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Effectiveness and Safety of Biodegradable Polymer-Coated Everolimus-Eluting Stent in Multivessel Coronary Artery Disease in Routine Clinical Practice: A Korean Multicenter, Prospective, and Observational Study

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ABSTRACT

Background: Multivessel coronary artery disease (CAD) poses a significant challenge in interventional cardiology due to its complexity and association with adverse clinical outcomes. Real-world data on the clinical performance of drug-eluting stents in Korean patients with multivessel disease (MVD) are limited. This study aimed to evaluate the efficacy and safety of the biodegradable polymer-coated everolimus-eluting stents (SYNERGY™, Boston Scientific Corporation, Natick, MA, USA) in treating patients with MVD in real-world clinical setting.

Methods: This multicenter, prospective, observational registry involved 22 hospitals in the Republic of Korea. Eligible patients presented with $\geq 70\%$ stenosis in at least two vessels and were amenable for receiving percutaneous coronary intervention (PCI). The primary endpoint was target lesion failure ([TLF], the composite of cardiac death; target vessel myocardial infarction [MI]; and target lesion revascularization [TLR]) at 1 year.

Results: Between August 2016 and September 2018, 542 patients were enrolled. The mean age of the patients was 66.2 ± 10.4 years, and most of them were male (73.7%). Diabetes mellitus (DM) was present in 40.8% of patients, while 68.2% had acute coronary syndrome (ACS). The 1-year TLF was in 2.1%, with incidences of cardiac death 0.9%, MI 0.3%, TLR 0.9%, and stent thrombosis 0.3%. Subgroup analysis revealed no significant differences in the primary endpoint between patients with or without ACS, and DM. In-stent restenosis (hazard ratio [HR], 11.20; 95% confidence interval [CI], 2.20–56.91) and total stent length (HR, 1.02; 95% CI, 1.01–1.03) were identified as independent predictors of TLF.

Conclusion: The 1-year TLF rate observed in our cohort (2.1%) was comparable to or lower than rates previously reported in studies evaluating drug-eluting stents in patients undergoing multivessel PCI. These results suggest that the biodegradable polymer-coated everolimus-eluting stents provide favorable clinical outcomes for this patient population in real-world clinical practice.

Keywords: Drug-Eluting Stent; Coronary Artery Disease; Multivessel Disease, Percutaneous Coronary Intervention

INTRODUCTION

Multivessel coronary artery disease (CAD) remains a significant challenge in interventional cardiology.¹⁻⁴ This condition, characterized by a higher ischemic burden, necessitates interventions on multiple vessels, thereby increasing procedural complexity. Consequently, multivessel disease (MVD) often leads to less favorable outcomes.¹⁻⁴ The complex nature of this disease highlights the need for more refined and effective interventional tools and techniques.

Biodegradable-polymer coated stents have been introduced to minimize the potential long-term complications associated with continuous polymer exposure to the vessel wall that

Author Contributions

Conceptualization: Park S, Kim W, Rha SW, Choi CU, Park CG. Data curation: Park S, Kim W, Choi BG, Mark S, Choi SY, Cha JA, Hyun SJ. Formal analysis: Park S, Kim W, Choi BG, Mark S, Choi SY, Cha JA, Hyun SJ. Investigation: Hahn JY, Park S, Lee HC, Cho JH, Bong JM, Hwang BH, Seo JB, Jeong YH, Choi KY, Lee SU, Cho YH, Hwang SH, Park K, Choi YJ, Her AY, Lee JB, Hwang JY, Choi JH. Methodology: Kim W, Rha SW. Supervision: Rha SW, Choi CU, Park CG. Writing - original draft: Park S, Kim W. Writing - review & editing: Park S, Rha SW.

are inherent to durable-polymer coated stents.^{5,6} Theoretically, by facilitating enhanced vascular healing, they were postulated to yield superior clinical outcomes. However, despite their innovative design, previous studies comparing biodegradable-polymer coated stents to durable-polymer coated stents have often reported analogous outcomes, indicating a need for more specific assessments.⁷⁻⁹

In percutaneous coronary intervention (PCI) for MVD, the use of more stents results in greater exposure of the vessel wall to metallic components and polymers. This increased exposure leads to the hypothesis that biodegradable-polymer coated stents, which reduce the long-term exposure of these materials to the vessel wall, might have more favorable outcomes. Nonetheless, current literature provides limited evidence supporting this hypothesis in the multivessel PCI.

