Comparison of drug-eluting stents and drug-coated balloon for the treatment of drug-eluting coronary stent restenosis: A randomized RESTORE trial

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Background This study sought to evaluate the optimal treatment for in-stent restenosis (ISR) of drug-eluting stents (DESs).

Methods This is a prospective, multicenter, open-label, randomized study comparing the use of drug-eluting balloon (DEB) versus second-generation everolimus-eluting stent for the treatment of DES ISR. The primary end point was in-segment late loss at 9-month routine angiographic follow-up.

Results A total of 172 patients were enrolled, and 74 (43.0%) patients underwent the angiographic follow-up. The primary end point was not different between the 2 treatment groups (DEB group 0.15 ± 0.49 mm vs DES group 0.19 ± 0.41 mm, $P = .54$). The secondary end points of in-segment minimal luminal diameter (MLD) (1.80 ± 0.69 mm vs 2.09 ± 0.46 mm, $P = .03$), in-stent MLD (1.90 ± 0.71 mm vs 2.29 ± 0.48 mm, $P = .005$), in-segment percent diameter stenosis (34% ± 21% vs 26% ± 15%, $P = .05$), and in-stent percent diameter stenosis (33% ± 21% vs 21% ± 15%, $P = .002$) were more favorable in the DES group. The composite of death, myocardial infarction, or target lesion revascularization at 1 year was comparable between the 2 groups (DEB group 7.0% vs DES group 4.7%, $P = .51$).

Conclusions Treatment of DES ISR using DEB or second-generation DES did not differ in terms of late loss at 9-month angiographic follow-up, whereas DES showed better angiographic results regarding minimal MLD and percent diameter stenosis. Both treatment strategies were safe and effective up to 1 year after the procedure. (Am Heart J 2018;197:35-42.)

Drug-eluting stent (DES) has dramatically reduced the incidence of in-stent restenosis (ISR) and subsequently the need for target lesion revascularization (TLR).[1-3] Nevertheless, 5%-10% of patient who underwent DES implantations still suffered from ISR,[1-7] and the rate of restenosis would increase with lesion complexity. However, there were few studies to evaluate the optimal strategy to manage ISR after DES implantation, mainly because of the relatively low incidence of this condition. There have been several options for treatment of ISR including balloon angioplasty using cutting balloon, brachytherapy, and repeated DES implantation. Repeated DES implantation could achieve more favorable clinical outcome as compared with other modalities.[8-10] However, repeated percutaneous coronary intervention (PCI) using DES in this setting has been challenging and problematic in clinical practice because of considerable incidence of recurrent ISR as high as 40%-50%.[11]

Multiple thick metal layers and concern for late stent thrombosis were the major limitations of DES treatment for ISR. Subsequently, paclitaxel-coated balloon catheter has been introduced in treatment of ISR. Treatment with paclitaxel-coated balloon catheters significantly reduced

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neointimal hyperplasia and the incidence of restenosis compared with uncoated balloon catheter.[12] In addition, paclitaxel-coated balloon showed lower late loss than paclitaxel-coated stent in such a situation.[13]

Therefore, comparison of drug-eluting balloon (DEB) with DES is required to judge the potential benefit of this alternative treatment option. We sought to compare the efficacy and safety of DEB and DES for the treatment of coronary ISR after DES implantation.

Methods

Study populations

The Treatment of Drug-Eluting Stent REstenosis Using Drug-Eluting STents versus Drug-COated Balloon for Preventing REcurrent In-Stent Restenosis (RESTORE) (www.clinicaltrials.gov; identifier NCT01967199) trial was a prospective, multicenter, open-label, randomized comparison trial conducted in 10 clinical centers in South Korea from April 2013 to October 2016. Patients with DES restenosis with diameter stenosis >50% who were eligible for PCI were enrolled into the study. Exclusion criteria included contraindications to the use of paclitaxel, everolimus, or antiplatelet drugs and a life expectancy <1 year. The study was approved by the institutional review board at each institution, and written informed consents were obtained from all participants. This study was supported by the CardioVascular Research Foundation, Seoul, Korea. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

