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Safety and Efficacy of Biodegradable Polymer-biolimus-eluting Stents (BP-BES) Compared with Durable Polymer-everolimus-eluting Stents (DP-EES) in Patients Undergoing Complex Percutaneous Coronary Intervention

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ABSTRACT

Background and Objectives: There are no data comparing clinical outcomes of complex percutaneous coronary intervention (PCI) between biodegradable polymer-biolimus-eluting stents (BP-BES) and durable polymer-everolimus-eluting stents (DP-EES). We sought to evaluate the safety and efficacy of BP-BES compared with DP-EES in patients undergoing complex PCI.
Methods: Patients enrolled in the SMART-DESK registry were stratified into 2 categories based on the complexity of PCI. Complex PCI was defined as having at least one of the following features: unprotected left main lesion, ≥2 lesions treated, total stent length >40 mm, minimal stent diameter ≤2.5 mm, or bifurcation as target lesion. The primary outcome was target lesion failure (TLF), defined as a composite of cardiac death, target vessel-related myocardial infarction (TV-MI), or target lesion revascularization (TLR) at 2 years of follow-up.
Results: Of 1,999 patients, 1,145 (57.3%) underwent complex PCI: 521 patients were treated with BP-BES and 624 with DP-EES. In propensity-score matching analysis (481 pairs), the risks of TLF (3.8% vs. 5.2%, adjusted hazard ratio [HR], 0.578; 95% confidence interval [CI], 0.246–1.359; p=0.209), cardiac death (2.5% vs. 2.5%, adjusted HR, 0.787; 95% CI, 0.244–2.539; p=0.689), TV-MI (0.5% vs. 0.4%, adjusted HR, 1.128; 95% CI, 0.157–8.093; p=0.905), and TLR

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Conflict of Interest
The authors have no financial conflicts of interest.

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(1.1% vs. 2.9%, adjusted HR, 0.390; 95% CI, 0.139–1.095; p=0.074) did not differ between 2 stent groups after complex PCI.

Conclusions: Clinical outcomes of BP-BES were comparable to those of DP-EES at 2 years after complex PCI. Our data suggest that use of BP-BES is acceptable, even for complex PCI.

Keywords: Coronary artery disease; Percutaneous coronary intervention; Drug-eluting stents

INTRODUCTION

Lasting adverse clinical events such as very late stent thrombosis and late target lesion revascularization (TLR) occurring beyond 1 year have emerged as new complications after implantation of first-generation drug-eluting stents (DES).[1] Inflammatory reactions against the durable polymer (DP) coating on first-generation DES are considered at least partly responsible for these adverse late events. The second-generation DES using biocompatible DP or biodegradable polymer (BP) were designed to overcome the long-term adverse vascular reactions related to the bio-incompatible DP coated on the first-generation DESs. The use of biocompatible DP-everolimus-eluting stents (EES) or BP-biolimus-eluting stents (BES) was associated with superior safety and efficacy outcomes compared with the first-generation DES in a higher-risk population with complex features.[2)3] In addition, the BP-BES showed similar safety and efficacy profiles at 5 years compared with the gold standard DP-EES in an all-comers percutaneous coronary intervention (PCI) population.[4] However, there are no data comparing clinical outcomes of complex PCI between BP-BES and DP-EES. The likelihood of treatment failure directly correlates with the complexity of underlying coronary artery disease[5)6]; and lesion complexity may have a significant impact on the capacity of a stent-versus-stent trial to detect differences between the investigated devices.[7] The BP-BES has a relatively thick strut stainless steel platform (120 μm) and the unfavorable effect of thick struts may be clinically apparent, particularly in vessels with complex features. Therefore, investigating the relative efficacy and safety of BP-BES in these high-risk lesion subsets is of paramount clinical importance. The objectives of the current study were: 1) to evaluate the safety and efficacy of BP-BES compared with DP-EES in patients undergoing complex PCI; and 2) to characterize the effect of procedural complexity for the current generation of DES.

METHODS

Study population

This is a sub-analysis of the SMART-DESK (Real World Drug-Eluting Stenting Registry in Korea: BioMatrix Stents versus Xience stents by Smart Angioplasty Research Team) registry. The SMART-DESK registry is an unrestricted, prospective, multicenter, and observational registry. A total of 1,999 patients who underwent PCI with BP-BES (BioMatrix Flex; Biosensors Inc., Newport Beach, CA, USA) or DP-EES (Xience V or Prime; Abbott Vascular, Santa Clara, CA, USA) at the 16 major coronary intervention centers in Korea between July 2010 and June 2012 were enrolled.[8] We did not restrict the number, location, size, and length of lesions to be treated and registered all patients who were older than 20 and underwent PCI with BP-BES or DP-EES. Principal exclusion criteria were as follows: cardiogenic shock; allergy to study medication, metal alloys, or contrast media; planned surgery within 1 year of PCI unless the dual antiplatelet therapy could be maintained throughout the peri-operative period;