To address this gap in the knowledge, we conducted a prospective multi-vessel SYNERGY registry study, designed to evaluate the effectiveness and safety of biodegradable polymer-coated everolimus-eluting stents (BP-EES) (SYNERGY™, Boston Scientific Corporation, Natick, MA, USA) in patients with multivessel CAD.

METHODS**Study design and population**

This study was designed as a prospective, observational, single-arm, multi-center registry. Multivessel CAD was defined as the presence of $\geq 70\%$ stenosis in two or more epicardial coronary arteries that require revascularization. Patients were eligible if they had the SYNERGY™ stent implanted at least two vessels for MVD. We excluded patients if other stent type of drug-eluting stents (DESs) were additionally implanted, had a life expectancy of less than a year, or were hemodynamically unstable. The inclusion and exclusion criteria for the study are detailed in the **Supplementary Table 1**.

Procedure and medications

PCI was conducted according to standard guidelines.^{10,11} Decisions regarding pre/post-dilatation before and after stent implantation, and the use of intravascular imaging, and the timing (immediate or staged) of PCI for MVD were at the discretion of the operator. Medications, including statins, were prescribed based on standard guidelines. Patients with chronic coronary disease were advised to receive dual antiplatelet treatment for 6 months, while those with acute coronary syndrome (ACS) were recommended to continue for 12 months.

Follow-up and data collection

All enrolled patients were subjected to follow-up evaluations at intervals of 1, 6, and 12 months post-procedure. These evaluations were conducted via phone or outpatient clinic visits. During these assessments, information regarding major adverse cardiovascular events (MACEs) was meticulously collected.

Outcome measures

The primary endpoint was target lesion failure (TLF) at 12 months, comprising cardiac death, target vessel myocardial infarction (MI), and ischemia driven-target lesion revascularization (TLR). The secondary outcomes included individual components of TLF, all-cause mortality,

target vessel revascularization (TVR), and stent thrombosis, defined according to the Academic Research Consortium criteria.¹²

All deaths in the study were presumed to be cardiovascular related unless evidence indicated a non-cardiovascular cause. TLR and TVR were deemed necessary if coronary angiography revealed a luminal narrowing of 70% or more, accompanied by either a history of ischemic symptoms or objective signs of ischemia from a functional study.

Statistical analysis

Continuous variables are expressed as means $\pm$ standard deviation and categorical variables as frequencies and percentages. For continuous variables, differences between the two groups were evaluated using the unpaired t test or Mann–Whitney rank test. For categorical variables, differences between the two groups were analyzed using the χ^2 or Fisher's exact test. Survival curves were plotted using the Kaplan–Meier method. Subgroup analysis was prespecified for patients with ACS and DM, as these represent clinically well-established high-risk populations. We compared each subgroup using a log-rank test without statistical adjustment. Univariable and multivariable analyses were performed to examine the predictors of TLF for each individual patient. Clinically important factors such as age $\geq$ 65 years, male, MI, previous PCI, hypertension (HTN), diabetes mellitus (DM), dyslipidemia, heart failure, dialysis, smoking, in-stent restenosis (ISR), chronic total occlusion (CTO), stent size $\leq$ 2.75 mm, total stent length, calcification, bifurcation, number of stents, use of imaging device, and staged PCI, were considered in the analysis. Lesion location variables specifically included left main and left anterior descending artery lesions, as these are known to have greater myocardial jeopardy areas, higher risks of cardiovascular events, and special considerations in current guidelines compared to other coronary artery lesions.^{10,11} For these adjustments, we employed a backward elimination procedure using the conditional likelihood ratio method. Specifically, a variable selection was followed in which all variables are initially entered into the model and then sequentially removed if their p-value exceeded 0.1. Cox proportional regression analysis was conducted to calculate hazard ratio (HR) for predictors of TLF. All statistical analyses were performed using SPSS (version 22.0; IBM Corp., Armonk, NY, USA) and the R software (version 4.1.1; R Foundation for Statistical Computing, Vienna, Austria). A two-sided *P* value $<$ 0.05 was considered significant.