Randomization, procedures, and adjunctive drug therapies

Patients were randomized into 2 treatment groups by 1:1 fashion: SeQuent Please (B. Braun Melsungen AG, Berlin, Germany) paclitaxel-eluting balloon angioplasty or Xience (Abbott Vascular, Santa Clara, CA) DES implantation. Patients were randomly assigned based on a computer-generated randomization schedule. The interactive Web response system assigned a unique treatment code, which dictated treatment assignment for the patient. All procedures were performed using standard techniques by experienced operators. The number of lesions treated during the index procedures was not limited by protocol, but only 1 eligible lesion would be chosen as the target lesion per patient for further analyses. Lesion preparations using predilation balloons, cutting balloons, directional atherectomy, or rotational atherectomy before DEB or DES treatment were at operators' discretions. Use of intracoronary imaging was strongly encouraged. The final angiographic objective would be a <30% residual stenosis for both treatment groups. If adequate procedural results could not be achieved in the DEB group because of severe dissection or significant residual stenosis, bailout stenting with Xience stents was allowed and counted as a crossover. After the procedure, patients received aspirin (100-200 mg daily) indefinitely and thienopyridines (clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor 90 mg bid) for at least 6 months for both treatment arms.

Quantitative coronary angiography

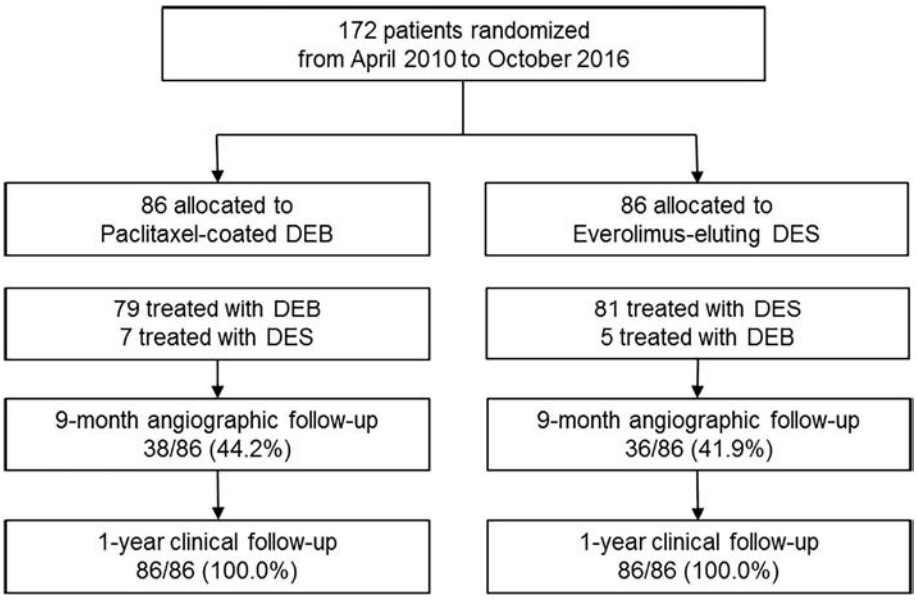
Digital records of coronary angiograms at baseline, immediately after the procedure, and at follow-up were obtained. A dedicated angiographic core laboratory (Asan Medical Center, Seoul, Korea) was used for analyses using an automated edge-detection system (CAAS V, Pie Medical Imaging, Maastricht, the Netherlands) by experienced staff. All measurements were performed on cineangiograms recorded after intracoronary administration of nitroglycerin. Standard qualitative and quantitative analyses and definitions were used for angiographic analysis.[14] All quantitative angiographic measurements were obtained within the stented segment (in-stent) and over the entire segment including the stent and its 5-mm proximal and distal margins (in-segment). Angiographic variables included absolute lesion length, stent length, reference vessel diameter, minimum lumen diameter, percent diameter stenosis, binary restenosis rate, immediate gain, late loss, and patterns of recurrent restenosis. The reference diameter was determined by interpolation. *Binary restenosis* was defined as percent diameter stenosis of 50% or greater on follow-up angiography, and patterns of angiographic restenosis were quantitatively assessed with the Mehran classification.[15]

Study end points

The primary end point was the late luminal loss in the target segment on quantitative coronary analysis at 9 months after the index procedure. The secondary angiographic end points were parameters in both in-segment and in-stent analyses including minimal luminal diameter (MLD), percent diameter stenosis, and binary restenosis at 9 months. Clinical outcomes including death, myocardial infarction (MI), TLR, target vessel revascularization (TVR), stent thrombosis, stroke, bleeding, and a composite of major adverse cardiac events (MACE), including death, MI, and TLR within 12 months, were regarded as secondary clinical end points.

