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

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Background—The aim of this prospective randomized noninferiority study was to compare the efficacy of paclitaxel-eluting balloon (PEB) catheters and everolimus-eluting stents (EES) in the treatment of bare metal stent restenosis.

Methods and Results—A total of 136 patients were enrolled in the study. Each treatment group included 68 patients with 74 in-stent restenotic lesions. The primary end point was in-segment late lumen loss (LLL) at 12 months. Secondary end points were the incidence of binary in-stent restenosis and 12-month major adverse cardiac events. The 2-sided 95% confidence interval of LLL difference between treatments (0.149–0.558) was greater than noninferiority margin (0.12), which demonstrates both noninferiority and superiority of PEB treatment. Furthermore, the PEB group had significantly less 12-month LLL than the EES group (0.02 versus 0.19 mm; P=0.0004). The difference in the incidence of repeated binary restenosis (8.7% versus 19.12%; P=0.078) and 12-month major adverse cardiac events (10.29% versus 19.12%; P=0.213) was not significant. The 12-month LLL was significantly less in the PEB group and also in subgroups with in-stent restenosis >10 mm (0.05 versus 0.26 mm; P=0.0002) and artery diameter <3 mm (0.05 versus 0.16 mm; P=0.003) compared with the EES groups, but not in the subgroup of patients with diabetes mellitus (P=0.254). In the EES group, repetitive binary restenosis had a significantly greater chance of occurring (odds ratio=3.132; 95% confidence interval, 1.058–9.269; P=0.039), even when adjusting for other risk factors.

Conclusions—Treatment of bare metal stent restenosis using PEB led to significantly less 12-month LLL than the implantation of second-generation EES.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01735825.

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Coronary stent implantation has significantly improved percutaneous coronary intervention and enabled the management of early complications of plain balloon angioplasty (POBA). By preventing elastic recoil and constrictive remodeling, coronary stent implantation decreases the frequency of restenosis after percutaneous coronary intervention. However, a new complication has accompanied these improvements: in-stent restenosis (ISR) arising from neointimal hyperplasia. The clinical incidence of ISR after bare-metal stent (BMS) implantation is ≈20% to 35%.[1,2] The use of drug-eluting stents (DESs) has led to a further decrease in the occurrence of ISR to 5% to 10%.[1,2]

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ISR after coronary angioplasty is currently one of the main limitations of this method, leading to the recurrence of exertional angina pectoris or acute coronary syndromes.[1,2] Repeated POBA or cutting balloon dilatation do not offer satisfactory results in restenosis therapy. Brachytherapy has also been abandoned.[3,4] Current therapy for ISR is based on DESs. A drug released locally from the stent prevents new neointimal hyperplasia.[1,2] This treatment is associated with a risk of late stent thrombosis because of late neoendothelialization and requires long-term dual antiplatelet treatment with the risk of bleeding complications.[1,2]

In contrast, drug-eluting balloon (DEB) catheters allow short-term passage of the active substance into the vascular

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WHAT IS KNOWN

- In-stent restenosis therapy with a paclitaxel-eluting balloon has been demonstrated to be efficacious when compared with a first-generation paclitaxel-eluting stent.

WHAT THE STUDY ADDS

- Our results suggest that the treatment of bare metal stent in-stent restenosis using a paclitaxel-eluting balloon reduces 12-month late lumen loss significantly compared with the implantation of second-generation everolimus-eluting stent.
- This effect was also confirmed for high-risk subgroups with in-stent restenosis >10 mm or a coronary artery diameter <3 mm.
- There was no difference in the incidence of repeated binary restenosis and 12-month MACE between groups.

wall, preventing hyperproliferation of smooth muscle cells in the vascular wall. Because of the short duration of the effect, DEBs do not affect stent neoendothelialization so much.[5] The effect of therapy for ISR with paclitaxel-eluting balloons (PEBs) has been demonstrated and compared with paclitaxel-eluting stents (PESs).[6,7] However, the development of DES has progressed; second-generation DESs release sirolimus derivatives and have higher efficacy and safety.[8–11]

The aim of this prospective randomized Treatment of In-Stent Restenosis (TIS) study (NCT01735825; ClinicalTrials.gov) was to compare (statistical proof of noninferiority) the efficacy of DEB with paclitaxel (PEB) with that of the new generation of DES with sirolimus derivatives (everolimus; EES) for the therapy of BMS restenosis.