Ethics statement

This study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki and received approval from the Institutional Review Board of Korea University Guro Hospital (2016GR0786). Written informed consent was obtained from all participants prior to their inclusion in the study.

RESULTS

Baseline characteristics

Between August 2016 and September 2018, data were collected from 542 patients across 22 Korean PCI capable hospitals where the SYNERGY™ coronary stent was available. Of these patients, 526 met the inclusion criteria. After excluding 5 participants who were lost to follow-up, a total of 521 patients were included in the final analysis (**Fig. 1**). Clinical follow-up was completed in 524 patients (99.6%) at 1 month, 522 patients (99.2%) at 6 months, and 521 patients (99.0%) at 12 months. **Table 1** demonstrates the baseline clinical, angiographic,

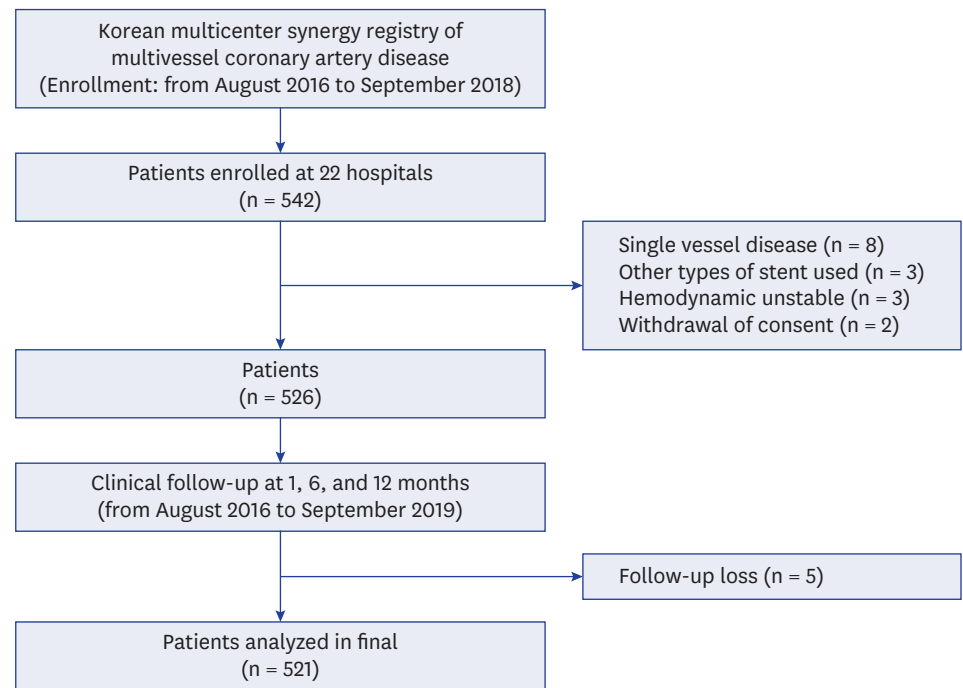


Fig. 1. Study flow chart.