All death events were considered to be of cardiac cause unless a noncardiac cause could be identified. *MI* was defined as an elevation of creatine kinase–MB or troponin to the upper reference limit, and *periprocedural MI* was defined as an elevation of creatine kinase–MB or troponin to at least 3 times the upper reference limit during the first 48 hours after PCI.[16] *TLR* and *TVR* were defined as any revascularization procedure involving target lesion and target vessel, respectively, due to luminal narrowing in the presence of symptoms or objective evidence of ischemia. *Stent thrombosis* was defined as definite or probable thrombosis by the Academic Research Consortium definitions.[16] *Device success* was defined as a residual stenosis of <30% at the target segment after treatment.

Figure 1



Study flowchart. A total of 172 patients with DES ISR were randomly allocated to paclitaxel-coated DEB or everolimus-eluting stents (DES).

Patient follow-up and data management

All data were collected using a Web-based dedicated case report form. Members of the academic coordinating center (Clinical Research Center, Asan Medical Center, Seoul, Korea) periodically performed monitoring and verification of the registry data in the participating hospitals. Routine angiographic follow-up at 9 months were mandatory. Clinical follow-ups were conducted during hospitalization and at 30 days, 3 months, 6 months, and 12 months after the index procedure. The patients' clinical status, all interventions, and adverse events were recorded at each visit.

Statistics analysis

The trial was designed as a superiority trial: a sample size of 130 patients per arm was calculated to provide 90% power and 5% two-sided significance level to demonstrate a significant reduction in the in-segment late lumen loss from 0.35 ± 0.5 mm in the EES group to 0.15 ± 0.4 mm in the DEB group, assuming a dropout rate of 15% in both groups. Sample size was calculated by PASS 11.0 software (NCSS, LLC, Kaysville, UT).

Continuous variables were expressed as means ± SD or median (interquartile range [IQR]) where appropriate; categorical variables were shown as counts and percentages. All analyses were based on the intention-to-treat principle. The statistician was blinded to treatment options in each cohort during statistical analysis. Continuous variables were compared using Student t tests or Mann-Whitney U test; categorical variables were compared using χ^2 statistics or Fisher exact test, as appropriate. Cumulative frequency distribution curves in each group were compared with Kolmogorov-Smirnov test. Applicable P values were 2-sided, and $P < .05$ was considered statistically significant. All statistical analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC), and R software, version 2.10.1.

Results

Patient characteristics and procedural results

A total of 172 patients were randomized to receive SeQuent Please DEB (n = 86) or Xience DES (n = 86) as treatment for DES ISRs (Figure 1). The study was prematurely terminated because of slow enrollment. Table I shows the baseline clinical characteristics, whereas Table II shows the lesion and procedural characteristics of the study populations. Most of the baseline characteristics were not statistically different between the 2 groups. The exceptions were the number of DEBs or stents used (DEB group 1.4 ± 0.8 vs DES 1.1 ± 0.2, $P < .001$), the average diameters of DEBs or stents used (2.98 ± 0.4 mm vs 3.14 ± 0.35 mm, $P = .01$), and the maximal pressure used at deployment (10.3 ± 3.6 mmHg vs 12.7 ± 3.7 mmHg, P < .001) in the procedures. Device success rate was 98.8% for DEB group and 100% for DES group ($P = .32$). The crossover rate from DEB to DES was 8.1%, and that from DES to DEB was 5.8% ($P = .55$).

Angiographic results at baseline and immediate postintervention

Quantitative angiographic results at baseline and immediate postintervention were shown in Table III.

Table I. Baseline clinical characteristics

	DEB (n = 86)	DES (n = 86)	*P*
Age, y	67 ± 10	66 ± 9	.29
Male	61 (70.9%)	62 (72.1%)	.87
Hypertension	60 (69.8%)	65 (75.6%)	.39
Diabetes mellitus	43 (50.0%)	38 (44.2%)	.45
Previous or current smoker	40 (46.5%)	37 (43.0%)	.65
Hyperlipidemia	49 (57.0%)	53 (61.6%)	.54
History of MI	26 (30.2%)	22 (25.6%)	.50
LVEF, %	59.4 ± 8.4	59.9 ± 7.8	.63
Multivessel disease	22 (25.6%)	18 (20.9%)	.47
Clinical presentation			.88
Silent ischemia	2 (2.3%)	3 (3.5%)	
Stable angina	34 (39.5%)	36 (41.9%)	
Unstable angina	39 (45.3%)	33 (38.4%)	
NSTEMI	5 (5.8%)	7 (8.1%)	

Values are numbers (percentage) or mean ± SD.
LVEF, Left ventricular ejection fraction; *NSTEMI*, non–ST-segment elevation myocardial infarction.

Table II. Baseline lesion and procedural characteristics

	DEB (n = 86)	DES (n = 86)	*P*
Lesion characteristics			
Target vessel			.47
LM	0 (0.0%)	2 (2.3%)	
LAD	48 (55.8%)	52 (60.5%)	
LCX	13 (15.1%)	11 (12.8%)	
RCA	24 (27.9%)	21 (24.4%)	
Ramus	1 (1.2%)	0 (0.0%)	
Bifurcation	19 (22.4%)	22 (26.2%)	.56
Moderate or severe calcifications	5 (5.8%)	4 (4.8%)	.76
Procedural characteristics			
Use of predilation balloons	65 (75.6%)	72 (83.7%)	.41
Use of intracoronary imaging	49 (57.0%)	52 (60.5%)	.16
No. of stents/balloons	1.3 ± 0.8	1.1 ± 0.2	<.001
Total length of stents/balloons, mm	28.5 ± 14.7	25.5 ± 11.5	.14
Average diameters of stents/balloons, mm	2.98 ± 0.40	3.14 ± 0.35	.01
Maximal pressure at deployment, mm Hg	10.3 ± 3.6	12.7 ± 3.7	<.001
Device success	84 (98.8%)	84 (100.0%)	.32
Crossover	7 (8.1%)	5 (5.8%)	.55

Values are numbers (percentage) or mean ± SD.
LM, Left main artery; *LAD*, left anterior descending artery; *LCX*, left circumflex artery; *RCA*, right coronary artery.

The baseline reference vessel diameter of the DES group was larger (2.85 ± 0.50 mm vs 3.06 ± 0.45 mm, $P = .01$). There was a trend that the DEB group contained more diffuse lesions (lesion length >10 mm) (80.6% vs 67.6%, $P = .09$). Other baseline angiographic characteristics were similar between 2 groups. Immediately after the index procedures, larger in-segment MLD (1.97 ± 0.43 mm vs 2.24 ± 0.48 mm, $P = .001$), lower in-segment percent diameter stenosis (26 ± 10% vs 20 ± 11%, P = .001), and larger in-segment acute gain (1.34 ± 0.52 mm vs 1.61 ± 0.54 mm, $P = .004$) were achieved in the DES group. Similar findings were observed for the in-stent analyses (Table III).

Table III. Angiographic characteristics at baseline and immediately postintervention

