SEB with Nanoluté coating that included both de novo and ISR lesions. The Nanoluté registry followed 408 patients (45% of them with ISR) treated with SEB. The 24-month MACE occurred in 4.2% of cases and that of the ISR subgroup in 5.5%, respectively.[11]

In the largest registry, EASTBOURNE (All-Comers Sirolimus-Coated Balloon European Registry), which included 2123 patients (44% of them with ISR) treated with SEB. TLR was more common in patients treated for ISR compared with de novo lesions (RR, 1.90 [95% CI, 1.13–3.19]). ISR was also an independent risk factor for the need for repeat TLR (odds ratio, 5.5 [95% CI, 3.38–8.88]).[12]

Recently, some randomized trials comparing Nanoluté-coated SEB and PEB have been published. The TRANSFORM I trial (A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Navitoclax in Combination With Ruxolitinib Versus Ruxolitinib in Subjects With Myelofibrosis) compared SEB with iopromide-PEB in the treatment of de novo small vessel disease. Similar to our study, they did not confirm the noninferiority of SEB in 6-month net lumen gain (opposite of LLL; net gain=MLD_{6M}-$MLD_{baseline}$; p for noninferiority=0.173).[13]

In addition, comparisons of other SEB versus PEB in the treatment of ISR have been made. In their DES-ISR study, Han et al[14] demonstrated that crystalline-SEB was

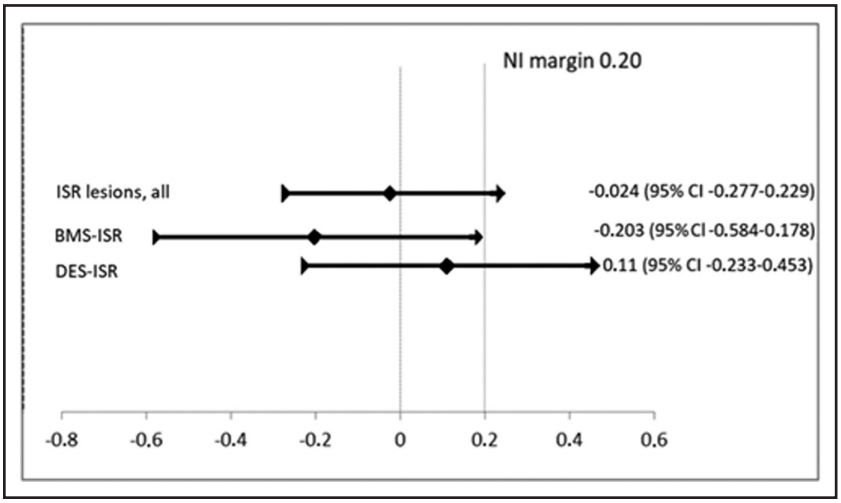

Figure 1. The 2-sided 95% CI for the difference between treatments and the noninferiority (NI) margin.
BMS indicates bare metal stent; DES, drug eluting stent; and ISR, in-stent restenotis.