Table 1. Baseline clinical, angiographic and procedural characteristics

Variables	Values
Baseline clinical characteristics (n = 521)	
Sex, male	384 (73.7)
Age, yr	66.2 ± 10.4
Blood pressure, mmHg	
Systolic	134.0 ± 21.0
Diastolic	78.0 ± 13.0
Heart rates, bpm	76.0 ± 15.0
LV ejection fraction, %	55.8 ± 12.3
Body mass index, kg/m ²	24.7 ± 3.2
Length of hospital stay, day (median, IQR)	4.0 (3.0–6.0)
Diagnosis	
MI	169 (32.4)
STEMI	62 (11.9)
NSTEMI	107 (20.5)
Unstable angina	187 (35.8)
Stable angina	113 (21.6)
Others	52 (9.9)
Risks of patients	
Hypertension	330 (63.3)
Diabetes	213 (40.8)
Dyslipidemia	278 (53.3)
Stroke	37 (7.1)
Heart failure ^a	27 (5.1)
Peripheral artery disease	20 (3.8)
Chronic renal insufficiency	41 (7.8)
Dialysis	14 (2.6)
Smoking	227 (43.5)
Currently	135 (25.9)
Alcohol drinking	223 (42.8)
Currently	141 (27.0)

(continued to the next page)

Table 1. (Continued) Baseline clinical, angiographic and procedural characteristics

Variables	Values
Family history of CAD	23 (4.4)
Prior MI	22 (4.2)
Prior PCI	45 (8.6)
Laboratory findings	
Total cholesterol, mg/dL	169 ± 58
Triglyceride, mg/dL	156 ± 96
HDL-C, mg/dL	41 ± 11
LDL-C, mg/dL	102 ± 41
Glucose, mg/dL	147 ± 67
Hb A1c, %	6.7 ± 1.5
Creatinine, mg/dL (median, IQR)	1.0 (0.8–1.2)
Angiographic and procedural characteristics	
Per lesion (n = 1,225)	
ACC/AHA lesion classification ≥ B2	923 (75.3)
Chronic total occlusions	132 (10.7)
Small vessel ≤ 2.50 mm	207 (16.9)
In-stent restenosis	31 (2.5)
Presence of thrombus	64 (5.2)
Heavy calcification	142 (11.6)
Bifurcation	165 (13.5)
Treated artery	
Left main	56 (4.5)
Left anterior descending	568 (46.3)
Left circumflex	323 (26.3)
Right coronary	264 (21.5)
Ramus	14 (1.4)
Stent procedure	
No of stents used	1.2 ± 0.5
Stent diameter, mm (max)	3.0 ± 0.4
Total stent length, mm	31.0 ± 15.9
Adjuvant balloon inflation	967 (78.9)
Stent balloon	151 (12.3)
Noncompliant balloon	812 (66.2)
Failed PCI procedure	31 (2.5)
Per patient (n = 521)	
Staged procedure	55 (10.6)
Imaging-guided PCI	195 (37.4)
No. disease artery	2.2 ± 0.4
Complications after PCI	
Dissection	8 (1.5)
No-reflow	3 (0.5)
Perforation	2 (0.3)
Stent malposition	1 (0.1)
Side branch loss	2 (0.3)
Acute thrombosis	1 (0.1)
Noncompliant balloon	812 (66.2)
Failed PCI procedure	31 (2.5)

Values are presented as means ± standard deviations, medians (interquartile ranges), or number (%).

LV = left ventricular, IQR = interquartile range, MI = myocardial infarction, STEMI = ST-elevation myocardial infarction, NSTEMI = non-ST-elevation myocardial infarction, CAD = coronary artery disease, PCI = percutaneous coronary intervention, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, Hb = hemoglobin, ACC/AHA = American College of Cardiology/American Heart Association.

^aHeart failure is defined as an LV ejection fraction of 40% or less.

and procedural characteristics of the study population. The majority of the patients were male (384; 73.7%) with a mean age of 66.2 ± 10.4 years. HTN was present in 63.3% of patients, and 40.8% had DM. Clinical presentations included ST elevation MI in 11.9%, Non-ST elevation MI in 20.5%, unstable angina in 35.8%, and stable angina in 21.6%. The median duration of hospital stay was 4 days (interquartile range, 3–6 days). Staged PCI was

performed in 55 patients (10.6%), of whom 30 had AMI, 20 had CTO, 13 had bifurcation lesion, 9 had severe calcification, and 22 had three-vessel disease.