Methods

Patients

The study included adult patients (aged >18 years) with BMS ISR (≥50% diameter stenosis [DS]) treated in the Cathlab of University Hospital Ostrava in 2012 to 2014. The main exclusion criteria were concomitant diseases with an expected survival time of <12 months or that limited the possibility of control coronary angiography (eg, advanced renal failure). Patients in which long-term dual antiplatelet treatment was not possible (eg, because of allergy to aspirin or clopidogrel and bleeding complications) were also excluded from the study. The primary end point was in-segment late lumen loss (LLL) at 12 months as measured by quantitative control angiography.[12] Secondary end points were the incidence of binary ISR (≥50% DS) and the overall incidence of 12-month major adverse cardiac events (MACE; cardiovascular death, nonfatal acute myocardial infarction [AIM], or target vessel revascularization [TVR]).

The patients were randomized 1:1 to treatment with Sequent Please (PEB) or the implantation of Promus Element EES (Pt/Cr). Investigators and patients were not blinded to treatment allocation, but clinical events and angiographic measurements were performed by an independent, blinded investigator to avoid any bias. 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 (NCT01735825). Written informed consent was obtained from each patient before enrollment in the study.

Interventions

Percutaneous coronary intervention was performed under standard conditions from the radial or femoral approach using a 6F guiding catheter and Axiom X-ray system (Siemens AG, Forchheim, Germany). The patients were pretreated with aspirin and clopidogrel (600-mg loading dose), and full anticoagulation was achieved by administering 100 IU/kg nonfractionated heparin with the target activated clotting time of 250 to 300 s.

Relatively shorter or scoring balloon catheters were used to predilate the lesions and prevent any edge dissection. After predilatation, the PEB Sequent Please (B. Braun AG, Melsungen, Germany) was inflated for 30 s or EES Promus Element (Boston Scientific, Marlborough, MA) was implanted at the recommended pressures of 12 to 14 atm. Post dilatation using a noncompliant balloon catheter in the case of a suboptimal outcome and implantation of another bail-out stent in the case of edge dissection were performed as necessary. The patients received standard therapy after coronary intervention. Dual antiplatelet therapy (aspirin 100 mg+75 mg of clopidogrel per day) was administered for 3 months after PEB dilatation and 6 to 12 months after EES implantation.

Follow-Up

The clinical follow-up was performed at 6 and 12 months and angiographic follow-up at 12 months (±2 months) unless needed earlier. All deaths were considered cardiac related if not clearly from noncardiac causes. AIM was defined according to the third universal definition of AIM ESC[13] and stent thrombosis using the Academic Research Consortium (ARC) criteria.[14]

Angiographic Follow-Up

Imaging was performed after intracoronary administration of 1-mg isosorbide dinitrate in appropriate orthogonal projections to best avoid potential shortening or overlap of the reporting segment and the lateral branches. Similar projections were used at the 12-month coronary angiography. American College of Cardiology/American Heart Association criteria[15] and Mehran's classification[16] were used to evaluate the type of lesions and ISR. Angiographic parameters were evaluated off-line by an independent, blinded investigator using syngo Quantification software, version 2007 (Siemens AG, Forchheim, Germany).

Lesions were evaluated in an in-segment section (±5 mm from the proximal and distal edges of the stent) and the following parameters measured: minimum lumen diameter (MLD), reference lumen diameter (RefD=½ proximal+distal diameter), acute gain, lesion length, diameter of the stenosis (%DS), and late lumen loss (LLL=MLD postintervention−MLD control). Binary ISR was defined as DS ≥50% in the stented segment.

Statistical Analysis

The study was designed as a noninferiority study. The statistical estimate of the size of the file was based on the data from Spirit trials[9–11] in which LLL of 0.24 (±0.27) mm was reached in an everolimus stent after 12 months. A noninferiority margin of 0.12 (half of the average of 0.24 in the reference group of everolimus stents), α type I error of 5%, and β test strength of 80% were used to determine the required group size of 128 patients (ie, 64 per arm). When including an expected loss of 5% of patients in the 12-month follow-up, the resulting size of our group was 136 patients (68 per arm). Evaluation was based on intention to treat.