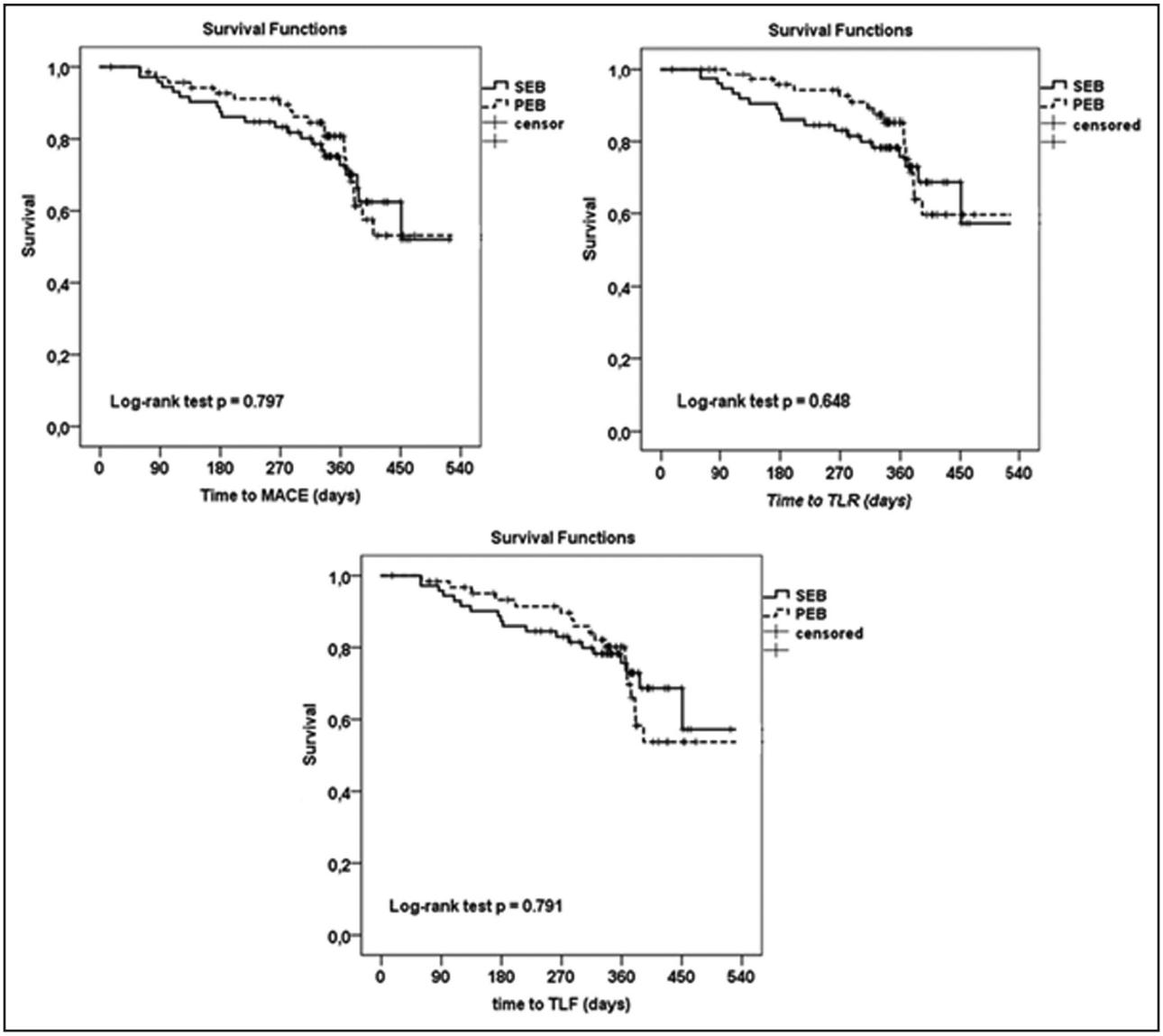

Figure 2. Kaplan-Meier analysis of event-free survival.
MACE indicates major adverse cardiac events; PEB, paclitaxel-eluting balloon; SEB, sirolimus-eluting balloon; TLF, target lesion failure; and TLR, target lesion revascularization.

noninferior to iopromide-PEB at 9 months LLL (ΔLLL, 0.05 mm [95% CI, −0.0523 to 0.1476]; with noninferiority margin of 0.20 mm). The incidence of 12-month target lesion failure and patient-oriented composite end points was similar in both groups.

A combined analysis of 2 parallel studies (Malaysian and German-Swiss studies) also compared the efficacy of crystalline-SEB with iopromide-PEB in the treatment of DES-ISR. The study demonstrated noninferiority of SEB at the primary end point, 6-month LLL (P=0.794). However, the follow-up time in their research was shorter, and the chosen noninferiority margin of 0.35 mm was higher than in our study. Similar to our study, the 2 groups did not differ in the 12-month incidence of MACE (P>0.99).[15]

Differences between these 2 studies and our study include different SEB coating (phospholipid-encapsulated versus crystalline) and concentrations (1.27 mg/mm^2 versus 4 μg/mm^2); both these factors likely (similar to PEB) affect the SEB efficacy and require further analysis.