Enrolled patients had a mean of 2.23 ± 0.43 coronary arteries involved. In total, 1,225 lesions were treated. On average, each patient received 2.57 ± 0.89 stents, with an average stent diameter of 3.19 ± 0.46 mm and an average length of 68.9 ± 31.5 mm. The overall procedural success rate was 94.1%. Intravascular ultrasound or optical coherence tomography assessment was used in less than half of the patients (37.4%). Post-PCI complications included dissection (1.5%), no-reflow phenomenon (0.5%), perforation (0.3%), stent malposition (0.1%), loss of side branch (0.3%), and acute stent thrombosis (0.1%).

Medications at discharge are detailed in **Table 2**. Aspirin was prescribed to 97.1% of patients. The most commonly used P2Y12 receptor inhibitor was clopidogrel, prescribed to 74.0% of patients, followed by ticagrelor at 18.6%, with prasugrel being the least prescribed at 4.7%. Statin usage was at 88.6%. Over 80% of patients were prescribed P2Y12 inhibitors at the 12-month follow-up (**Supplementary Fig. 1**).

Clinical follow-up and outcomes

Angiographic follow-up was performed on 48 patients (9.2%), with binary stenosis observed in only 0.3% (2 out of 48 patients) of these cases. Clinical outcomes at 1, 6, and 12 months are presented in **Table 3**. Acute and sub-acute stent thrombosis occurred in 2 patients (0.3%), with both cases being MI-related. At the 12-month clinical follow-up (**Fig. 2**), TLF occurred in 11 patients (2.1%), including 5 cardiac deaths (0.9%), 2 instances of target vessel-related MI (0.3%), and 5 cases of TLR (0.9%).

Subgroup analysis in patients with ACS and DM

The results for the primary and secondary endpoints in the subgroups of patients according to comorbidities of ACS and DM are presented in **Table 4**. No significant differences in the risks of TLF, MACE, total death, cardiac death, MI, and repeat revascularization were observed between patients with and without ACS. Similarly, the subgroup analysis based on DM status revealed no significant difference in the risks for primary and secondary endpoints, although a trend was observed towards a higher incidence of cardiac death in patients with DM (1.9% vs. 0.3%, $P = 0.076$). Subgroup analyses for other clinical and lesion characteristics are presented in the **Supplementary Table 2**.

Table 2. Discharge medications

Variables	Values (N = 521)
Aspirin	506 (97.1)
Clopidogrel	386 (74.0)
Cilostazol	48 (9.2)
Ticagrelor	97 (18.6)
Prasugrel	25 (4.7)
Warfarin	3 (0.5)
NOAC	8 (1.5)
Beta blocker	61 (11.7)
Calcium channel blockers	128 (24.5)
Renin-angiotensin system inhibitors	278 (53.3)
Angiotensin-converting enzyme	123 (23.6)
Angiotensin receptor blockers	155 (29.7)
Diuretics	81 (15.5)
Statin	462 (88.6)

Values are presented as number (%).

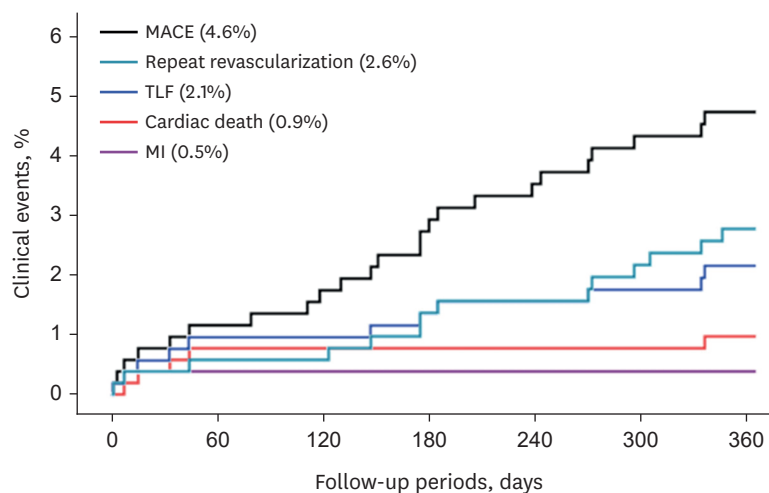
NOAC = non-vitamin K antagonist oral anticoagulants.