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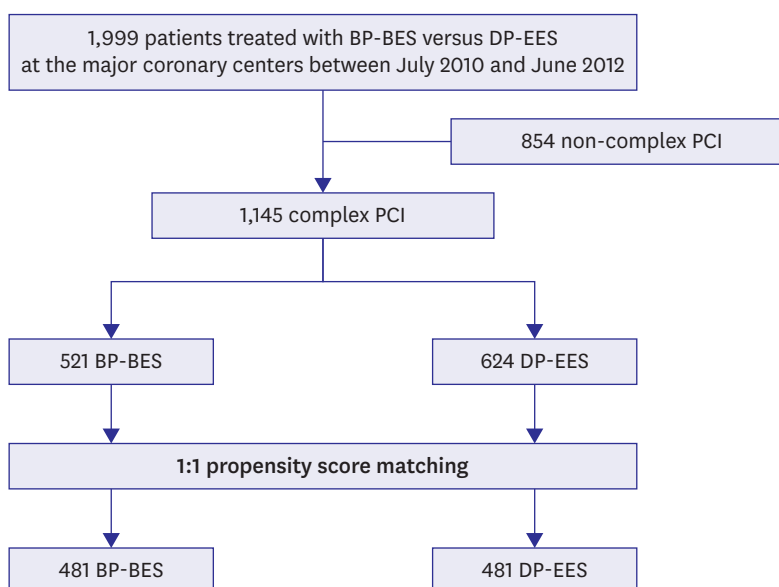
Figure 1. Study population.
BP-BES = biodegradable polymer biolimus-eluting stents; DP-EES = durable polymer everolimus-eluting stents; PCI = percutaneous coronary intervention.

pregnancy; non-cardiac comorbidities with life expectancy of <1 year or that might result in protocol noncompliance according to the investigator's medical judgment; and inability to give informed consent. In the present study, patients enrolled in the SMART-DESK registry were stratified into 2 categories on the basis of the complexity of PCI (**Figure 1**). Complex PCI was defined as the inclusion of one of the following characteristics: unprotected left main trunk as target vessel, ≥2 lesions treated (stenting), total stent length >40 mm, minimal stent diameter ≤2.5 mm, or bifurcation as target lesion. Outcomes in patients receiving BP-BES were compared with those of patients receiving DE-EES after complex PCI. We also performed an analysis of procedural and clinical outcomes according to PCI complexity.

Procedure and medical treatment

All interventions were performed according to current practice guideline. All patients received loading doses of aspirin (300 mg) and clopidogrel (300–600 mg) before PCI unless antiplatelet medications had previously been prescribed. During the study period, P2Y12 receptor inhibitors other than clopidogrel were not available in Korea. Unfractionated heparin was administered during PCI in order to achieve an activated clotting time of 250 seconds or longer throughout the procedure. Balloon pre-dilation and post-dilation, choice of BP-BES or DP-EES, use of glycoprotein IIb/IIIa inhibitors, and intravascular imaging were performed at the operators' discretion. After the procedure, all patients were recommended to receive optimal pharmacologic therapy including statins, beta-blockers, or renin-angiotensin system blockade following the current guidelines. Duration of dual antiplatelet therapy (aspirin 100 mg/day plus clopidogrel 75 mg/day) was also at the operator's discretion.

Data collection and follow-up

Clinical, angiographic, procedural, and outcome data were collected prospectively by independent research personnel using a web-based reporting system. Patients were followed up at 1, 6, and 12 months after their index procedure and annually thereafter. Additional information was obtained by telephone contact or medical records, if necessary. This study

was conducted according to the principles outlined in the Declaration of Helsinki. This study was approved by ethics committees at each participating institution and all patients provided written informed consent for access to an institutional registry (IRB approved by Samsung Medical Center, 2010-05-085).

Outcomes and definitions

The primary outcome was target lesion failure (TLF) at 2 years after the index procedure, defined as a composite of cardiac death, target vessel-related myocardial infarction (TV-MI), or TLR. The secondary outcome included the individual components of the composite primary outcomes and definite or probable stent thrombosis at various time points. All deaths were considered cardiac unless a definite non-cardiac cause could be established. Myocardial infarction (MI) was defined as elevated cardiac enzymes (troponin or myocardial band fraction of creatine kinase) greater than the upper limit of the normal value that occurred concurrent with ischemic symptoms or electrocardiography findings indicative of ischemia. TV-MI was defined as MI not clearly attributable to a non-target vessel. TLR was defined as revascularization within the stent or within a 5-mm border of stent deployment. Definite or probable stent thrombosis was assessed according to the definition of the Academic Research Consortium.[9]