In our study, a 12-month angiographic follow-up was used to account for neointimal hyperplasia that continues beyond 6 months, potentially yielding more accurate findings.

Compared with BMS-ISR, the incidence of DES-ISR is lower, but the treatment of the remaining DES-ISR is more challenging due to its more complex underlying causes and is associated with poorer long-term outcomes.[16] Despite this fact, we included both BMS- and DES-ISR patients in our study to be as close to real-world clinical practice as possible (with regard not only to developed countries). Patients' 1:1 randomization to SEB or PEB arms was stratified by the type of the original stent

Table 4. Subgroup Analysis

BMS-ISR	SEB	PEB	*P* value
Patients/lesions, n	35/36	37/39	
Preprocedural parameters; ISR			
RefD, mm	2.64 (2.04–3.63)*	2.56 (1.78–3.62)*	0.446†
MLD, mm	0.70 (0–1.50)*	0.71 (0–1.31)*	0.885†
%DS	74.0 (51–100)*	74.5 (52–100)*	0.859†
ISR length	12.6 (6.3–36.9)*	12.5 (4.0–44.3)*	0.674†
Postprocedural parameters; post re-PCI			
RefD, mm	2.88 (2.20–3.57)*	2.83 (1.98–3.79)*	0.768†
Acute gain, mm	1.48 (0.63–2.87)*	1.44 (0.43–3.20)*	0.419†
MLD, mm	2.29 (1.67–2.87)*	2.19 (1.36–3.20)*	0.293†
%DS	21 (1–40)*	25.4 (7–39)*	0.205†
Twelve months follow-up parameters			
RefD, mm	2.65 (1.89–3.90)*	2.82 (1.98–4.30)*	0.953†
MLD, mm	2.00 (0–3.14)*	1.87 (0–2.89)*	0.438†
%DS	29 (0–100)*	34 (8–100)*	0.419†
Binary re-ISR	9 (25.0)	10 (25.6)	0.949‡
DES-ISR			
Patients/lesions, n	37/43	36/40	
Preprocedural parameters; ISR			
RefD (mm)	2.72 (1.87–3.47)*	2.83 (1.90–3.85)*	0.427†
MLD (mm)	0.53 (0–1.61)*	0.68 (0–2.10)*	0.768†
%DS	80 (53–100)*	78 (35–100)*	0.915†
ISR length	11.5 (4.69–54.5)*	9.96 (3.68–51.3)*	0.100†
Postprocedural parameters; post re-PCI			
RefD (mm)	2.91 (2.15–3.87)*	3.02 (2.19–3.71)*	0.828†
Acute gain (mm)	1.81 (0.81–2.83)*	1.62 (0.40–2.89)*	0.180†
MLD (mm)	2.36 (1.57–3.19)*	2.30 (1.53–3.15)*	0.182†
%DS	20 (5–33)*	24 (6–41)*	0.033†
Twelve months follow-up parameters			
RefD, mm	2.91 (1.96–3.78)*	2.95 (1.96–3.94)*	0.760†
MLD, mm	1.81 (0–3.58)*	1.60 (0–2.77)*	0.755†
%DS	32 (3–100)*	38 (15–100)*	0.371†
Binary re-ISR	16 (37.2)	14 (35.0)	1.000‡

Qualitative data are given as n (%). BMS indicates bare metal-stent; DES, drug-eluting stent; DS, diameter stenosis; ISR, in-stent restenosis; MLD, minimal lumen diameter; PCI, percutaneous coronary intervention; PEB, paclitaxel-eluting balloon; RefD, reference lumen diameter; and SEB, sirolimus-eluting balloon.

*Quantitative data are given as median (range: min-max).

†*P* value: significance of Mann-Whitney *U* test.

‡*P* value: significance of χ^2 test.