Table 3. Clinical outcomes

Outcomes	1 mon	6 mon	12 mon
Total death	3 (0.5)	11 (2.1)	15 (2.8)
Cardiac death	2 (0.3)	4 (0.7)	5 (0.9)
MI	2 (0.3)	2 (0.3)	2 (0.3)
STEMI	2 (0.3)	2 (0.3)	2 (0.3)
Repeat revascularization	2 (0.3)	7 (1.3)	14 (2.6)
TLR	2 (0.3)	4 (0.7)	5 (0.9)
TVR	2 (0.3)	5 (0.9)	8 (1.5)
Non-TVR	0 (0.0)	3 (0.5)	8 (1.5)
Stent thrombosis	2 (0.3)	2 (0.3)	2 (0.3)
Acute	1 (0.1)	1 (0.1)	1 (0.1)
Sub-acute	1 (0.1)	1 (0.1)	1 (0.1)
MACE	4 (0.7)	15 (2.8)	24 (4.6)
TLF	3 (0.5)	7 (1.3)	11 (2.1)

Values are presented as number (%).

MI = myocardial infarction, STEMI = ST-elevation myocardial infarction, TLR = target lesion revascularization, TVR = target vessel revascularization, MACE = major adverse cardiac events, defined as the composite of total death, myocardial infarction, and repeat revascularization, TLF = target lesion failure, defined as the composite of cardiac death, target vessel myocardial infarction, and ischemia driven-target lesion revascularization.



No. of subjects at risk							
MACE	520	514	511	504	501	497	493
Repeat revascularization	520	514	511	505	501	497	493
TLF	520	514	511	505	501	497	493
Cardiac death	520	516	513	510	508	507	506
MI	520	515	512	509	507	506	504

Fig. 2. Kaplan-Meier curves of clinical events. Cumulative event rates of MACE (black line), repeat revascularization (green line), TLF (blue line), cardiac death (red line), and MI (purple line). MACE = major adverse cardiac events, defined as the composite of total death, myocardial infarction, and repeat revascularization, MI = myocardial infarction, TLF = target lesion failure, defined as the composite of cardiac death, target vessel myocardial infarction, and ischemia driven-target lesion revascularization.

Predictors of TLF at 1 year for patients with MVD

The results of the univariable and multivariable analyses for the primary endpoint are presented in **Table 5**. ISR (HR, 9.80; 95% confidence interval [CI], 1.98–48.35) and stent length (HR, 1.02; 95% CI, 1.01–1.03) were identified as independent predictors of TLF. However, in the multivariable analysis, left main disease and number of stents were not identified as independent predictors in this study.

Table 4. Subgroup analysis of patients with acute coronary syndrome and diabetes mellitus

Variables	ACS			DM		
	Yes (n = 356)	No (n = 165)	Log rank P	Yes (n = 213)	No (n = 308)	Log rank P
TLF	6 (1.7)	5 (3.0)	0.319	7 (3.3)	4 (1.3)	0.127
MACE	17 (4.8)	7 (4.2)	0.813	10 (4.7)	14 (4.5)	0.946
Total death	10 (2.8)	5 (3.0)	0.981	6 (2.8)	9 (2.9)	0.942
Cardiac death	2 (0.6)	3 (1.8)	0.172	4 (1.9)	1 (0.3)	0.076
MI	1 (0.3)	1 (0.6)	0.579	0 (0)	2 (0.6)	0.239
Repeat revascularization	9 (2.5)	5 (3.0)	0.729	6 (2.8)	8 (2.6)	0.886
TLR	3 (0.8)	2 (1.2)	0.676	3 (1.4)	2 (0.6)	0.388
TVR	6 (1.7)	2 (1.2)	0.700	4 (1.9)	4 (1.3)	0.605

Values are presented as number (%).