The 2-sided 95% confidence interval (CI) for the difference of LLL between treatments was calculated and compared with a noninferiority margin.

Because of strongly non-normal distribution of LLL values, a post hoc analysis of LLL for both arms was also performed using a suitable nonparametric (Mann–Whitney *U*) test.

Table 1. Baseline Characteristics

	PEB	EES	*P* Value
Demographic parameters			
Patients, n	68	68	…
ISR lesions, n	74	74	…
Male/female	43 (63.24%)/25 (36.74%)	46 (67.65%)/22 (32.35%)	0.589*
Age, y	65.6±10.9†	65.5±10.6†	0.930†
Body mass index, kg/m^2	28.7±4.0†	29.3±4.2†	0.365†
Ejection fraction, %	49.74±11.95†/50.0‡	49.57±11.44†/50.0‡	0.956§
Diabetes mellitus	17 (25.00%)	18 (26.47%)	0.844*
Renal insufficiency	2 (2.94%)	7 (10.29%)	0.165‖
CABG	3 (4.41%)	6 (8.82%)	0.493‖
Ever smoked	31 (45.59%)	29 (42.65%)	0.730*
Previous MI	43 (63.24%)	41 (60.29%)	0.724*
2VD/3VD	38 (55.88%)	41 (60.29%)	0.602*
Multi-ISR	4 (5.88%)	5 (7.35%)	1.000‖
Baseline PCI			
ACSy (STEMI/NSTEMI)	45 (66.18%)	50 (73.53%)	0.350*
Stable AP	23 (33.82%)	18 (26.47%)	
Type of lesion			
B2/C	51 (68.92%)	47 (63.51%)	0.487*
Lesion localization			
LAD/D	35 (47.30%)	40 (54.05%)	0.576‖
RCx/OM	16 (21.62%)	10 (13.51%)	
RCA	22 (29.73%)	22 (29.73%)	
SVG	1 (1.35%)	2 (2.70%)	
Diameter of the previous stent, mm	3.18±0.43/3.0‡	3.20±0.41†/3.0‡	0.609§
Length of the previous stent, mm	22.65±11.70†/19.0‡	19.39±9.27†/16.0‡	0.077§
In-stent restenosis			
ACSy, STEMI/NSTEMI	24 (35.29%)	25 (36.76%)	0.098*
Stable AP	41 (60.29%)	33 (48.53%)	
Other, silent ischemia	3 (4.41%)	10 (14.71%)	
Time to ISR, mo	12.10±8.47†/9.0‡	16.51±9.49†/24.0‡	0.009§
Type of ISR			
I (focal; all)	30 (40.54%)	21 (28.38%)	0.266*
II (diffuse)	34 (45.95%)	35 (47.30%)	
III (proliferative)	5 (6.76%)	8 (10.81%)	
IV (occlusion)	5 (6.76%)	10 (13.51%)	
Periprocedural parameters			
Cutting predilatation	16 (21.62%)	5 (6.76%)	0.010*
ISR; PEB/EES diameter, mm	3.32±0.39/3.5‡	3.31±0.43†/3.5‡	0.989§
ISR; PEB/EES length, mm	22.53±8.13†/20.0‡	28.47±12.76†/24.0‡	0.001§
Postdilatation, atm	14.84±2.77†/16.0‡	14.11±2.45†/12.0‡	0.093§
Second stent implantation	11 (14.86%)	11 (14.86%)	1.000*

Qualitative data are given as n (%). Quantitative data are given as †mean (±SD) and ‡median. 2VD indicates 2-vessel disease; 3VD, 3-vessel disease; ACSy, acute coronary syndrome; AP, angina pectoris; CABG, coronary artery bypass grafting; D, diagonal branch; EES, everolimus-eluting stent; ISR, in-stent restenosis; LAD, left anterior descending; 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; RCx, ramus circumflexus; STEMI, ST-segment–elevation myocardial infarction; and SVG, saphenous vein graft.

P value: significance of *χ^2 test; †Student 2-sample *t* test, §Mann–Whitney *U*, and ‖Fisher exact test.

Table 2. Baseline, Postprocedural, and 12-Month QCA Parameters

	PEB	EES	*P* Value
Patients/lesions, n	63/69	62/68	
Preprocedural parameters: ISR			
Minimal lumen diameter, mm			
Mean	0.92	0.79	0.062*
SD	0.45	0.48	
Median	1.00	0.77	
Reference diameter, mm			
Mean	2.64	2.66	0.672*
SD	0.47	0.45	
Median	2.63	2.66	
% Diameter stenosis			
Mean	71.8	78.0	0.007*
SD	13.9	13.4	
Median	70.0	76.0	
Postprocedural parameters: post re-PCI			
Minimal lumen diameter, mm			
Mean	2.18	2.51	<0.0001*
SD	0.39	0.38	
Median	2.13	2.49	
Reference diameter, mm			
Mean	2.79	3.01	0.006*
SD	0.41	0.40	
Median	2.79	2.96	
Acute gain, mm			
Mean	1.25	1.72	<0.0001*
SD	0.54	0.47	
Median	1.12	1.69	
% Diameter residual stenosis			
Mean	19.5	16.3	0.005*
SD	7.4	5.9	
Median	20.0	16.0	
12-mo QCA parameters			
Minimal lumen diameter, mm			
Mean	2.09	2.07	0.481*
SD	0.57	0.80	
Median	2.13	2.23	
Reference diameter, mm			
Mean	2.81	2.96	0.188*
SD	0.48	0.50	
Median	2.81	2.86	
% Diameter stenosis			
Mean	26.2	30.9	0.816*
SD	18.0	24.6	
Median	22.0	21.5	
Late lumen loss, mm			
Mean	0.09	0.44	0.0004*
SD	0.44	0.73	
Median	0.02	0.19	
Binary restenosis (%DS ≥50%)			
(n/%)	6 (8.7%)	13 (19.12%)	0.078†

DS indicates diameter stenosis; EES, everolimus-eluting stents; ISR, in-stent restenosis; PCI, percutaneous coronary intervention; PEB, paclitaxel-eluting balloon; and QCA, quantitative control angiography.

P value: significance of *Mann–Whitney *U* test, and †χ^2 test.

Continuous variables with normal distribution are presented as mean and SD and were compared using Student 2-sample *t* test. Continuous variables with non-normal distribution are presented as the median and range (minimum–maximum or lower and higher percentile) and were compared using the nonparametric Mann–Whitney *U* test. Categorical variables are presented as counts and percentages and were compared using the χ^2 or Fisher exact test. Odds ratios (ORs) are expressed with 95% CIs. A $P<0.05$ was considered significant.

Time-to-event data are shown as Kaplan–Meier curves and were compared using the log-rank test. Multiple logistic regression (enter method) was used to identify the most significant predictive factors for repeated binary restenosis, adjusting for diabetes mellitus and other possible confounding factors. Spearman correlation analysis was used to determine the relationships between postprocedural parameters and 12-month LLL. All statistical analyses were performed using IBM SPSS Statistics version 22.

Results

A total of 136 patients were enrolled in the study (n=68 in each group), with a total of 74 ISR lesions in each group. Baseline demographic, clinical, angiographic, and ISR characteristics are provided in Table 1. No significant differences were found between the 2 treatment groups with respect to the main demographic parameters, clinical risk factors, extent of coronary disease, primary or ISR lesions, or periprocedural characteristics. However, the PEB group had significantly earlier manifestation of ISR, cutting balloon predilatation was more frequent in this group, and the lengths of the DEB catheters used in the PEB group were shorter than the stents used in the EES group.

Two patients in the DEB arm required crossover to EES because of a hudge spiral dissection (2.7%). However, additional stent implantation was needed in 11 cases (14.86%) in the DEB arm because of edge dissection. The same need for the second stent implantation was observed in the EES arm.