Statistical analyses

Continuous variables were expressed as mean±standard deviation or median and interquartile range, and compared using an independent t-test or the Mann-Whitney U test. Categorical variables were summarized as numbers with percentages and compared using the χ^2 test or Fisher's exact test. Cumulative event rates were estimated using the Kaplan-Meier method and compared using the Log-rank test. Adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were derived from multiple imputation estimated Cox regressions adjusting for baseline variables associated with the clinical outcomes. For the DES-level analysis (BP-BES versus DP-EES), DP-EES was the reference category; for the PCI complexity analysis, non-complex PCI was the reference category. To match the patients for various clinical and angiographic characteristics, we used the propensity score matching method in a pairwise manner. The propensity score, which represents the probability of use of BP-BES, was estimated without regard to outcome using multiple logistic regression analysis including all the available covariates.[10] The pairs were matched using one-to-one individual matching between the BP-BES and DP-EES group. The matching was deemed satisfactory when the standardized mean differences were less than 10%. Within the propensity score matched population, the reduction in the risk of an adverse clinical outcome was compared using a clustered Cox regression model.[11] All tests were 2-tailed, and p values less than 0.05 were considered significant. R software version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analysis.

RESULTS

Baseline characteristics in the overall population

Of 1,999 patients included in the registry database, 1,145 (57.3%) underwent complex PCI. Median age was 65 years (interquartile range, 56–72 years) with 69.1% male patients and 31.8% with diabetes. More than half of the patients (56.5%) presented with acute coronary syndrome. The median follow-up was 748 days (interquartile range, 721–980 days).

BP-BES versus DP-EES in complex PCI

Of 1,145 patients undergoing complex PCI, 521 (45.5%) received BP-BES and 624 (54.5%) received DP-EES. Baseline characteristics according to stent type in patients undergoing complex PCI are reported in **Table 1**. Compared with the DP-EES group, the BP-BES group had a higher prevalence of hypertension, previous cerebrovascular accident, and current smoking. However, the incidence of dyslipidemia was lower in the BP-BES group than in the DP-EES group. In terms of clinical presentation, patients who were treated with BP-BES had less acute coronary syndrome than those who were treated with DP-EES. Multi-vessel disease was less common in the BP-BES group than in the DP-EES group. PCI for left anterior descending artery was performed less frequently in the BP-BES group than in the DP-EES group. Propensity score matching yielded 481 pairs with complex PCI, and baseline characteristics were well balanced between the 2 groups except for left ventricular ejection fraction on 2D-echocardiography, which showed a significant but small difference (57.0±12.9% for BP-BES versus 59.1±12.1% for DP-EES, p=0.022, **Table 2**).

The median follow-up was 751 days (interquartile range, 722–1,002 days). The administration of dual antiplatelet therapy was continued similarly between the 2 groups at 1 year (81.7%

Table 1. Baseline characteristics of overall population undergoing complex PCI

Overall population	All (n=1,145)	BP-BES (n=521)	DP-EES (n=624)	p value
Age	64.3±10.7	64.4±10.2	64.2±11.1	0.689
Sex (male)	772 (67.4)	365 (70.1)	407 (65.2)	0.082
Diabetes mellitus	396 (34.6)	179 (34.4)	217 (34.8)	0.882
Hypertension	683 (59.7)	329 (63.1)	354 (56.7)	0.028
Dyslipidemia	490 (42.8)	197 (37.8)	293 (47.0)	0.002
Prior cerebrovascular accident	67 (5.9)	42 (8.1)	25 (4.0)	0.004
Prior myocardial infarction	82 (7.2)	29 (5.6)	53 (8.5)	0.056
Prior PCI	147 (12.8)	61 (11.7)	86 (13.8)	0.296
Current smoker	298 (26.0)	151 (29.0)	147 (23.6)	0.037
Hemoglobin (g/dL)	13.3±2.5	13.4±2.5	13.3±2.5	0.815
Creatinine (mg/dL)	1.13±3.16	1.26±4.60	1.02±0.76	0.217
Total cholesterol (mg/dL)	176.5±44.2	175.7±41.6	177.2±46.1	0.596
LDL cholesterol (mg/dL)	110.0±41.8	107.8±36.5	111.8±45.7	0.134
Peak CK-MB (ng/mL)	24.4±68.3	25.1±66.3	23.9±70.0	0.758
Left ventricular ejection fraction (%)	57.9±12.5	57.2±12.8	58.5±12.2	0.124
Acute coronary syndrome as presentation	631 (55.1)	260 (49.9)	371 (59.5)	0.001
Extent of disease				<0.001
1 vessel disease	362 (31.6)	194 (37.2)	168 (26.9)	
2 vessel diseases	461 (40.3)	210 (40.3)	251 (40.2)	
3 vessel diseases	322 (28.1)	117 (22.5)	205 (32.9)	
Multi-vessel disease	783 (68.4)	327 (62.8)	456 (73.1)	<0.001
Bifurcation	455 (39.9)	198 (38.4)	257 (41.2)	0.348
Lesion type B2/C	829 (75.7)	352 (69.0)	477 (81.5)	<0.001
PCI				
Left main	50 (4.4)	21 (4.0)	29 (4.6)	0.611
Left anterior descending	717 (62.6)	304 (58.3)	413 (66.2)	0.006
Left circumflex	391 (34.1)	197 (37.8)	194 (31.1)	0.017
Right coronary artery	418 (36.5)	182 (34.9)	236 (37.8)	0.312
≥2 lesions treated	658 (57.5)	273 (52.4)	385 (61.7)	0.002
Stent (mm)				
Minimal diameter	2.84±0.40	2.83±0.41	2.86±0.40	0.280
Length, total	40.7±22.7	36.2±19.6	44.8±24.3	<0.001
Duration of dual antiplatelet therapy > 65 days (n=1,013)	816 (80.6)	367 (81.7)	449 (79.6)	0.395
Follow-up duration (days)	854±291	848±293	860±289	0.484