ACS = acute coronary syndrome, DM = diabetes mellitus, TLF = target lesion failure, defined as the composite of cardiac death, target vessel myocardial infarction, and ischemia driven-target lesion revascularization, MACE = major adverse cardiac events, defined as the composite of total death, myocardial infarction, and repeat revascularization, MI = myocardial infarction, TLR = target lesion revascularization, TVR = target vessel revascularization.

Table 5. Predictors of target lesion failure for patients with multivessel disease

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age (≥ 65 yr)	1.103	0.337–3.613	0.872			
Male	1.041	0.276–3.926	0.962			
MI	1.771	0.540–5.820	0.345			
Previous PCI	2.411	0.521–11.161	0.260			
HTN	1.543	0.409–5.815	0.522			
DM	2.520	0.738–8.608	0.140			
Dyslipidemia	0.722	0.220–2.365	0.590			
Heart failure	1.852	0.237–14.470	0.557			
Dialysis	3.686	0.472–28.798	0.214			
Smoking	1.613	0.492–5.285	0.430			
Left main	4.497	1.316–15.363	0.016			
LAD	1.997	0.243–14.817	0.542			
ISR	6.269	1.354–29.024	0.019	9.795	1.984–48.347	0.005
Chronic total occlusion	1.502	0.399–5.663	0.548			
Stent size ≤ 2.75 mm	1.574	0.461–5.378	0.469			
Total stent length (increased by 1 mm)	1.019	1.008–1.030	0.001	1.021	1.009–1.032	< 0.001
Calcification	1.986	0.527–7.486	0.311			
Bifurcation	0.720	0.156–3.333	0.674			
Number of stent (increased by one)	1.669	1.267–2.199	< 0.001			
Imaging-guided PCI	0.950	0.278–3.245	0.935			
Staged PCI	0.308	0.082–1.161	0.082			

The Cox proportional hazards regression analysis was performed to calculate hazard ratios presented in this table. HR = hazard ratio, CI = confidence interval, MI = myocardial infarction, PCI = percutaneous coronary intervention, HTN = hypertension, DM = diabetes mellitus, LAD = left anterior descending, ISR = in-stent restenosis.

Clinical outcomes according to coronary artery lesion combinations

Subgroup analysis based on the combination of lesion locations showed differences in clinical outcomes at 1 year (Table 6). Patients with left main disease and those with three-vessel disease had higher rates of TLF (6.5% and 5.6%, respectively), compared with other lesion combinations (Table 6). Similarly, cardiac death rates were numerically higher in patients with three-vessel disease (2.8%) and left main involvement (1.6%). In contrast, no event of TLF occurred among patients with disease involving only the left circumflex artery (LCX) and right coronary artery (RCA). Kaplan-Meier analysis demonstrated that specific combination of lesion location influenced clinical outcomes (Supplementary Fig. 2).

Table 6. Clinical outcomes according to disease artery combination at 1 year

Disease artery combination	No. (%)	TLF			Cardiac death			MI	TLR
		No. (%)	HR (95% CI)	P value	No. (%)	HR (95% CI)	P value		
Two-vessel disease ^a									
LAD and LCX	161 (30.9)	1 (0.6)	-	-	1 (0.6)			0 (0)	0 (0)
LAD and RCA	168 (32.2)	3 (1.8)	2.887 (0.300–27.757)	0.358	1 (0.6)	0.960 (0.060–15.352)	0.977	0 (0)	2 (1.2)
LCX and RCA	75 (14.4)	0 (0)	^b	^b	0 (0)	^b	^b	0 (0)	0 (0)
Three-vessel disease	107 (20.5)	6 (5.6)	9.242 (1.113–76.771)	0.040	3 (2.8)	4.543 (0.473–43.672)	0.190	2 (1.9)	2 (1.9)
Left main disease	62 (11.9)	4 (6.5)	9.478 (1.059–84.812)	0.044	1 (1.6)	2.314 (0.145–36.998)	0.553	2 (3.2)	2 (3.2)

Values are presented as number (%).