The 12-month clinical data were obtained for all patients. The 12-month quantitative control angiography was performed in 69 lesions (93.24%; 95% CI, 84.93–97.77) in 63 patients (92.65%; 95% CI, 83.67–97.57) in the PEB group and

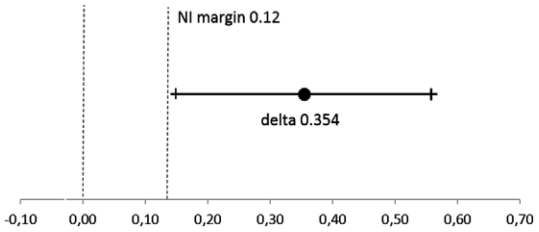

Figure 1. The 2-sided 95% confidence interval for the difference between treatments and the noninferiority (NI) margin.

in 68 lesions (91.89%; 95% CI, 83.18–96.97) in 62 patients (91.18%; 95% CI, 81.78–96.69) in the EES group (*P*=0.753). Angiographic parameters are provided in Table 2. Before the procedure, the groups did not differ in the MLD or RefD of the restenotic segment, but the %DS was significantly higher in the EES group than in the PEB group (*P*=0.007).

The difference in LLL (primary end point) between PEB and EES groups in our study (delta) was 0.354 (eg, 0.442–0.088). The 2-sided 95% CI for the difference between treatments (0.149–0.558) was greater than the noninferiority margin (0.12), thus both noninferiority and superiority of PEB treatment were demonstrated (NI assumption delta ≥0.12; Figure 1).

The Mann–Whitney *U* test showed that the EES group had significantly better early postprocedural results (postprocedural MLD, *P*<0.0001; RefD, *P*=0.006; acute gain, *P*<0.0001; and %DS, *P*=0.005). However, the 12-month angiographic parameters (MLD, *P*=0.481; RefD, *P*=0.188; and %DS, *P*=0.816) were not significantly different compared with the PEB group. In contrast, the PEB group had significantly less 12-month LLL than the EES group (mean, 0.09±0.44 mm; median, 0.02 mm [–0.15 to 0.21] versus mean 0.44±0.73 mm; median 0.19 mm [0.02–0.60]; *P*=0.0004).

However, the difference in the incidence of repeated binary restenosis did not reach significance (*P*=0.078).

Also in the clinical follow-up (Table 3), the differences in 12-month MACE and TVR were not significant (*P*=0.213 and 0.11, respectively).

The number of AIMs and deaths in both groups was the same: 1 AIM developed in the PEB group because of definite stent thrombosis (*P*>0.05). There were 2 deaths, 1 patient died in each group, both of them were treated for ISR at saphenous vein graft. Because the deaths were sudden, the events were evaluated as cardiac and a possible stent thrombosis as defined by ARC. The groups also did not differ in the incidence of residual angina pectoris or signs of heart failure (New York Heart Association class).

Estimates of event-free survival are presented in Figure 2. The average event-free survival was 13.67 months (95% CI, 13.39–13.94 months) and 14.22 months (95% CI, 13.40–15.05 months) in the PEB and EES groups, respectively. The log-rank test revealed no significant difference between the balloon catheter and stent in terms of event-free survival (time to MACE; *P*=0.098).

Table 4 shows the results of a subanalysis of the highest-risk patient subgroups. Patients treated with PEB in subgroups with ISR length >10 mm (type II–IV) and vessel diameter <3 mm had significantly less 12-month LLL than patients with

Table 3. Twelve-Month Clinical Parameters

	PEB, n (%)	EES, n (%)	*P* Value
Patients/lesions, n	68/74	68/74	…
MACE all	7 (10.29)	13 (19.12)	0.213*
CV death	1 (1.47)	1 (1.47)	1.000*
AIM	1 (1.47)	1 (1.47)	1.000*
TVR	5 (7.35)	11 (16.18)	0.110*
Definite stent thrombosis	1 (1.45)	0 (0)	1.000†
Event-free survivor	61 (89.71)	55 (80.88)	0.110*
Angina pectoris, Canadian Cardiovascular Society (CCS) grade			
0–1	48 (78.69)	43 (78.18)	0.947*
2	13 (21.31)	12 (21.82)	
NYHA			
1	14 (22.95)	20 (36.36)	0.199†
2	44 (72.13)	31 (56.36)	
3	3 (4.92)	4 (7.27)	

AIM indicates acute myocardial infarction; CV, cardiovascular; EES, everolimus-eluting stents; MACE, major adverse cardiac events; NYHA, New York Heart Association; PEB, paclitaxel-eluting balloon; and TVR, target vessel revascularization.