BP-BES = biodegradable polymer-biolimus-eluting stents; CK-MB = myocardial band fraction of creatine kinase; DP-EES = durable polymer-everolimus-eluting stents; LDL = low density lipoprotein; PCI = percutaneous coronary intervention.

Table 2. Baseline characteristics of propensity score matched population undergoing complex PCI

Propensity score matched population	All (n=962)	BP-BES (n=481)	DP-EES (n=481)	p value
Age	64.3±10.6	64.3±10.2	64.4±11.0	0.890
Sex (male)	663 (68.9)	334 (69.4)	329 (68.4)	0.721
Diabetes mellitus	329 (34.2)	166 (34.5)	163 (33.9)	0.844
Hypertension	591 (61.4)	299 (62.2)	292 (60.7)	0.630
Dyslipidemia	388 (40.3)	186 (38.7)	202 (42.0)	0.256
Prior cerebrovascular accident	54 (5.6)	30 (6.2)	24 (5.0)	0.377
Prior myocardial infarction	57 (5.9)	28 (5.8)	29 (6.0)	0.891
Prior PCI	114 (11.9)	59 (12.3)	55 (11.4)	0.687
Current smoker	266 (27.7)	137 (28.5)	129 (26.8)	0.545
Hemoglobin (g/dL)	13.6±1.9	13.6±1.8	13.6±1.9	0.744
Creatinine (mg/dL)	1.24±3.43	1.33±4.76	1.14±0.81	0.390
Total cholesterol (mg/dL)	175.4±43.3	176.7±41.9	174.2±44.6	0.378
Left ventricular ejection fraction (%)	58.1±12.5	57.0±12.9	59.1±12.1	0.022
Acute coronary syndrome as presentation	504 (52.4)	244 (50.7)	260 (54.1)	0.261
Multi-vessel disease	651 (67.7)	317 (65.9)	334 (69.4)	0.184
PCI of LAD	586 (60.9)	292 (60.7)	294 (61.1)	0.890
Follow-up duration (days)	856±287	850±288	862±287	0.540

BP-BES = biodegradable polymer-biolimus-eluting stents; DP-EES = durable polymer-everolimus-eluting stents; LAD = left anterior descending coronary artery; PCI = percutaneous coronary intervention.

versus 79.6%, p=0.395). The cumulative outcomes in patients undergoing complex PCI using BP-BES or DP-EES are summarized in **Table 3**. At 2 years, the primary outcome of TLF — a composite of cardiac death, TV-MI, or TLR — occurred in 15 patients in the BP-BES group and 29 patients in the DP-EES group. Cumulative rates for the primary outcome at 2 years were 3.5% for the BP-BES group and 5.1% for the DP-EES group (Log-rank p=0.121, **Supplementary Figure 1A**). There were no significant differences between the 2 treatments with respect to cardiac death (2.3% versus 2.4%, Log-rank p=0.703), TV-MI (0.4% versus 0.7%, Log-rank p=0.694), or definite or probable stent thrombosis (0.8% versus 0.5%, Log-rank p=0.708). However, TLR occurred less frequently in the BP-BES group compared with the DP-EES group (1.1% for BP-BES versus 2.7% for DP-EES, Log-rank p=0.044, **Supplementary Figure 1B**). After adjustment for several risk factors, the risks of TLF (adjusted HR, 0.607; 95% CI, 0.262–1.404; p=0.244), cardiac death (adjusted HR, 0.777; 95% CI, 0.258–2.337; p=0.653), TV-MI (adjusted HR, 0.665; 95% CI, 0.121–3.651; p=0.638), TLR (adjusted HR, 0.425; 95% CI, 0.154–1.177; p=0.100), or definite or probable stent

Table 3. Clinical outcomes of patients undergoing complex PCI

	All	BP-BES	DP-EES	p value[*]	Adjusted HR	95% CI	p value
Overall population							
No. of patients	1,145	521	624				
Cardiac death	24 (2.5)	10 (2.3)	14 (2.4)	0.703	0.777	0.258–2.337	0.653
TV-MI	6 (0.6)	2 (0.4)	4 (0.7)	0.694	0.665	0.121–3.651	0.638
TLR	21 (2.0)	5 (1.1)	16 (2.7)	0.044	0.425	0.154–1.177	0.100
ST	7 (0.7)	4 (0.8)	3 (0.5)	0.708	1.836	0.409–8.242	0.428
TLF	44 (4.7)	15 (3.5)	29 (5.1)	0.121	0.607	0.262–1.404	0.244
Propensity score matched population							
No. of patients	962	481	481				
Cardiac death	21 (2.6)	10 (2.5)	11 (2.5)	0.825	0.787	0.244–2.539	0.689
TV-MI	4 (0.5)	2 (0.5)	2 (0.4)	>0.99	1.128	0.157–8.093	0.905
TLR	18 (2.1)	5 (1.1)	13 (2.9)	0.057	0.390	0.139–1.095	0.074
ST	5 (0.6)	4 (0.9)	1 (0.2)	0.374	4.342	0.484–38.927	0.189
TLF	38 (4.8)	15 (3.8)	23 (5.2)	0.185	0.578	0.246–1.359	0.209

TLF: cardiac death, TV-MI, and TLR.
BP-BES = biodegradable polymer-biolimus-eluting stents; CI = confidence interval; DP-EES = durable polymer-everolimus-eluting stents; HR = hazard ratio; ST = stent thrombosis; TLF = target lesion failure; TLR = target lesion revascularization; TV-MI = target vessel-related myocardial infarction.
[*]Log-rank p value.

thrombosis (adjusted HR, 1.836; 95% CI, 0.409–8.242; p=0.428) did not differ significantly between stent groups (**Table 3**). Our main results remained after propensity score matched population analysis: the cumulative rate of TLF was not significantly different between the 2 groups (3.8% versus 5.2%, adjusted HR, 0.578; 95% CI, 0.246–1.359; p=0.209); and the individual risks of cardiac death (2.5% versus 2.5%, adjusted HR, 0.787; 95% CI, 0.244–2.539; p=0.689), TV-MI (0.5% versus 0.4%, adjusted HR, 1.128; 95% CI, 0.157–8.093; p=0.905), and TLR (1.1% versus 2.9%, adjusted HR, 0.390; 95% CI, 0.139–1.095; p=0.074), were also not significantly different (**Table 3** and **Figure 2**). In the subgroup analyses, safety and the magnitude and direction of the effect on clinical outcomes of BP-BES compared with DP-EES were uniform among patients undergoing complex PCI, without evidence of interaction for the studied outcomes (**Figure 3**). In a landmark analysis between 6 months and 2 years, there was a strong trend for a lower rate of adjusted TLR (0.8% vs 2.0%; adjusted HR, 0.375; 95% CI, 0.121–1.164; p=0.090) with BP-BES than DP-EES, but no difference in TLF (**Figure 4**).
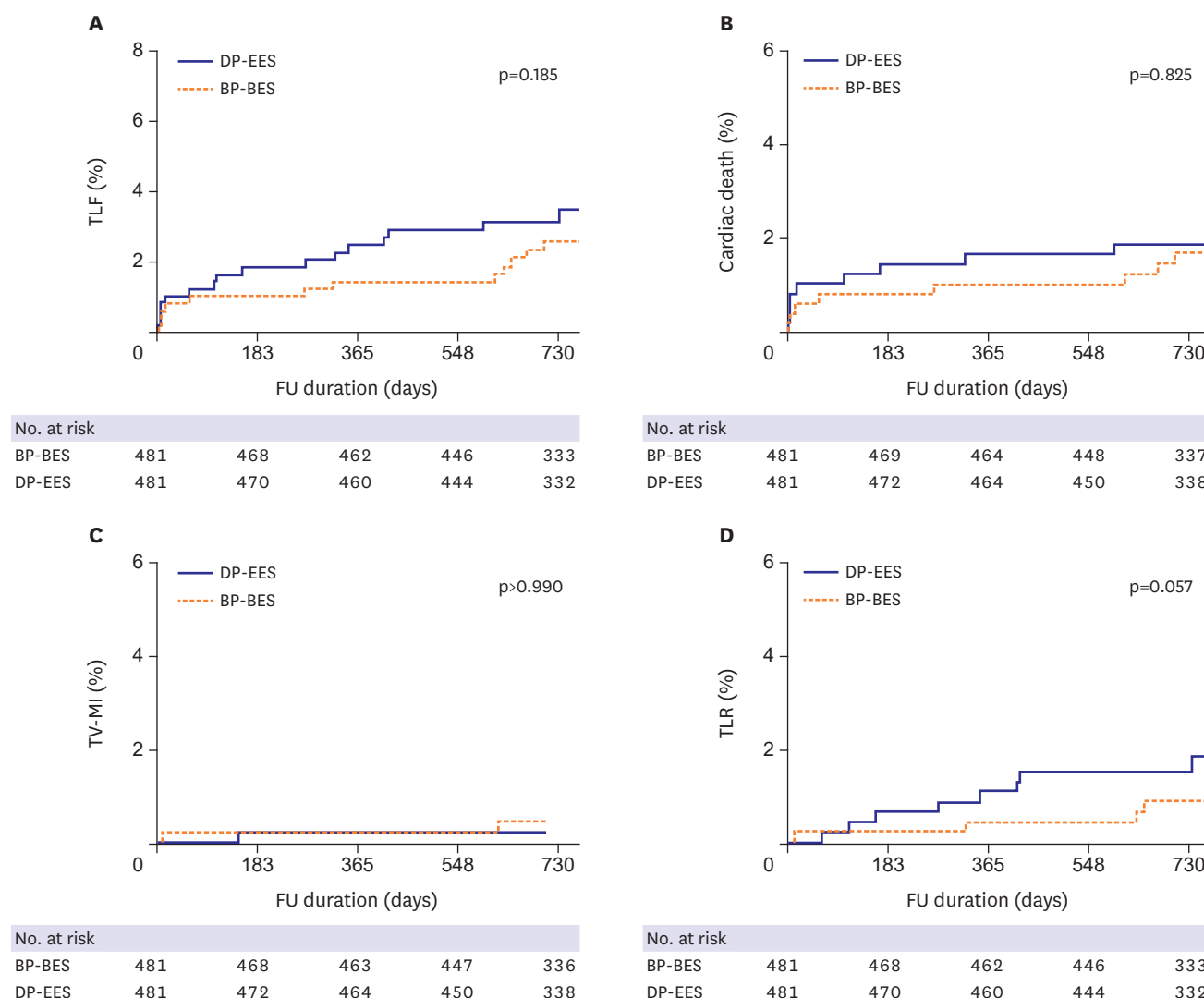

Figure 2. Kaplan-Meier curves for clinical outcomes in the propensity score matched population. TLF: cardiac death, TV-MI, and TLR.
BP-BES = biodegradable polymer-biolimus-eluting stents; DP-EES = durable polymer-everolimus-eluting stents; FU = follow-up; TLF = target lesion failure; TLR = target lesion revascularization; TV-MI = target vessel-related myocardial infarction.

Variable	Overall (n=1,145)	BP-BES (n=521)	DP-EES (n=624)	TLF	HR (95% CI)	p value	Interaction p
Sex							0.632
Female	373 (32.6)	5 (3.2)	9 (4.1)		0.721 (0.241–2.158)	0.559	
Male	772 (67.4)	10 (2.7)	20 (4.9)		0.554 (0.259–1.185)	0.128	
Age (years)							0.862
≤65	578 (50.5)	5 (1.8)	10 (3.3)		0.294 (0.195–1.670)	0.306	
>65	567 (49.5)	10 (4.0)	19 (6.0)		0.644 (0.299–1.387)	0.261	
DM							0.929
No	749 (65.4)	8 (2.3)	15 (3.7)		0.628 (0.266–1.481)	0.288	
Yes	396 (34.6)	7 (3.9)	14 (6.5)		0.680 (0.272–1.699)	0.409	
HTN							0.972
No	462 (40.3)	5 (2.6)	11 (4.1)		0.630 (0.219–1.814)	0.392	
Yes	683 (59.7)	10 (3.0)	18 (5.1)		0.615 (0.284–1.332)	0.218	
ACS as presentation							0.836
No	514 (44.9)	10 (3.8)	16 (6.3)		0.627 (0.284–1.382)	0.247	
Yes	631 (55.1)	5 (1.9)	16 (3.5)		0.549 (0.196–1.542)	0.255	
No. of complexity							0.878
1/5	520 (45.4)	6 (2.3)	10 (3.9)		0.564 (0.205–1.554)	0.268	
2/5	317 (27.7)	4 (2.9)	8 (4.4)		0.695 (0.209–2.310)	0.552	
3/5	237 (20.7)	4 (4.2)	9 (6.3)		0.659 (0.202–2.150)	0.490	
4/5	69 (6.0)	1 (3.7)	1 (2.4)		3.261 (0.179–59.365)	0.425	
5/5	2 (0.2)	-	1 (50.0)		-	-	