TLF = target lesion failure, defined as the composite of cardiac death, target vessel myocardial infarction, and ischemia driven-target lesion revascularization, HR = hazard ratio, CI = confidence interval, MI = myocardial infarction, TLR = target lesion revascularization.

^aReference is LAD and LCX group. The Cox proportional hazards regression analysis was performed to calculate hazard ratios presented in this table; ^bZero events.

DISCUSSION

The main finding of our study is that the incidence of clinical event rate was remarkably low in patients treated with the BP-EES SYNERGY™ stent for MVD. At the 12-month follow-up, TLF was observed in 11 patients (2.1%), with cardiac death, target vessel MI, and TLR occurring in 5 patients (0.9%), 2 patients (0.3%), and 5 patients (0.9%), respectively. Stent thrombosis was noted in only 2 patients (0.3%) within the first month. Secondly, these low clinical event rates were consistent regardless of the presence of ACS and DM. Third, ISR and stent length were independent predictors for TLF following BP-EES implantation in patients with MVD. Fourth, clinical outcomes differed according to lesion location combinations, with events predominantly observed in patients with left main or three-vessel disease, whereas no clinical events occurred in patients with lesions only involving LCX and RCA.

Although complete revascularization for patients with MVD is believed to improve clinical outcomes, the prognosis of MVD remains challenging.^{13–16} For decades, the optimal revascularization strategy for patients with MVD has been a subject of controversy. Early evidence reported a clear decrease in future clinical events with coronary artery bypass grafting (CABG) surgery over PCI for patients with MVD.^{17,18} The increase in stent length and number correlates with a higher risk of ISR and stent thrombosis, making patients with MVD inevitably more susceptible to stent-related adverse events.^{19–21} Thus, in treating MVD, the current evidence suggests that PCI does not yet outperform CABG. Particularly, in a large-scale randomized trial conducted a decade ago, CABG has been shown to be superior to PCI in patients with both MVD and DM.²² However, since that time, there has been advancements in both the procedure of PCI and medical treatment, which have enabled PCI rapidly emerge as a safe and effective option for these patients. Among the patients with MVD, who achieved complete revascularization, there was no differences in outcomes between PCI and CABG over a follow-up period of 10 years.²³ Patients with MVD and relatively low anatomical complexity would have favorable outcomes when treated with PCI strategy.²⁴

Second generation-DES is well known to have lower rates of TLR and stent thrombosis compared to first-generation DES.^{25,26} Consequently, the use of second-generation DES has become the standard of treatment for PCI in real-world clinical settings. Recent-generation DES differ from earlier generation DES in their design, thinner struts, different polymers, and different drugs delivered.²⁷ Although the efficacy and safety of newer generation DES have been established in numerous clinical trials, patients with MVD were frequently excluded from these studies. Similarly, in all-comer stent registries, there is a lack of evidence

regarding the clinical profile according to use of each stent type in second-generation DES era for this specific patient subset. This is mainly attributed to the challenges of extrapolating data from enrolling selective patients with MVD.

A previous study dedicated to patients with MVD reported that the 1-year risk of MACE was 9.2% in the XIENCE (everolimus-eluting stent) single-arm registry.²⁸ In a subgroup analysis of patients with MVD in the e-Ultimaster registry, patients who achieved complete revascularization had a 1-year risk of TLF 3.3%, while those who did not achieved complete revascularization had a risk of 4.4%. These patients were exclusively treated with ULTIMASTER (sirolimus-eluting stent).¹⁶ In current study, the risk of TLF at 1 year is extremely low (2.1%) compared to that in previous studies. The favorable result mentioned above could be attributed to several key features of the BS-EES. Firstly, these stents have a low profile with a strut thickness of 74 μ m. Such thin-strut stents have been linked to a reduction in rates of restenosis.^{29,30} