Propensity Score-matched Lesion-based Comparison of Mid-term Angiographic Outcomes of TAXUS Liberté with Cypher Bx Velocity Stents for *De Novo* Native Coronary Stenosis and in Patients with Diabetes

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Abstract

Objective We sought to perform a propensity score-matched lesion-based comparison of mid-term angiographic outcomes of sirolimus- (SES, Cypher Bx Velocity) and paclitaxel- (PES, TAXUS Liberté, the 2nd-generation TAXUS) eluting stents to treat *de novo* coronary stenosis and, particularly, in patients with diabetes mellitus (DM) in a daily practice environment.

Methods The present study was a non-randomized, retrospective, lesion-based, single center study that included 1,287 *de novo* native coronary stenosis cases after successful SES or PES placement between February 2007 and April 2011. The primary endpoint was angiographic-based binary in-stent restenosis (% diameter stenosis >50 at secondary angiogram) within 550 days of placement. A propensity score-matched analysis was used to adjust the baselines.

Results Among 360 baseline-adjusted angiographic lesions followed up in each arm, the incidence of the primary endpoint in the PES group (11.7%, follow-up period: 350±76 days) was not significantly different from that in the SES group (10.3%, $p=0.645$, 354±81 days, $p=0.912$). PES was not associated with the primary endpoint by logistic regression analysis (odds ratio: 1.15, 95% confidence interval: 0.68-1.93, $p=0.605$). In the DM specific sub-analysis, the primary endpoint in the PES group (19.6%) was not significantly different from that in the SES group (12.8%, $p=0.105$) in 148 baseline-adjusted lesions in each arm.

Conclusion The mid-term angiographic outcomes after TAXUS Liberté placement for all-comer *de novo* native coronary stenosis and in patients with DM were not significantly different from those of SES in a Japanese daily practice environment.

Key words: paclitaxel-eluting stent, sirolimus-eluting stent, follow-up result, restenosis, stent thrombosis

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Introduction

Coronary stent technology has been advancing, and the outcomes of innovative drug-eluting stent (DES) should be examined by comparing outcomes with those of previously approved types of DES. The paclitaxel-eluting TAXUS Liberté stent, which is the 2nd-generation TAXUS (PES; Boston Scientific, Natick, USA), was designed with thinner and more even strut spacing to provide more uniform drug dis-

tribution with the identical polymer, drug dosage, and release kinetics compared to the earlier paclitaxel-eluting (TAXUS Express) stent (1, 2).

Because sirolimus-eluting stents (SES: Cypher Bx Velocity; Cordis Corp., Miami, USA) and TAXUS Express stents were widely used in the early phase of the DES era, numerous reports have compared the outcomes between those first generation DESs throughout the world (3-6) and in Japan (7-11). However, no studies have compared the outcomes of PES (TAXUS Liberté) and SES, the most standard

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evidence-based first-generation DES (12-16), after placement in Japanese daily practice environment, where the incidence of severe cardiac events, including stent thrombosis (17), is less frequent than that in Western countries (12-16, 18, 19).

In the present study, we sought to investigate the mid-term (approximately 1.5 years) lesion-based angiographic outcomes of PES versus SES in a Japanese daily practice environment. We also performed the first diabetes mellitus (DM)-specific sub-analysis of these stents. We examined the angiographic lesion-based binary in-stent restenosis (ISR) within 550 days after PES implantation to all-comer *de novo* coronary stenosis and compared patients with DM with those of SES by adjusting the baselines using our previously described propensity matching score analysis (11, 20, 21).

Materials and Methods

Study design, population, follow-up secondary angiogram, and definition of DM

The present study was a retrospective, non-randomized, lesion-based, single-center study performed at the Saitama Cardiovascular Respiratory Center. The rationale was approved by the local ethics committee. The retrospective examination was performed in February 2013. The selection of stent (DES or bare metal stents [BMS]) and the use of percutaneous coronary intervention (PCI) modalities (e.g., intravascular ultrasound [IVUS] and rotational atherectomy with a rotablator), duration of thienopyridine agent administration after stent placement, and indication for follow-up coronary angiography (fu-CAG) were not randomized. The inclusion criteria were lesions with *de novo* stenosis in native coronary arteries that were successfully and exclusively treated by elective SES or PES in patients who had not undergone a prior coronary artery bypass graft (CABG). The treatment was considered successful in the absence of peri-procedural complications (i.e., death, Q-wave myocardial infarction [MI], and emergency CABG). Furthermore, lesions were enrolled when post-procedural antegrade coronary flow assessment revealed thrombolysis in myocardial infarction (TIMI) grade 3 flow with acceptable stent expansion on angiography and IVUS (22, 23). As in our previous report, we excluded lesions in patients who underwent PCI supported by intra-aortic balloon pumping, bailout stenting, hybrid stenting, or those with a pre-procedural reference diameter >5.0 mm (8).

From February 2007 to February 2009, the numbers of lesions successfully stented with SES, TAXUS Express, and BMS were 384, 682, and 62, respectively. From February 2009 (the time for approval of TAXUS Liberté [PES]) to April 2011 (before approval of Nobori; biolimus A9-eluting stent [Terumo Corp., Tokyo, Japan]), the number of lesions successfully stented with SES, TAXUS Liberté, Cypher select+ (Cordis Corp.), Endeavor (zotarolimus-eluting stent, Medtronic Corp., Minneapolis, USA), Xience V/Promus (everolimus-eluting stent: Abbott Vascular, Santa Clara,

USA/Boston Scientific), and BMS were 150, 753, 39, 4, 241, and 118 lesions, respectively.

The angiographic outcomes assessed with fu-CAG through December 2012 were included in the analyses. The fu-CAG was planned approximately 8-18 months (within 550 days) after the stenting procedure. The rate of fu-CAG was 70.1% (528 lesions among 753 cases) in the PES group and 72.5% in the SES group (387 lesions among 534 cases) ($p=0.359$). Overall 444 patients with 534 lesions and 643 patients with 753 lesions received SES and PES, respectively. Of these, 223 patients were treated with both SES and PES. Thus, in the present study, the patient-based characteristics (described below) were not compared between the SES and PES groups. There were six cases of severe cardiac events (cardiac death and non-fatal MI): four patients died after exclusive SES treatment for five lesions, one patient died after exclusive PES treatment for two lesions, and one patient experienced a non-fatal MI after PES treatment for one lesion.

DM was defined as a previous clinical diagnosis, current therapy, serum fasting blood glucose level ≥ 126 mg/dL, or serum hemoglobin A1c level $\geq 6.5\%$. The percentages of SES and PES placement in patients with DM were 47.5% and 46%, respectively. Overall, 184 and 243 lesions in patients with DM were treated with SES and PES, respectively.

Procedures for stenting and medications

All patients were informed of the necessity of PCI and stenting, and informed consent was obtained. Heparin (5,000-8,000 IU) was administered during the procedure. The stents were implanted by visual angiographic estimation to cover the entire baseline lesion under the guidance of IVUS.

Peri-procedural anti-platelet therapy was conducted as previously described (8, 11). When elective PCI was planned, aspirin (81-100 mg) and a thienopyridine agent (either ticlopidine [200 mg] or clopidogrel [75 mg]) prescribed at the doctor's discretion were orally administered approximately 10 days before the index procedure. At our center, the administration of aspirin plus a thienopyridine agent (dual anti-platelet therapy, DAPT) was determined by doctors, nurses, and pharmacists. The very high percentages of DAPT would be statistically equivalent in both groups, although the precise percentages of DAPT in the early phase of index PCI were not available. Oral beta-blockers, as well as angiotensin-converting enzyme inhibitors or angiotensin receptor-blockers (renin-angiotensin system (RAS) inhibitors), were administered by checking for a contraindication. A lipid-lowering therapy using an HMG-CoA reductase (statin) was also administered after checking the level of serum low-density lipoprotein and the plaque volume of coronary by IVUS. The percentages of these three drugs at discharge after PCI in the SES group (80.9%, 89.9%, 92.0%) were not significantly different from those in the PES group (79.0%, 90.9%, 91.5%, respectively) ($p=0.479, 0.615, 0.781$, respec-

Table 1. Baseline and the Incidences of the Primary Endpoints

(n)	SES 387	PES 528	p value
Age (yr)	67.1 ± 9.2	66.2 ± 10.2	0.163
Male gender (%)	77.5	81.8	0.108
Diabetes (%)	47.5	46.0	0.648
Insulin use (%)	6.2	4.9	0.401
Hemodialysis (%)	1.6	1.9	0.695
LV dysfunction (%)	3.4	4.7	0.303
LAD (%)	42.6	37.7	0.131
LCX (%)	31.8	25.8	0.046
RCA (%)	23.8	33.7	0.002
Severe calcification (%)	10.6	12.5	0.376
RCA ostium (%)	1.8	1.1	0.396
LCX ostium (%)	4.1	4.7	0.664
Main branch of bifurcation 2-stent (%)	7.0	6.8	0.925
Side branch of bifurcation 2-stent (%)	9.0	7.6	0.423
CTO (%)	10.6	18.2	0.002
IVUS (%)	96.0	99.1	0.002
Rotablator (%)	7.0	3.2	0.009
Number of stent	1.35 ± 0.61	1.43 ± 0.67	0.060
Diameter of stent (mm)	3.11 ± 0.49	3.21 ± 0.42	0.011
Length of stent (mm)	33.1 ± 18.8	38.6 ± 21.5	< 0.001
Maximum pressure (atm)	19.1 ± 3.0	18.2 ± 3.0	< 0.001
Direct stenting (%)	26.4	24.4	0.508
Pre-procedural MLD (mm)	0.91 ± 0.56	0.81 ± 0.52	0.006
Pre-procedural %DS	66.3 ± 18.5	69.7 ± 18.2	0.006
Post-procedural MLD (mm)	2.50 ± 0.51	2.53 ± 0.44	0.351
Post-procedural %DS	12.2 ± 9.6	10.9 ± 8.8	0.036
Post-procedural RD (mm)	2.87 ± 0.63	2.86 ± 0.54	0.801
Follow-up MLD (mm)	2.20 ± 0.71	2.03 ± 0.65	< 0.001
Follow-up %DS	24.9 ± 18.7	27.2 ± 18.5	0.054
Acute gain (mm)	1.58 ± 0.53	1.71 ± 0.58	< 0.001
Late loss (mm)	0.29 ± 0.67	0.50 ± 0.63	< 0.001
Interval for fu-CAG (day)	355 ± 74	341 ± 80	< 0.01
Binary restenosis (%)	10.0	13.1	0.130
Target lesion revascularization (%)	10.4	13.1	0.197

The baseline and the angiographic outcomes in the SES group (n = 387) and the PES group (n = 528) were shown. The definitions of the variables and estimated outcomes were described in the text.

tively).

Quantitative coronary artery evaluation

The quantitative coronary artery (QCA) parameters were measured using a test circulatory cardiovascular network system (CAAS-2 or CAAS-5 system, The Netherlands) as described previously (8, 11). Values were obtained at three time points: before PCI (pre-procedural), immediately after successful PCI (post-procedural), and during the chronic phase (follow-up). The measurements included the minimal lumen diameter (MLD), percent diameter stenosis (%DS), and reference diameter (RD). In cases showing occlusions at the pre-procedural and follow-up stages, the MLD was considered as 0 and the %DS as 100%. Additionally, we calculated the acute gain (post-procedural MLD minus pre-procedural MLD) and late loss (post-procedural MLD minus MLD at the chronic phase). Binary in-stent restenosis (binary restenosis) was defined as a %DS >50% at the fu-CAG. When the multiple restenotic sites were observed in the long stented lesion, late luminal loss and follow-up %DS

were calculated in the most tightly restenotic site. In the present daily practice environment cohort, the angiographic in-stent restenosis pattern could not be fully examined as in our previous report (24) because we observed an unclassified type of in-stent restenosis, particularly after long stented lesions using PES (e.g., focal tight binary in-stent restenosis [type-I] with diffuse [type-II] moderate binary restenosis). The in-segment QCA and at-edge QCA were not estimated because they included approximately 10% of the ostial lesions. The frequency of target lesion revascularization (TLR) after the fu-CAG indicating in-stent restenosis, including definite stent thrombosis and edge restenosis, were compared between the SES and PES groups. The decision to perform TLR was mainly based on the binary restenosis by QCA and if one of the following occurred: (1) a positive history of recurrent angina, presumably related to the target vessel; (2) objective signs of ischemia at rest (electrocardiogram [ECG] changes) or during exercise test (or equivalent), presumably related to the target vessel; (3) abnormal results of any invasive functional diagnostic test (e.g., fractional

Table 2. Adjusted Baseline and the Incidence of the Primary End-point

(n)	SES 360	PES 360	p value
Age (yr)	66.7 ± 9.3	66.5 ± 9.5	0.526
Male (%)	80.0	79.2	0.850
Diabetes (%)	47.5	44.7	0.518
Insulin use (%)	6.0	5.0	0.520
Hemodialysis (%)	1.7	1.4	0.739
Prior MI (%)	50.6	49.7	0.787
LV dysfunction (%)	3.6	5.3	0.377
LAD (%)	43.1	40.0	0.428
LCX (%)	30.6	33.3	0.460
RCA (%)	24.4	23.1	0.712
Severe calcification (%)	9.2	13.1	0.080
RCA ostium (%)	1.7	1.9	0.782
LCX ostium (%)	4.2	5.0	0.711
Main branch of bifurcation 2-stent (%)	7.2	3.6	0.047
Side branch of bifurcation 2-stent (%)	8.6	8.1	0.782
CTO (%)	10.8	12.8	0.399
IVUS (%)	98.6	97.5	0.424
Rotablator (%)	5.3	7.5	0.280
Number of stent	1.36 ± 0.61	1.30 ± 0.58	0.172
Diameter of stent (mm)	3.14 ± 0.50	3.14 ± 0.40	0.711
Length of stent (mm)	33.5 ± 18.9	33.5 ± 19.2	0.969
Direct stenting (%)	26.9	26.9	1.000
Pre-procedural MLD (mm)	0.91 ± 0.57	0.91 ± 0.49	0.705
Pre-procedural %DS	66.5 ± 18.5	66.1 ± 17.0	0.595
Post-procedural MLD (mm)	2.50 ± 0.51	2.51 ± 0.42	0.518
Post-procedural %DS	12.0 ± 9.6	12.1 ± 8.6	0.787
Post-procedural RD (mm)	2.87 ± 0.64	2.88 ± 0.49	0.766
Follow-up MLD (mm)	2.21 ± 0.73	2.09 ± 0.67	0.073
Follow-up %DS	25.1 ± 19.1	25.5 ± 18.1	0.779
Acute gain (mm)	1.59 ± 0.54	1.61 ± 0.47	0.789
Late loss (mm)	0.29 ± 0.67	0.42 ± 0.61	0.003
Interval for fu-CAG (day)	350 ± 76	354 ± 81	0.912
Binary restenosis (%)	10.3	11.7	0.645
Target lesion revascularization (%)	11.4	12.5	0.645

The adjusted baseline and the incidence of the primary endpoint in the SES group and the PES group (n = 360 in each arm) were shown. The definitions of the variables and estimated outcomes were described in the text.

flow reserve [FFR]); or (4) a TLR with a diameter stenosis >70%, even in the absence of the above-mentioned ischemic signs or symptoms.

Estimated endpoints

The efficacy (primary) endpoint of the mid-term angiographic outcome was the incidence of binary in-stent restenosis (defined above) within 550 days after the index procedure. All (early, late, and very late) of the definite stent thromboses (STs), as defined by the Academic Research Consortium criteria (17), within 550 days after the index procedure was also included. In addition, the frequencies of the angiographic lesion-based TL (defined above) were also compared.

Estimated variables

The variables used as baseline characteristics, in particular, patient, angiographic, and procedural characteristics and QCA were as follows: age at the index procedure, gender, diabetes status (determined by blood tests for plasma glu-

cose and hemoglobin A1c), insulin use, hemodialysis, left ventricular (LV) dysfunction (LV ejection fraction <40 as evaluated by ultrasonography or left ventriculogram), lesion location (left anterior descending [LAD], left circumflex [LCX], or right coronary arteries [RCA]), severe calcification (estimated using angiography and IVUS), RCA and LCX ostium lesions (25), main and side branches after treatment with the bifurcation two-stent technique (main branch of bifurcation two-stent, side branch of bifurcation two-stent) (11), chronic total occlusion (CTO), IVUS (IVUS availability during PCI); rotablator use, number of stents per lesion, stent diameter (maximum diameter of the balloon used to dilate the stent), stent length (calculated by summing the length of each stent, regardless of overlap), maximum pressure at the maximum balloon inflation diameter, placement of stent without pre-dilation (direct stenting), and the interval from index PCI to fu-CAG (interval for fu-CAG).

Statistical analyses

Baseline characteristic variables are expressed as the mean

Table 3. Predictors of Binary Restenosis in the Baseline Adjusted Cohort

	Odds ratio	95%CI	p value
Diabetes	2.35	1.36-4.05	0.002
Side branch of bifurcation 2-stent	3.30	1.35-8.08	0.009
Length of stent	1.01	1.00-1.03	0.045
LCX ostium	2.97	0.99-8.94	0.053
:	:	:	:
PES	1.15	0.68-1.93	0.605
:	:	:	:

Predictors of binary restenosis analyzed by logistic regression analysis in the baseline adjusted cohort in turn of p value were arranged. The first 3 variables were the significant predictors, and the lower 2 variables including PES were not significant.

value $\pm$ standard deviation (SD). The variables and endpoints in the SES group were compared with those in the PES group with unpaired *t* tests for continuous values and χ^2 or Fisher's tests for categorical values. A propensity score-matching analysis was performed to adjust the baseline values in the two groups because this was a retrospective and non-randomized study and a historical comparison (26). In order to evaluate the angiographic endpoint (binary restenosis), 25 variables were adjusted with the caliper value of 0.01. The maximum pressure was excluded at the adjustment because the rated burst pressure of SES (20 atm) usually inflated in our institute was different from that of PES (16 atm). After the adjustment, the variables and endpoints in the SES group were compared with those in the PES group by using sign-rank tests for continuous values and McNemar's chi-squared test for categorical values. A logistic regression analysis was performed to evaluate the predictors of binary restenosis involving 22 variables, including PES, after the baseline adjustments shown. A p value less than 0.05 was considered statistically significant. The Stata for Windows version 12 software program (StataCorp, College Station, USA) was used for the statistical analyses.

Results

Baseline and the primary endpoints

Table 1 shows the baseline and the angiographic outcomes in the SES group (n=387) and the PES group (n=528). The percentages of LCX (31.8%), RCA (23.8%), CTO (10.6%), IVUS (96.0%), and rotablator (7.0%) in the SES group were significantly different from those in the PES group (25.8%, 33.7%, 18.2%, 99.1%, and 3.2%, respectively) (p=0.046, 0.002, 0.002, 0.002, and 0.009, respectively). The mean values of stent diameter (3.11 $\pm$ 0.49 mm), stent length (33.1 $\pm$ 18.8 mm), maximal pressure (19.1 $\pm$ 3.0 atm), pre-procedural MLD (0.91 $\pm$ 0.56 mm), pre-procedural %DS (66.3 $\pm$ 18.5 mm), acute gain (1.58 $\pm$ 0.53 mm), and post-procedural %DS (12.2 $\pm$ 9.6) in the SES group were significantly different from those in the PES group (3.21 $\pm$ 0.42 mm, 38.6 $\pm$ 21.5 mm, 18.2 $\pm$ 3.0 atm, 0.81 $\pm$ 0.52 mm, 69.7 $\pm$ 18.2, 1.71 $\pm$ 0.58 mm, and 10.9 $\pm$ 8.8, respectively) (p=0.011,

<0.001, <0.001, 0.006, 0.006, <0.001, and 0.036, respectively). The mean interval for fu-CAG (355 $\pm$ 74 day), follow-up MLD (2.20 $\pm$ 0.71 mm), and the magnitude of late loss (0.29 $\pm$ 0.67 mm) in the SES group were significantly different from those in the PES group (341 $\pm$ 80 day, 2.03 $\pm$ 0.65 mm, 0.50 $\pm$ 0.63 mm, p<0.01, <0.001, and <0.001, respectively).

The incidences of binary restenosis and TLR in the SES group (10.0% and 10.4%) were not significantly different from those in the PES group (13.1% and 13.1%, p=0.130 and 0.197, respectively).

Adjusted baseline and the primary endpoint

Table 2 shows the adjusted baseline and the incidences of angiographic outcomes in the SES and PES groups (n=360 each). Although the magnitude of late loss in the SES group (0.29 $\pm$ 0.67 mm) was significantly lower than that in the PES group (0.42 $\pm$ 0.61 mm, p=0.003), the incidence of binary restenosis in the SES group was not significantly different from that in the PES group (p=0.645).

Predictors of binary restenosis after baseline adjustment

In the 720 angiographic cohort followed, diabetes (odds ratio [OR]: 2.35, 95% confidence interval [CI]: 1.36-4.05, p=0.002), side branch of bifurcation stent (OR: 3.30, 95% CI: 1.35-8.08, p=0.009), and stent length (OR: 1.01, 95% CI: 1.00-1.03, p=0.045) were the significant predictors of the secondary endpoint. PES use was not related to binary restenosis according to a logistic regression analysis (OR: 1.15, 95% CI: 0.68-1.93, p=0.605) (Table 3).

DM-specific sub-analysis of the baseline and the primary endpoint

Table 4 shows the baseline and angiographic outcomes in patients with DM in the SES (n=184) and PES groups (n=243). The percentages of RCA (24.5%), side branch of bifurcation stent (12.5%), CTO (12.0%), and rotablator (8.7%) in the SES group were significantly different from those in the PES group (33.3%, 5.3%, 21.0%, and 1.2%, respectively; p<0.046, 0.008, 0.014, and <0.001, respectively). The mean values of age (67.0 $\pm$ 9.1 y), stent diameter (3.15 $\pm$ 0.50 mm), stent length (34.6 $\pm$ 20.7 mm), maximal pressure (19.1 $\pm$ 3.1 atm), pre-procedural MLD (0.90 $\pm$ 0.56 mm), pre-procedural %DS (66.5 $\pm$ 19.3 mm), and acute gain (1.58 $\pm$ 0.54 mm) were significantly different from those in the PES group (64.0 $\pm$ 10.7 y, 3.25 $\pm$ 0.43 mm, 40.4 $\pm$ 22.8 mm, 18.0 $\pm$ 3.0 atm, 0.76 $\pm$ 0.51 mm, 71.7 $\pm$ 17.9, and 1.75 $\pm$ 0.55 mm, respectively; p=0.002, 0.030, 0.006, 0.008, 0.004, and 0.001, respectively). The mean follow-up MLD (2.16 $\pm$ 0.81 mm) and the magnitude of late loss (0.33 $\pm$ 0.72 mm) in the SES group were significantly different from those in the PES group (1.95 $\pm$ 0.71 mm and 0.56 $\pm$ 0.68 mm, p=0.005 and <0.001, respectively).

The incidences of binary restenosis and TLR in the SES group (13.6% and 13.0%) were not significantly different

Table 4. DM-specific Sub-analysis of Baseline and the Incidences of the Primary Endpoints

(n)	SES 184	PES 243	p value
Age (yr)	67.0 ± 9.1	64.0 ± 10.7	0.002
Male (%)	73.4	79.0	0.173
Insulin use (%)	13.0	10.7	0.456
Hemodialysis (%)	1.6	2.5	0.550
LV dysfunction (%)	3.7	4.1	0.871
LAD (%)	39.7	36.2	0.465
LCX (%)	33.2	27.2	0.180
RCA (%)	24.5	33.3	0.046
Severe calcification (%)	12.0	10.3	0.585
RCA ostium (%)	1.6	1.6	0.990
LCX ostium (%)	6.0	3.3	0.183
Main branch of bifurcation 2-stent (%)	8.2	4.5	0.121
Side branch of bifurcation 2-stent (%)	12.5	5.3	0.008
CTO (%)	12.0	21.0	0.014
IVUS (%)	98.4	99.2	0.442
Rotablator (%)	8.7	1.2	< 0.001
Number of stent	1.39 ± 0.68	1.46 ± 0.69	0.295
Diameter of stent (mm)	3.15 ± 0.50	3.25 ± 0.43	0.030
Length of stent (mm)	34.6 ± 20.7	40.4 ± 22.8	0.006
Maximum pressure (atm)	19.1 ± 3.1	18.0 ± 2.9	< 0.001
Direct stenting (%)	20.7	26.3	0.508
Pre-procedural MLD (mm)	0.90 ± 0.56	0.76 ± 0.51	0.008
Pre-procedural %DS	66.5 ± 19.3	71.7 ± 17.9	0.004
Post-procedural MLD (mm)	2.49 ± 0.49	2.51 ± 0.43	0.660
Post-procedural %DS	12.0 ± 10.5	10.9 ± 8.5	0.245
Post-procedural RD (mm)	2.84 ± 0.60	2.84 ± 0.53	1.000
Follow-up MLD (mm)	2.16 ± 0.81	1.95 ± 0.71	0.005
Follow-up %DS	28.0 ± 21.8	29.4 ± 20.3	0.499
Acute gain (mm)	1.58 ± 0.54	1.75 ± 0.55	0.001
Late loss (mm)	0.33 ± 0.72	0.56 ± 0.68	< 0.001
Interval for fu-CAG (day)	352 ± 80	346 ± 88	0.462
Binary restenosis (%)	13.6	17.3	0.298
Target lesion revascularization (%)	13.0	16.9	0.275

The baseline and the angiographic outcomes in the SES group (n = 184) and the PES group (n = 243) were shown. The definitions of the variables and estimated outcomes were described in the text.

from those in the PES group (17.3% and 16.9%, $p=0.298$ and 0.275, respectively).

DM-specific sub-analysis of the adjusted baseline and the primary endpoint

Table 5 shows the DM-specific sub-analysis of the adjusted baseline and the incidences of angiographic outcomes in the SES and PES groups ($n=148$ in each arm). The mean follow-up MLD (2.21 ± 0.82 mm), follow-up %DS (26.9±21.2), and the magnitude of late loss (0.33 ± 0.71 mm) in the SES group were significantly different from those in the PES group (1.97 ± 0.67 mm, 30.1 ± 19.5 , and 0.56 ± 0.66 mm; $p=0.012$, 0.034, and 0.002, respectively).

The incidences of binary restenosis (12.8%) and TLR (12.8%) in the SES group were not significantly different from those in the PES group (19.6% and 18.2%, $p=0.105$ and 0.182, respectively).

DM-specific sub-analysis of predictors of binary restenosis after baseline adjustment

In the baseline adjusted DM-specific angiographic follow-

up cohort of 296 patients, rotablator (OR: 11.4, 95% CI: 2.20-59.0, $p=0.004$), stent diameter (OR: 2.66, 95% CI: 1.09-6.46, $p=0.031$), and pre-procedural MLD (OR: 0.16, 95% CI: 0.027-0.94, $p=0.042$) were the significant predictors of the primary endpoint. PES use was not related to binary restenosis according to a logistic regression analysis (OR: 1.74, 95% CI: 0.90-3.37, $p=0.097$) (data not shown).

Discussion

The present study demonstrated that the mid-term lesion-based angiographic binary ISR ratio after PES (TAXUS Liberté stent) placement was not significantly different (a 13.6% increase) from that of SES (Cypher stent, the most standard evidence-based first-generation DES (11-16)) in 720 baseline-adjusted all-comer *de novo* native coronary stenosis lesions (Table 1-3). Our results reflected the daily practice environment by including various consistent predictors of ISR and TLR (Table 1, 4): >40% of lesions were in patients with DM (27), more than 10% of lesions displayed severe calcification (28), approximately 10-15% were ostial

Table 5. DM-specific Sub-analysis of Adjusted Baseline and the Incidence of the Primary Endpoint

(n)	SES 148	PES 148	p value
Age (yr)	66.0 ± 9.3	66.4 ± 9.3	0.756
Male (%)	75.0	76.4	0.777
Insulin use (%)	10.8	8.8	0.532
Hemodialysis (%)	2.0	0.7	0.317
LV dysfunction (%)	4.7	4.1	0.782
LAD (%)	37.8	44.6	0.239
LCX (%)	33.8	33.8	1.000
RCA (%)	25.0	20.3	0.274
Severe calcification (%)	8.1	8.8	0.835
RCA ostium (%)	2.0	0.7	0.317
LCX ostium (%)	5.4	3.4	0.366
Main branch of bifurcation 2-stent (%)	7.4	6.1	0.655
Side branch of bifurcation 2-stent (%)	8.8	6.8	0.491
CTO (%)	14.2	9.5	0.194
IVUS (%)	99.3	100	0.317
Rotablator (%)	4.1	2.7	0.527
Number of stent	1.38 ± 0.67	1.43 ± 0.60	0.277
Diameter of stent (mm)	3.19 ± 0.51	3.17 ± 0.39	0.742
Length of stent (mm)	34.9 ± 20.9	35.2 ± 17.3	0.475
Direct stenting (%)	25.0	32.4	0.172
Pre-procedural MLD (mm)	0.88 ± 0.57	0.92 ± 0.47	0.317
Pre-procedural %DS	68.0 ± 19.8	66.4 ± 15.5	0.442
Post-procedural MLD (mm)	2.53 ± 0.49	2.51 ± 0.42	0.906
Post-procedural %DS	12.0 ± 10.7	12.5 ± 8.5	0.535
Post-procedural RD (mm)	2.89 ± 0.60	2.93 ± 0.60	0.637
Follow-up MLD (mm)	2.21 ± 0.82	1.97 ± 0.67	0.012
Follow-up %DS	26.9 ± 21.2	30.1 ± 19.5	0.034
Acute gain (mm)	1.66 ± 0.53	1.61 ± 0.47	0.617
Late loss (mm)	0.33 ± 0.71	0.56 ± 0.66	0.002
Interval for fu-CAG (day)	351 ± 85	354 ± 85	0.833
Binary restenosis (%)	12.8	19.6	0.105
Target lesion revascularization (%)	12.8	18.2	0.182

The adjusted baseline and the incidence of the primary endpoint in the SES group and the PES group (n = 148 in each arm) were shown. The definitions of the variables and estimated outcomes were described in the text.

lesions (29), diffuse lesions were treated with long stents (mean length >33 mm) (30), and the bifurcation two-stent technique was used in approximately 7-8% of lesions (15, 29). Although the mean late loss after PES placement was significantly larger than that after SES placement, the larger late loss in the PES group did not translate into significantly higher ISR and TLR ratios compared to those of SES after the baseline adjustment (Table 2). This mid-term angiographic outcome of TAXUS Liberté stent compared to SES was the same with TAXUS Express, suggesting that the difference in the potency of suppression of neointima growth between sirolimus (Cypher stent) and paclitaxel (TAXUS stent) was not related to the present primary endpoint (3-5). This was also consistent with the observation that TLR did not increase within the threshold of the mean late luminal loss of 0.65 mm between SES and PES (31). The details of cases involving the use side branch of bifurcation two-stent technique and long stents should be further examined because the platform was quite different between SES (closed-cell based rigid platform) and PES (open-cell based), and the longest standard PES (38 mm)

was widely used in daily practice (Table 3). Recently, we reported that the TAXUS Liberté stent did not have a statistically beneficial impact on the mid-term (700-day) angiographic outcomes after placement in a daily practice environment compared to the TAXUS Express stent in a study of more than 1,000 patients with *de novo* coronary stenosis (21). Thus, although the more uniform neointimal distribution was brought about by the improved diffusion of paclitaxel to the vessel wall due to the thinner TAXUS Liberté stent struts compared to TAXUS Express (1, 2), the angiographic ISR rate of the TAXUS Liberté stent was not significantly different from the other first-generation DESs (Cypher BxV, TAXUS Express) after the baseline adjustment (11, 21). The difference in the long-term angiographic efficacy (late restenosis and late TLR) between SES and PES should be further examined in future (16).

We also conducted a DM-specific sub-analysis to assess the impact of DM on the angiographic ISR ratios in the PES and SES groups. This issue has been widely examined between SES and TAXUS Express, so it should also be investigated after TAXUS Liberté stent placement. With regard to

the controversy regarding the superiority of SES or PES for DM, (1) paclitaxel exerted different effects than rapamycin under experimental hyperglycemic and insulin-resistant conditions (32), (2) SES showed lower mid-term effectiveness than BMS in patients with DM (33), (3) DM was a consistent predictor of mid-term angiographic restenosis of SES (34), and (4) PES showed equivalent mid-term efficacy in patients with and without DM (35). The present study showed that the magnitude of mean late loss and the binary ISR (SES: 24.3% increase, PES: 67.5% increase, Tables 2, 5) ratio increased in both groups in the DM groups, although the present study did not identify any substantial interaction between the effects of DM and the stent type. The binary ISR and TLR ratios in the PES group were increased by 42-53% compared to those of SES, which is consistent with a previous large-scale study (repeat revascularization, SES: 14.8% versus PES: 17.8%, $p=0.36$) (36). However, the binary ISR ratio after PES placement was not significantly different from that of SES (Table 5). Therefore, this issue should be further evaluated in the long-term by investigating the late ISR and TLR (16) of SES and PES in patients with DM.

The present study has several limitations that should be considered when interpreting the results. First, this is a retrospective, non-randomized, single-center analysis. The selection of stents and the choice of treatment (PCI or CABG) were not randomized. However, we considered that the baseline adjustment of the characteristics of several hundred lesions in each arm was sufficient to allow comparison of the outcomes. Second, because this was a lesion-based study, patient-based severe cardiac events, an important issue in estimating the safety of novel stent, were not fully investigated. There were only small percentages of lesion-based severe cardiac events during a mean follow-up period of approximately 540-550 days, but it would be acceptable to compare these results with reports from Western countries about SES and prior TAXUS Express stents (3-5) because we included various consistent predictors of severe cardiac events and restenosis as discussed above (27-30). Third, the duration of dual anti-platelet therapy and the choice of thienopyridine agent (ticlopidine or clopidogrel) depended on the doctor's judgment. In addition, the number of patients who were non-compliant or discontinued dual anti-platelet therapy because of surgical and bleeding complications was not fully examined. However, there was no increase in the number of severe cardiac events. Fourth, we did not examine other predictors of cardiac events, such as the durations of medications, renal dysfunction, and anemia. Finally, the impact of stent fracture on the clinical and angiographic outcomes in the SES and PES group was not fully understood because it was difficult to define the stent fracture only by a visual angiographic estimation, particularly after bifurcation two-stent technique using SES (37) and due to the radiopacity of PES.

Conclusion

For *de novo* native coronary stenosis, the mid-term angiographic in-stent binary restenosis rate after placement of the second generation TAXUS Liberté was not significantly different from that of SES in a Japanese daily practice environment. In addition, the angiographic in-stent binary restenosis after TAXUS Liberté placement was not significantly different from that of SES in the DM-specific sub-analysis.

The authors state that they have no Conflict of Interest (COI).

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