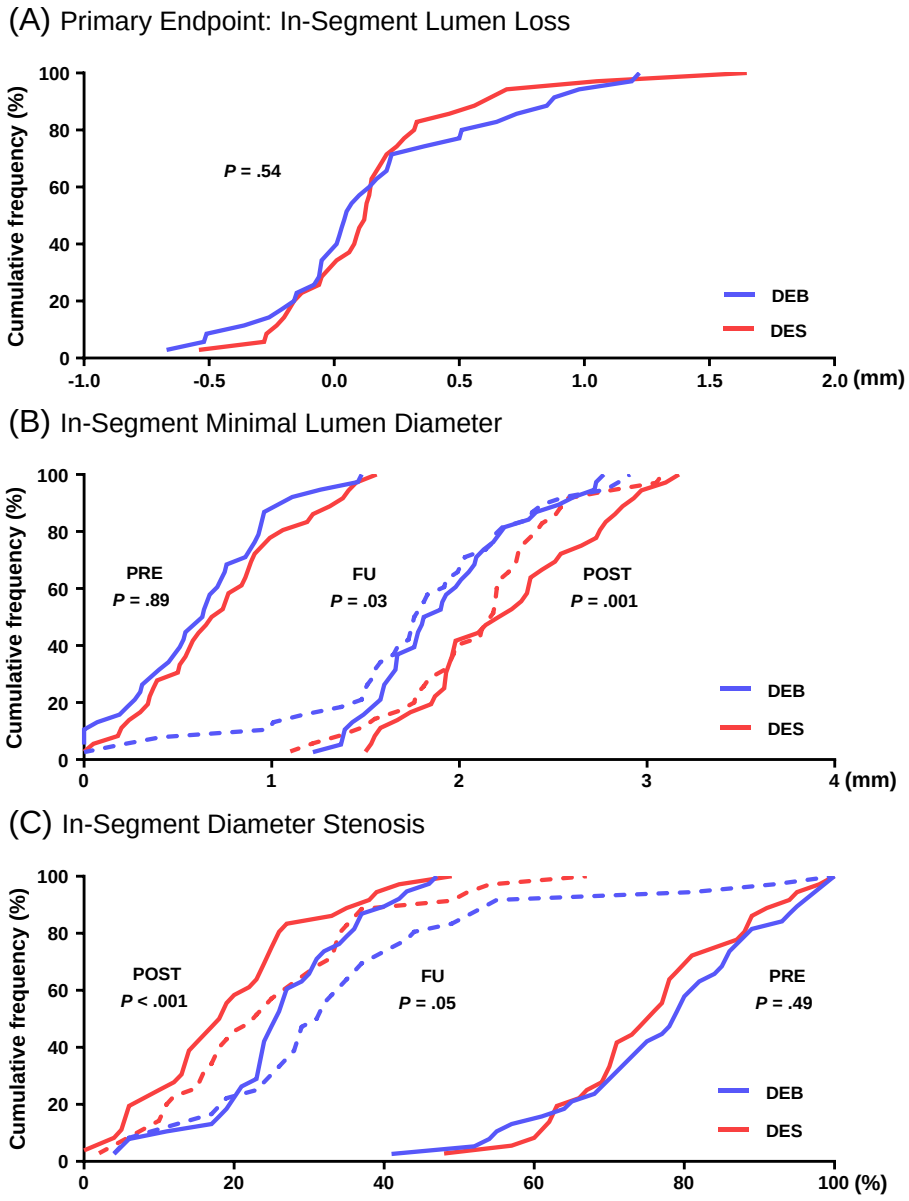
	DEB (n = 67)	DES (n = 68)	*P*
Qualitative features			
Mehran classification			.78
I	45 (67.2%)	45 (66.2%)	
II	10 (14.9%)	13 (19.1%)	
III	6 (9.0%)	3 (4.4%)	
IV	6 (9.0%)	7 (10.3%)	
Focal ISR	45 (67.2%)	45 (66.2%)	.90
Diffuse ISR	22 (32.8%)	23 (33.8%)	.90
Edge ISR	20 (29.9%)	17 (25.0%)	.53
Quantitative features			
Baseline			
RVD, mm	2.85 ± 0.50	3.06 ± 0.45	.01
MLD, mm	0.63 ± 0.40	0.63 ± 0.42	.89
% diameter stenosis	77 ± 17	79 ± 13	.49
Lesion length, mm	18.1 ± 9.7	17.4 ± 11.4	.23
Diffuse lesion >10 mm	54 (80.6%)	46 (67.6%)	.09
Immediately postprocedure			
In-segment RVD, mm	2.68 ± 0.50	2.82 ± 0.49	.14
In-segment MLD, mm	1.97 ± 0.43	2.24 ± 0.48	.001
In-segment % diameter stenosis	26 ± 10	20 ± 11	.001
In-segment acute gain, mm	1.34 ± 0.52	1.61 ± 0.54	.004
In-stent RVD, mm	2.76 ± 0.49	2.95 ± 0.46	.03
In-stent MLD, mm	2.12 ± 0.43	2.54 ± 0.41	<.001
In-stent % diameter stenosis	23 ± 11	13 ± 10	<.001
In-stent acute gain, mm	1.49 ± 0.49	1.90 ± 0.55	<.001

Values are count (percentage) or mean ± SD.
RVD, Reference vessel diameter.