Favor BP-BES   1   Favor DP-EES

Figure 3. HRs for target lesion failure according to various subgroups in complex PCI. TLF: cardiac death, TV-MI, and TLR. Complexity was defined as left main PCI, bifurcation PCI, ≥2 lesions treated, total stent length >40 mm, or minimal stent diameter ≤2.5 mm.
ACS = acute coronary syndrome; BP-BES = biodegradable polymer-biolimus-eluting stents; CI = confidence interval; DM = diabetes mellitus; DP-EES = durable polymer-everolimus-eluting stents; HR = hazard ratio; HTN = hypertension; PCI = percutaneous coronary intervention; TLF = target lesion failure; TLR = target lesion revascularization; TV-MI = target vessel-related myocardial infarction.
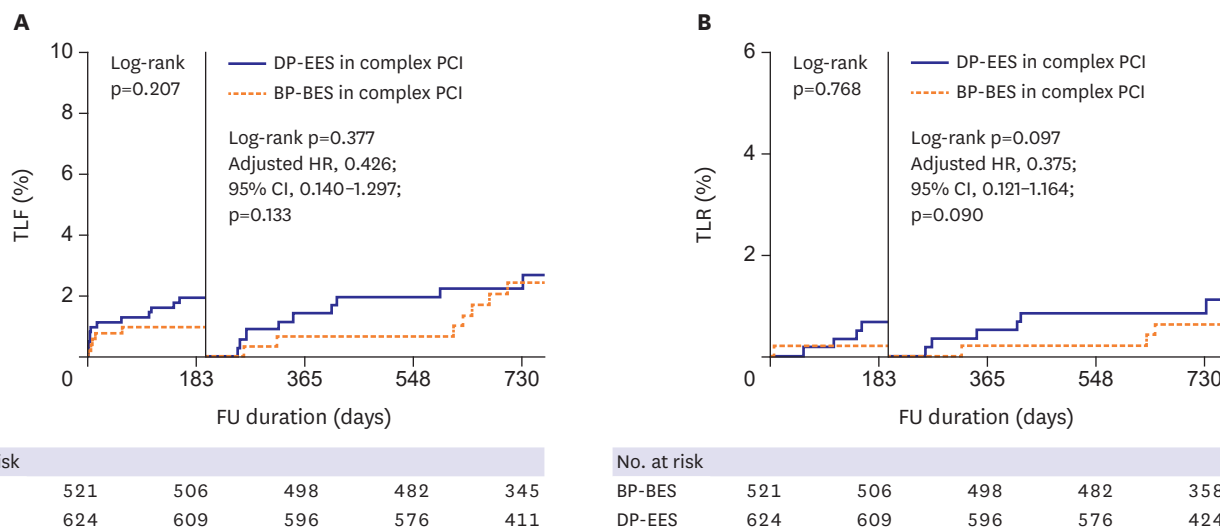

Figure 4. Kaplan-Meier curves for clinical outcomes of complex PCI in a landmark analysis between 6 months and 2 years. TLF: cardiac death, TV-MI, and TLR. BP-BES = biodegradable polymer-biolimus-eluting stents; CI = confidence interval; DP-EES = durable polymer-everolimus-eluting stents; FU = follow-up; HR = hazard ratio, PCI = percutaneous coronary intervention; TLF = target lesion failure; TLR = target lesion revascularization; TV-MI = target vessel-related myocardial infarction.

Complex PCI versus non-complex PCI

Among a total of 1,999 patients included in the registry database, 1,145 (57.3%) patients underwent complex PCI. Clinical, angiographic, and procedural characteristics according to PCI complexity are presented in **Supplementary Table 1**. The 2-year outcomes according to PCI complexity are reported in **Supplementary Table 2** and **Supplementary Figure 2**. Compared

with non-complex PCI, patients who underwent complex PCI showed a higher 2-year risk of TLR (adjusted HR, 3.209; 95% CI, 1.099–9.370; p=0.033). However, complex PCI was not independently associated with higher risks of TLF, cardiac death, or TV-MI. Similarly, no significant difference was observed between complex PCI and non-complex PCI with regard to definite or probable stent thrombosis (adjusted HR, 4.645; 95% CI, 0.568–38.014; p=0.152).

DISCUSSION

To the best of our knowledge, our investigation provides the first comparison of clinical outcomes for 2 second-generation DES designs, BP-BES versus DP-EES, in the treatment of complex coronary lesions from a multicenter real-world registry. The main findings of our study are: 1) compared with DP-EES, use of BP-BES was associated with similar safety and efficacy even in complex PCI; 2) the treatment effect was consistent after propensity score matching analysis and across various subgroups; and 3) procedural complexity was associated with increased long-term risk of TLR, but not with cardiac death, TV-MI, or stent thrombosis, after BP-BES and DP-EES implantations.

Although several randomized control trials comparing BP-BES with DP-EES showed that BP-BES have similar safety and efficacy profiles to DP-EES,[12)13)] recent network meta-analyses have suggested that BP-BES have an excess risk for stent thrombosis or MI compared with second-generation DP-EES.[14-16)] It was also reported that BP-BES might be associated with a higher risk of target vessel revascularization up to 3 years after stent deployment compared with DP-EES.[17)] The BP-BES is a second-generation DES that consists of a stainless steel platform with a relatively thick strut and an abluminal coating of BP (poly-lactic acid) eluting A9.[18)] The thickness of the stent strut may strongly influence the incidence of adverse events after stenting.[19)] Compared with thinner struts, thicker strut platforms have been shown to increase platelet aggregation and inflammatory cell adhesion.[20)] Especially in complex PCI, a thick stent strut may have an unfavorable influence on clinical outcomes relative to DES with thinner strut platforms. To date, however, there is a paucity of data evaluating clinical outcomes of BP-BES versus DP-EES for complex PCI. In the present study, although the BP-BES had a thicker stent strut than DP-EES (120 μm versus 89 μm) the safety and efficacy outcomes of the 2 DES were similar at 24 months after complex PCI. Optimal PCI techniques such as post-dilation and intracoronary imaging devices, and guideline-adherent medical therapies might mitigate the disadvantage of BP-BES in terms of strut thickness. In landmark analysis in the time window of 6 months to 2 years, patients undergoing PCI with BP-BES had a tendency to have lower risk of TLR than those undergoing PCI with DP-EES. This late benefit of BP-BES might be attributable to biocompatibility through polymer biodegradation, although the lower risk profile of the BP-BES group compared with the DP-EES group could be another explanation. It was reported that BP-BES showed a strong trend of lower inflammation score and had significantly lower fibrin and injury scores than DP-EES in histopathological assessments.[21)] Taken together, the possible drawbacks of the thicker strut in BP-BES, which is associated with a higher risk of adverse clinical outcome, might be offset by the advantages of its BP.