Table 5. Twelve-Months Clinical Follow-Up

	SEB	PEB	
	n (%)	n (%)	*P*
MACE	22 (30.6)	23 (31.5)	0.858
Cardiovascular death	0 (0)	2 (2.7)	0.497
MI	3 (4.2)	2 (2.7)	1.000
TLR	19 (26.4)	19 (26.0)	1.000
Noncardiovascular death	0 (0)	1 (1.4)	1.000
TLF	19 (26.4)	20 (27.4)	0.891
Stent thrombosis	2 (2.5)	1 (1.3)	1.0002
2nd MACE	4 (5.6)	0 (0)	0.057

Qualitative data are given as n (%). *P* value: significance of χ^2 test. MACE indicates major adverse cardiac events; MI, myocardial infarction; PEB, paclitaxel-eluting balloon; SEB, sirolimus-eluting balloon; TLF, target lesion failure; and TLR, target lesion revascularization.

implant (BMS or DES-ISR) to achieve the best balance of treatment allocation. A post hoc subanalysis confirmed the differential outcomes of DEB in BMS- and DES-ISR treatment. Only the BMS-ISR subgroup exhibited noninferiority of SEB versus PEB for the primary end point, 12-month LLL. However, it should be noted that the results of these subgroup analyses are merely exploratory in nature.

Compared with studies using DEB for de novo lesions treatment, a higher incidence of bailout stenting was noted in our study, mainly due to a higher rate of in-segment dissection (>type B), possibly arising due to the aggressive ISR lesion predilatation.

The 12-month in-segment LLL served as the primary end point. The use of these surrogate angiographic end points makes it possible to reduce the required file size while maintaining adequate statistical power.[7,17] Several clinical studies have shown a correlation, especially between LLL and %DS and the incidence of TLR.[7,17]

Intravascular imaging allows more accurate assessment of coronary ISR. However, many ISR studies continue to use angiographic primary end points. To facilitate a comparison between those studies and our earlier TIS 1 study, we have adopted a similar approach. To exclude the main mechanical causes of ISR, an X-ray postprocessing system was used.

Recent ESC guidelines advise against DEB use in DES-ISR.[18] Nevertheless, this amendment is based on earlier meta-analyses comparing PEB and DES efficacy.[16] Further studies are needed to evaluate SEB efficacy with novel DES.

In their meta-analysis comparing SEB with PEB in the treatment of both de novo and ISR lesions, Sedhom et al[19] found no significant difference in the incidence of clinically driven TLR and other clinical outcomes, including MACE, cardiovascular death, or target vessel myocardial infarction. A subsequent subgroup analysis revealed no significant differences between the studies in regard to de novo and ISR lesions. However, the use of SEB was associated with a significantly higher rate of binary ISR, LLL, and a lower MLD compared with PEB. In addition, late lumen enlargement was more frequently observed in the PEB group compared with the SEB group.

Limitations

Several limitations of our study should be mentioned. Neither the patients nor the investigators were blinded as to the chosen method of treatment. However, the 12-month quantitative coronary angiography was evaluated by a blinded, independent investigator. The noninferiority margin

of 0.2 mm, based on previous DEB versus DES studies, reflects clinically significant LLL differences but may require further validation for DEB therapies, particularly between different drugs. The study included both BMS- and DES-ISR patients, despite the fact that the cause of DES-ISR is more complex and the treatment more challenging. The use of intravascular imaging could enhance understanding of ISR mechanisms and outcomes. Moreover, this study did not have sufficient statistical power to detect significant differences in clinical end points (ie, MACE).

Conclusions

This prospective randomized study compared the efficacy of novel SEB with that of PEB for the therapy of BMS or DES-ISR. We did not confirm the noninferiority of SEB compared with PEB in the treatment of BMS/DES-ISR with respect to LLL. The noninferiority of SEB was proven only in BMS-ISR patients.

ARTICLE INFORMATION

Received August 14, 2024; accepted March 11, 2025.

Affiliations

Department of Internal Medicine and Cardiology, University Hospital Ostrava, Czech Republic (L.P., P.K.). Faculty of Medicine, University of Ostrava, Czech Republic (L.P.). Second Department of Internal Cardiovascular Medicine, General University Hospital in Prague, First Faculty of Medicine, Charles University, Czech Republic (T.Z.). Department of Medical Biophysics, Palacky University, Olomouc, Czech Republic (J.Z.).

Acknowledgments

Dr Pleva contributed to the study design, data collection, data analysis, and article revision. Dr Kukla was responsible for the literature search, data collection, data analysis, and article revision. Dr Kovarnik assisted with data collection, data analysis, and article revision. Dr Zapletalova handled the statistical analysis. All authors read and approved the final article.

Sources of Funding

This study is supported by the Ministry of Health of the Czech Republic under the conceptual development of research organizations (FNOs/2022).

Disclosures

None.

REFERENCES

1. Speck U, Cremers B, Kelsch B, Biedermann M, Clever YP, Schaffner S, Mahnkopf D, Hanisch U, Böhm M, Scheller B. Do pharmacokinetics explain persistent restenosis inhibition by a single dose of paclitaxel? *Circ Cardiovasc Interv*.2012;5:392–400.doi:10.1161/CIRCINTERVENTIONS.111.967794
2. Clever YP, Cremers B, Krauss B, Böhm M, Speck U, Laufs U, Scheller B. Paclitaxel and sirolimus differentially affect growth and motility of endothelial progenitor cells and coronary artery smooth muscle cells. *EuroIntervention*. 2011;7:K32–K42. doi: 10.4244/EIJV7SKA6
3. Lemos PA, Farooq V, Takimura CK, Gutierrez PS, Virmani R, Kolodgie F, Christians U, Kharlamov A, Doshi M, Sojitra P, et al. Emerging technologies: polymer-free phospholipid encapsulated sirolimus nanocarriers for the controlled release of drug from a stent-plus-balloon or a stand-alone balloon catheter. *EuroIntervention*. 2013;9:148–156. doi: 10.4244/EIJV9I1A21
4. Pleva L, Kukla P, Kusnierova P, Zapletalova J, Hlinomaz O. Comparison of the efficacy of paclitaxel-eluting balloon catheters and everolimus-eluting stents in the treatment of coronary in-stent restenosis. The treatment of in-stent restenosis study. *Circ Cardiovasc Interv*. 2016;9:e003316. doi: 10.1161/CIRCINTERVENTIONS.115.003316
5. Kleber FX, Mathey DG, Rittger H, Scheller B; German Drug-eluting Balloon Consensus Group. How to use the drug eluting balloon: recommendations by the German consensus group. *EuroIntervention*. 2011;7:K125–K128. doi: 10.4244/EIJV7SKA21
6. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD; Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Task force for the universal definition of myocardial infarction. Fourth universal definition of myocardial infarction (2018). *Circulation*. 2018;138:e618–e651. doi: 10.1161/CIR.0000000000000617
7. Garcia-Garcia HM, McFadden EP, Farb A, Mehran R, Stone GW, Spertus J, Onuma Y, Morel MA, van Es GA, Zuckerman B, et al; Academic Research Consortium. Academic research consortium. standardized end point definitions for coronary intervention trials: the academic research consortium-2 consensus document. *Circulation*. 2018;137:2635–2650. doi: 10.1161/CIRCULATIONAHA.117.029289
8. Ryan TJ, Faxon DP, Gunnar RM, Kennedy JW, King SB 3rd, Loop FD, Peterson KL, Reeves TJ, Williams DO, Winters WL Jr. Guidelines for percutaneous transluminal coronary angioplasty. A report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee on Percutaneous Transluminal Coronary Angioplasty). *Circulation*. 1988;78:486–502. doi: 10.1161/01.cir.78.2.486