Angiographic outcome at follow-up

Routine follow-up angiography was performed in 38 (44.2%) patients in the DEB group and in 36 (41.9%) patients in the DES group ($P = .66$) at the median of 312 (IQR 281-387) and 289 days (IQR 255-333), respectively. The baseline clinical, procedural, and lesion characteristics between patients with and without 9-month angiographic follow-ups were not different (Supplementary Tables I, II, and III). The primary study end point of in-segment late loss at 9-month follow-up was not statistically different between the 2 groups (0.15 ± 0.49 mm vs 0.19 ± 0.41 mm, $P = .54$) (Figure 2). However, the secondary end points of in-segment MLD (1.80 ± 0.69 mm vs 2.09 ± 0.46 mm, $P = .03$), in-stent MLD (1.90 ± 0.71 mm vs 2.29 ± 0.48 mm, $P = .005$), in-segment percent diameter stenosis (34% ± 21% vs; 26% ± 15%, $P = .05$), and in-stent percent diameter stenosis (33% ± 21% vs 21% ± 15%, $P = .002$) were more favorable in the DES group. The DES group also showed a trend of lower binary restenosis rate (5.6% vs 19.5%, $P = .65$) (Table IV, Figure 2, and Supplementary Figure 1). The baseline characteristics and angiographic outcomes in as-treated

Figure 2



Cumulative frequency distribution curves for in-segment late lumen loss. Cumulative frequency distribution curves of the primary end point for the SeQuent Please DEB group and the Xience DES group before the procedure (PRE), after the intervention (POST), and at late follow-up (FU) (dashed lines).

analysis showed similar trend to that in the intention-to-treat analysis (Supplementary Table IV, V, and VI).

Clinical outcomes

The median time to the latest clinical follow-ups were 365 (IQR 322-388) and 362 days (IQR 327-378) (P = .27) for the DEB and DES groups, respectively. The results are shown in Table V. The incidences of all the major clinical events did not differ between the 2 groups. There was no mortality or stent thrombosis in both groups. The clinical outcomes in per-protocol analysis were also similar with those of the intention-to-treat analysis (Supplementary Table VII).

Discussion

In this randomized trial, we compared the efficacy and safety of a paclitaxel-coated DEB versus a second-generation everolimus-eluting DES for treatment of DES ISR. The primary end point of in-segment late loss

Table IV. Angiographic results at 9-month follow-up

	DEB (n = 38)	DES (n = 36)	*P*
In-segment			
RVD, mm	2.70 ± 0.52	2.84 ± 0.45	.20
MLD, mm	1.80 ± 0.69	2.09 ± 0.46	.03
% Diameter stenosis	34 ± 21	26 ± 15	.05
Late lumen loss, mm	0.15 ± 0.49	0.19 ± 0.41	.54
Loss index	0.12 ± 0.48	0.09 ± 0.22	.66
In-stent			
RVD, mm	2.79 ± 0.51	2.91 ± 0.43	.27
MLD, mm	1.90 ± 0.71	2.29 ± 0.48	.005
% Diameter stenosis	33 ± 21	21 ± 15	.002
Late lumen loss, mm	0.20 ± 0.52	0.27 ± 0.39	.27
Loss index	0.14 ± 0.41	0.13 ± 0.19	.48
Binary restenosis	8 (19.5%)	2 (5.6%)	.65

Values are numbers (percentage) or mean ± SD. Time to follow-up angiography was presented as median (IQR).

Table V. Clinical outcomes at 1-year follow-up

	DEB (n = 86)	DES (n = 86)	*P*
MACE	6 (7.0%)	4 (4.7%)	.51
Death	0 (0.0%)	0 (0.0%)	N/A
MI	1 (1.2%)	3 (3.5%)	.31
Death or MI	1 (1.2%)	3 (3.5%)	.31
Stent thrombosis	0 (0.0%)	0 (0.0%)	N/A
TVR	5 (5.8%)	1 (1.2%)	.10
TLR	5 (5.8%)	1 (1.2%)	.10
Stroke	0 (0.0%)	0 (0.0%)	N/A
Bleeding	18 (20.9%)	14 (16.3%)	.43

MACE was a composite of death, MI, or TLR.

at 9-month was not different between the 2 groups before and after multivariable adjustment for baseline angiographic differences. The current study could be underpowered to detect difference in clinical end points. Nevertheless, the very low event rates, especially the 0% mortality and stent thrombosis rate in both groups, demonstrated that both treatment strategies were safe up to 1 year after index procedure.

However, for secondary angiographic end points, namely, in-segment or in-stent MLD and percent diameter stenosis at follow-up, DES outperformed DEB (Table IV). This might be partially explained by the better angiographic results achieved by DES immediately postintervention (Table III). These included larger MLD, lower percent diameter stenosis, and larger acute gain in both in-segment and in-stent analyses in the DES group just after PCI. The difference in binary restenosis was also in favor of DES, although it did not achieve statistical significance likely as a consequence of small sample size. The superior secondary angiographic findings of DES partly derived from better acute postprocedural results. The DES group showed larger MLD, acute gain, and smaller diameter stenosis than the DEB group (Table III).

Previous studies consistently demonstrated that implantation of DES outperformed balloon angioplasty and brachytherapy for treatment of bare metal stent (BMS) ISR.[17,18] It has also been shown that DEB was at least comparable to first-generation DES when treating either BMS or DES ISR.[13,19,20] Second-generation DES provided superior long-term angiographic results compared with DEB for treating BMS ISR,[21] and a recent network meta-analysis showed that the everolimus-eluting stent was the most effective treatment for any type of ISR.[22] However, scanty evidence exists regarding the performance of second-generation DES versus DEB in treating DES ISR.

The RIBS IV trial was the only known large randomized study comparing DEB versus second-generation everolimus-eluting DES for treatment of DES ISR.[23,24] It showed that the primary end point of in-segment MLD at routine angiographic follow-ups 6 to 9 months after the index procedure was superior in the DES group. Instead, the current study chose the in-segment late loss at 9 months of angiographic follow-up as the primary study end point. Late loss is a measurement of the absolute amount of renarrowing due to vascular contraction, neointimal hyperplasia, or neoatherosclerosis. We believed this to be a more robust end point because it could better represent the future restenosis propensity.[25,26]

The RIBS IV study also showed that the clinical outcome of MACE at 1 year in the DES group was significantly better than that in the DEB group, mainly driven by a reduction of repeat revascularization (both TVR and TLR). In our study, the clinical outcomes were not statistically different between the 2 groups. But there were trends showing that DES might perform better than DEB in terms of TVR (DEB group 5.8% vs DES group 1.2%, $P = .10$) and TLR (DEB group 5.8% vs DES group 1.2%, $P = .10$) despite a small sample size. Larger trials with clinical outcome as the designated primary end point are needed to give a definitive answer.

There are a few potential advantages of using DEB rather than DES to treat DES ISR. First, the absence of another layer of metal stent is attractive in ISR lesions with major large side branches and in ISR lesions which have already been treated previously with more than 1 layer of metallic stents. Second, the duration of DAPT after DEB treatment may theoretically be shorter than that required by treatment with DES. This is particularly tempting in patients with bleeding tendency. In this study, 6-month minimum durations of DAPT were used for both treatment arms according to the protocol, thus mitigating the difference in clinical outcomes (especially bleeding) attributed to the difference in drug usage. Third, delivery of DEB can sometimes be done more easily than delivering DES to tortuous or heavily calcified vessels.

Study limitations

There were several limitations that deserve attention. First, this was a small study, limiting meaningful analyses only to the angiographic outcomes. The power of the study was further impaired by the premature termination due to slow enrollment. Second, the rate of follow-up angiography at 9 months was suboptimal. Third, the rate of predilation in the DEB group was low (75.6%), which could imply in part suboptimal treatment. Fourth, translation of angiographic end points to clinical outcomes was not guaranteed. However, we believed that late lumen loss at 9 months was a robust predictor for angiographic binary restenosis and hence TLR. Further large long-term studies are needed to provide more information regarding the clinical outcomes in these 2 groups of patients. Fifth, although randomized, this was an open-labeled study, so that might have affected the operators' decisions regarding reinterventions. However, the clinical protocol strictly limited revascularizations only to those clinically indicated stenoses.

Conclusion

Treatment of DES ISR using paclitaxel-coated DEB or second-generation DES did not differ in terms of late loss at 9-month angiographic follow-ups, whereas DES showed better angiographic results regarding minimal MLD and percent diameter stenosis. Both treatment strategies were safe and effective up to 1 year after the procedure. Further studies are needed to demonstrate the differences in clinical outcomes, if any, between these 2 treatment modalities.

Conflict of interest disclosures

Nothing to disclosure

Appendix. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2017.11.008.

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