The likelihood of treatment failure directly correlates with the complexity of underlying coronary artery disease.[5)6)] PCI for complex lesions (e.g., long lesions, small vessel disease, bifurcations, or highly calcified lesions) is associated with a higher risk for under expansion, malapposition, incomplete lesion coverage, and the likelihood of a slower or nonuniform

pattern of endothelialization compared with non-complex PCI.[22] The present study showed that the TLR rate was higher among complex PCI than non-complex PCI: the risk of TLR after complex PCI was approximately 3.6 times higher than that of non-complex PCI at 2 years. However, the rates of hard outcomes such as cardiac death or TV-MI were similar between the 2 groups in the present study. More importantly, both BP-BES and DP-EES were associated with exceedingly low rates of definite or probable stent thrombosis at 2 years of follow-up, even in complex procedures (0.6%). These findings suggest that procedural complexity does not influence the safety profile of second-generation DES. This is consistent with previous analysis, which reported that for patients with unprotected left main disease, high anatomical complexity as defined by a SYNergy between PCI with TAXus and Cardiac Surgery (SYNTAX) score ≥33 is not predictive of cardiac death, MI, or stroke after PCI.[23]

Several important limitations of the present analysis should be noted. First, procedural complexity was defined according to the available variables in the dataset. Although these include most of the high-level complexity scenarios encountered in daily clinical practice, coronary anatomy lesion complexity characteristics were site-reported and not reviewed by an angiographic core laboratory, and the definition of complex PCI in this study was too arbitrary. Also, some important variables, such as SYNTAX score, Medina class of bifurcation, or use of rotational atherectomy, were not available, and therefore not included in the present definition. Second, the study design was non-randomized, observational, and post-hoc, which may have significantly affected results due to confounding factors. Although we performed propensity score matching analysis to adjust for potential confounding factors, we did not correct for all possible and unmeasured variables. Because of subgroup analysis nature of the present study design, this analysis was not designed to address the causal versus associative interrelation of complexity factors with adverse outcomes. Therefore, the results of the present study should be considered as hypothesis generating only, being a post hoc analysis of a trial. A third limitation is that clinical outcomes of BP-BES or DP-EES in the present study were relatively low, and the power of the present study was inadequate to draw any definite conclusion, especially for stent thrombosis. Despite the all-comer nature of the study population the event rates were very low, which may raise the question of under-reporting. One possible reason for the low event rates is that our study population may have tended to be at lower risk. For example, mean left ventricular ejection fraction on 2D-echocardiography was 57.9±12.5% in the present population. In addition, most of the participating patients were treated with prolonged (> 12 months) dual antiplatelet therapies, which may have contributed to the low incidence of adverse clinical outcomes. There also may be an ethnic or genetic protective factor, as trials done in East Asian populations have consistently reported lower event rates.[24] In addition, the present sub-analysis was not pre-specified, and numbers are modest, compromising particularly the robustness of individual endpoint analyses. Finally, the current report was limited to a 2-year follow-up after stent implantation. A median follow-up duration of 2 years may have been insufficient to assess long-term safety and efficacy after BP-BES implantation compared with DP-EES implantation. Therefore, a longer duration of patient assessment is warranted because potential benefits of the BP-BES are expected due to complete polymer degradation at long-term follow-up.

In conclusion, 2-year clinical outcomes of BP-BES are similar to those of the current golden standard DP-EES in patients undergoing complex PCI. Our data suggest that the results of previous randomized controlled trials of BP-BES versus DP-EES can be extended to cases of complex PCI, and that the use of BP-BES is adequate for a high-risk subset of patients.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Baseline clinical and angiographic characteristics in overall population

Click here to view

Supplementary Table 2
Clinical outcomes according to lesion complexity in overall population

Click here to view

Supplementary Figure 1
Kaplan-Meier curves for clinical outcomes between BP-BES versus DP-EES after complex PCI. TLF: cardiac death, TV-MI, and TLR.

Click here to view

Supplementary Figure 2
Kaplan-Meier curves for clinical outcomes of the overall population between complex versus non-complex PCI. TLF: cardiac death, TV-MI, and TLR.

Click here to view

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