P value: significance of *χ^2 test, and †Fisher exact test.

EES (*P*=0.0002 and *P*=0.003, respectively). This difference did not reach significance in the subgroup of patients with diabetes mellitus (*P*=0.254). Multivariate regression analysis was performed to assess the impact of various risk factors on the incidence of repeated binary restenosis after catheter treatment of ISR, with correlations to individual parameters and in the whole group taking the type of treatment (PEB/EES) as an independent factor, as well as in each study arm separately (Table 5). An important risk factor in the whole group was EES implantation. The EES group had significantly higher chances of repeated binary restenosis (OR=3.132; 95% CI, 1.058–9.269; *P*=0.039) when adjusting for diabetes mellitus, renal insufficiency, the type of original lesion (B2/C),

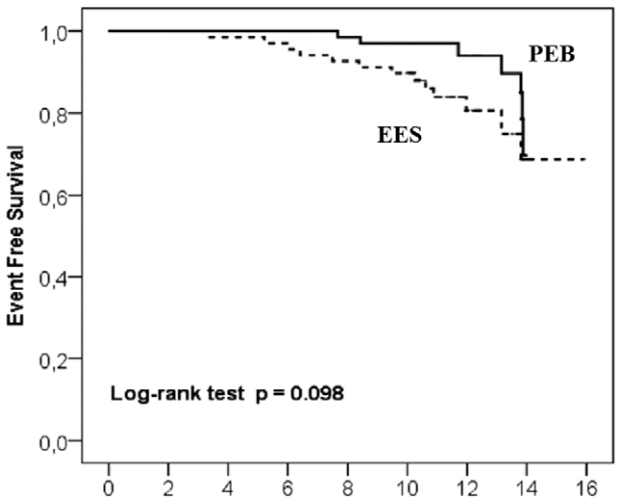

Figure 2. Kaplan–Meier analysis of event-free survival. EES indicates everolimus-eluting stents; and PEB, paclitaxel-eluting balloon.

Table 4. Subgroup Analysis of 12-Month LLL

	PEB	EES	*P* Value*
Diabetes mellitus			
Patients/lesions, n	16/16	15/16	
LLL, mm			
Mean	0.12	0.48	0.254
SD	0.33	0.86	
Median	0.06	0.12	
ISR length >10 mm			
Patients/lesions, n	42/44	44/47	
Late lumen loss, mm			
Mean	0.16	0.53	0.0002
SD	0.50	0.67	
Median	0.05	0.26	
Vessel diameter <3 mm			
Patients/lesions, n	49/54	47/52	
Late lumen loss, mm			
Mean	0.12	0.42	0.003
SD	0.48	0.63	
Median	0.05	0.16	

EES indicates everolimus-eluting stents; ISR, in-stent restenosis; LLL, late lumen loss; and PEB, paclitaxel-eluting balloon.

*Mann–Whitney *U* test.

artery diameter <3 mm, and ISR length >10 mm (nonadjusted OR=2.482; 95% CI, 0.884–6.971; *P*=0.085). No other significant risk factor for predicting repeated binary restenosis was found for the individual study branches (PEB/EES).

Correlation analysis demonstrated no significant dependence of 12-month LLL on the early postprocedural results in either group (postprocedural MLD, RefD, and % residual DS).

Discussion

Current treatment for ISR was established in the Sirolimus-Eluting Stent vs Intravascular Brachytherapy in In-Stent Restenotic Coronary Artery Lesions (SISR) and Randomized Trial Evaluating Slow-Release Formulation Taxus Paclitaxel-Eluting Coronary Stent in the Treatment of In-Stent Restenosis (TAXUS V ISR) trials, which compared the implantation of DES with relatively complicated brachytherapy. The SISR trial revealed a significant decrease in target vessel failure with the use of sirolimus-eluting stents (SES; *P*=0.02)[3] and the TAXUS V ISR trial a significant decrease in TVR (*P*=0.046) and angiographic restenosis (*P*<0.001) with the use of PESs compared with brachytherapy.[4]

The Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for In-Stent Restenosis (ISAR-DESIRE) and Restenosis Intrastent: Balloon Angioplasty Versus Elective Sirolimus-Eluting Stenting (RIBS II) trials compared BMS ISR treatment with DES implantation versus POBA. The ISAR-DESIRE trial revealed a significant decrease in recurrent restenosis (*P*<0.001) and TVR after implantation of SES or PES (*P*<0.001 and *P*=0.02) compared with POBA, whereas the direct comparison of both types of DES revealed a trend toward better outcomes in favor of SES (restenosis, *P*=0.19; TVR, *P*=0.02).[17] Similarly, the RIBS II study revealed a significant decrease in restenosis (*P*<0.001) and TVR (*P*<0.003) after SES compared with POBA.[18] Sun et al[19] found in their meta-analysis that DES implantation for ISR treatment was more effective in reducing TLR, MACE, restenosis, and LLL compared with the inhomogeneous group with conventional therapy (POBA, cutting balloon, repeated BMS, brachytherapy, etc).

The Paccocath I and II trials demonstrated significantly less LLL (*P*=0.002), lower incidence of recurrent restenosis (*P*=0.002), and fewer MACE (*P*=0.01) in the PEB groups than in POBA,[6] with continuing long-term clinical benefit.[20] Similarly, the Paclitaxel-Eluting PTCA-Balloon Catheter in Coronary Artery Disease to Treat In-Stent Restenoses (PEPCAD II) trial compared the treatment effect of PEB versus PES, showing significantly less 6-month LLL (*P*=0.03) in the PEB group with a trend toward reducing the incidence of binary restenosis (*P*=0.06) and 12-month MACE (*P*=0.08).[7] Also, Habara et al[21] reported significantly less LLL (*P*<0.001), recurrent restenosis (*P*<0.001), and target vessel failure (*P*<0.001) in patients with BMS/DES-ISR treated with PEB compared with POBA.

A meta-analysis of trials using PEB for the treatment of BMS or DES ISR showed a significant reduction in the risk of occurrence of MACE (*P*<0.001), TLR (*P*=0.006), and the recurrence of binary in-segment restenosis (*P*<0.001) in the group with PEB compared with an inhomogeneous control group (POBA, PES).[22]

Similarly, Gao et al[23] found that the treatment of ISR with PEB significantly reduced MACE (*P*<0.01), death (*P*=0.04), TLR (*P*<0.01), and LLL (*P*<0.01) compared with POBA; however, the differences were not significant when compared with DES (PES/EES).

The randomized comparations of an everolimus-eluting coronary stent with a bare metal coronary stent (First Clinical Trial of the Abbott Vascular Xience V Everolimus Eluting

Table 5. Logistic Regression Analysis (Enter Method)

All Patients	n	*P* Value	Adjusted OR	95% CI
Patients/lesions	136/148			
Diabetes mellitus (1=yes, 0=no)	35	0.246	2.045	0.611–6.842
Renal insufficiency (1=yes, 0=no)	9	0.999	…	…
Type B2/C lesion (1=yes, 0=no)	98	0.386	1.661	0.528–5.224
PEB=1/EES=2	74/74	0.039	3.132	1.058–9.269
Vessel diameter <3 mm (1=yes,0=no)	106	0.251	2.283	0.558–9.343
ISR length >10 mm (1=yes, 0=no)	92	0.272	1.975	0.587–6.646

CI indicates confidence interval; EES, everolimus-eluting stents; OR, odds ratio; and PEB, paclitaxel-eluting balloon.

Coronary Stent System [SPIRIT I]) and a paclitaxel-eluting coronary stent (A Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System [SPIRIT II] and Clinical Trial of the Xience V Everolimus Eluting Coronary Stent System [SPIRIT III]) trials demonstrated better angiographic and clinical outcomes using newer EES than BMS (LLL, $P<0.001$) or PES (LLL, $P\leq0.04$; MACE, $P=0.03$) in de novo lesions.[9–11] However, the Xience V US registry revealed significantly more target vessel failure after EES implantation in patients with ISR compared with those with non-ISR lesions ($P<0.001$).[24] In several registries and observational studies, EESs have been demonstrated to have at least the same results in the treatment of BMS ISR as the first-generation DES (PES/SES).[25,26]

In the recently published RIBS V trial, patients with BMS ISR were treated with PEB and EES (Xience, cobalt-chrome metallic platform). Patients with EES had significantly higher 9-month MLD (2.36±0.6 versus 2.01±0.6 mm; $P<0.001$) and lower %DS (13±17% versus 25±20%; $P<0.001$). However, no significant difference in LLL (0.04±0.5 versus 0.14±0.5 mm; $P=0.14$) or the incidence of binary restenosis (4.7% versus 9.5%; $P=0.22$) was found. They also did not demonstrate any significant difference in 12-month MACE (6% versus 8%; $P=0.6$) or TVR (2% versus 6%; $P=0.22$).[27]

Recently, several meta-analysis comparing different treatment of ISR were published.

Lee et al[28] demonstrated a significant reduction in TLR and MACE in PEB and DES groups versus POBA (OR, 0.28 and 0.84, respectively), whereas the PEB and DES groups did not differ from each other (OR, 0.92 and 0.84, respectively). Mamuti et al[29] showed no significant difference in MACE in BMS/DES ISR therapy using PEB versus PES/EES (RR, 1.04; $P=0.80$) as well. Goel et al[30] comparing the efficacy of DES, PEB, and POBA in the treatment of DES ISR suggested that DES and PEB seem to reduce the risk of TLR (OR, 0.50 and 0.31) and TVR (OR, 0.55 and 0.32) compared with POBA alone.

Contrary to RIBS V, our study comparing PEB and EES with platinum–chromium metallic platform demonstrated both noninferiority and superiority of PEB treatment for BMS ISR.

However, LLL analysis has shown that the values have a strongly non-normal distribution. Estimation of average and SD for LLL and of 95% CI for the average difference are thus burdened by a mistake. That is why a post hoc analysis of LLL for both arms using a suitable nonparametric (Mann–Whitney *U*) test was also performed.

This analysis confirmed significantly less 12-month LLL in the group treated with PEB. The significantly better early postprocedural angiographic results in the EES group, mainly because of a lower early elastic recoil after the second stent implantation, were not long-lasting, and the subsequent 12-month parameters (MLD, %DS) did not differ between the 2 groups.

This may suggest that EES implantation may be associated with greater neointimal hyperplasia. However, the EES group had a higher number of type IV occlusive lesions requiring a more aggressive approach compared with the PEB group. This may cause a greater vessel wall injury with subsequent extensive vascular healing response. Further investigation with IVUS or OCT imaging should be needed.

The beneficial effect of PEB on reducing LLL was found even in high-risk subgroups of patients with ISR length >10 mm and artery diameter <3 mm. However, the reduction in LLL was not significant in patients with diabetes mellitus.

In the clinical follow-up, the difference in 12-month MACE and TVR did not reach significance, probably because of the small sample size.

In contrast to DES, PEB allows short-term passage of the active substance into the vascular wall, preventing hyperproliferation of smooth muscle cells in the vascular wall. Because of the short duration of the effect, the influence on stent neoendothelialization is also shorter.

This could lead to a decreased occurrence of late stent thrombosis and allow shorter dual antiplatelet treatment which represents a bleeding risk factor.

Although the final in-stent minimal lumen diameter and % residual DS are risk factors for ISR development after implantation of BMS,[1,31] we did not find any correlation between early postprocedural angiographic results and LLL in either of the groups treated for BMS ISR.

Limitations

The patients and investigators were not blinded to the chosen method of treatment. However, the 12-month quantitative control angiography was evaluated by a blinded, independent investigator. Furthermore, this study did not have sufficient statistical power to detect significant differences in the clinical end points (ie, MACE).

Conclusions

Treatment of BMS restenosis using PEB led to significantly less 12-month LLL compared with the implantation of second-generation EES.

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Disclosures

None.

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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

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