9. Mehran R, Dangas G, Abizaid AS, Mintz GS, Lansky AJ, Satler LF, Pichard AD, Kent KM, Stone GW, Leon MB. Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. *Circulation*. 1999;100:1872–1878. doi: 10.1161/01.cir.100.18.1872
10. di Palma G, Sanchez-Jimenez EF, Lazar L, Cortese B. Should paclitaxel be considered an old generation DCB? The limus era. *Rev Cardiovasc Med*. 2021;22:1323–1330. doi: 10.31083/j.rcm2204138
11. El-Mokdad R, di Palma G, Cortese B. Long-term follow-up after sirolimus-coated balloon use for coronary artery disease. Final results of the Nanolutè study. *Catheter Cardiovasc Interv*. 2020;96:E496–E500. doi: 10.1002/ccd.28863
12. Cortese B, Testa L, Heang TM, Ielasi A, Bossi I, Latini RA, Lee CY, Perez IS, Milazzo D, Caiazzo G, et al; EASTBOURNE Investigators. Sirolimus-coated balloon in an all-comer population of coronary artery disease patients: the EASTBOURNE prospective registry. *JACC Cardiovasc Interv*. 2023;16:1794–1803. doi: 10.1016/j.jcin.2023.05.005
13. Ono M, Kawashima H, Hara H, Katagiri Y, Takahashi K, Kogame N, Wykrzykowska JJ, Piek JJ, Doshi M, Sharif F, et al. A prospective multicenter randomized trial to assess the effectiveness of the magictouch sirolimus-coated balloon in small vessels: rationale and design of the TRANSFORM I trial. *Cardiovasc Revasc Med*. 2021;25:29–35. doi: 10.1016/j.carrev.2020.10.004
14. Han Y, Li Z, Liu X, Zeng F, Wei S, Bai X, Li Z, Li Z, Wang J, Zuo J, et al. Comparative efficacy and safety of paclitaxel-coated balloon vs sirolimus-coated balloon for in-stent restenosis: a randomized clinical trial. *JACC Cardiovasc Interv*. 2022;15:1626–1636. doi: 10.1007/s00392-002-1309-x
15. Scheller B, Mangner N, Abdul Kader MASK, Wan Ahmad WA, Jeger R, Wöhrle J, Ong TK, Liew HB, Gori T, Mahfoud F, et al. Combined analysis of two parallel randomized trials of sirolimus-coated and paclitaxel-coated balloons in coronary in-stent restenosis lesions. *Circ Cardiovasc Interv*. 2022;15:e012305. doi: 10.1161/CIRCINTERVENTIONS.122.012305
16. Giacoppo D, Alfonso F, Xu B, Claessen BEPM, Adriaenssens T, Jensen C, Pérez-Vizcayno MJ, Kang DY, Degenhardt R, Pleva L, et al. Paclitaxel-coated balloon angioplasty vs. drug-eluting stenting for the treatment of coronary in-stent restenosis: a comprehensive, collaborative, individual patient data meta-analysis of 10 randomized clinical trials (DAEDALUS study). *Eur Heart J*. 2019;41:3715–3728. doi: 10.1093/eurheartj/ehz594
17. Pocock SJ, Lansky AJ, Mehran R, Popma JJ, Fahy MP, Na Y, Dangas G, Moses JW, Pucelikova T, Kandzari DE, et al. Angiographic surrogate end points in drug-eluting stent trials: a systematic evaluation based on individual patient data from 11 randomized, controlled trials. *J Am Coll Cardiol*. 2008;51:23–32. doi: 10.1016/j.jacc.2007.07.084
18. Vrints C, Andreotti F, Koskinas KC, Rossello X, Adamo M, Ainslie J, Banning AP, Budaj A, Buechel RR, Chiariello GA, et al; ESC Scientific Document Group. ESC Guidelines for the management of chronic coronary syndromes. *Eur Heart J*. 2024;45:3415–3537. doi: 10.1093/eurheartj/ehae177
19. Sedhom R, Hamed M, Elbadawi A, Mohsen A, Swamy P, Athar A, Bharadwaj AS, Prasad V, Elgendy IY, Alfonso F. Outcomes with limus- vs paclitaxel-coated balloons for percutaneous coronary intervention: meta-analysis of randomized controlled trials. *JACC Cardiovasc Interv*. 2024;17:1533–1543. doi: 10.1016/j.jcin.2024.04.042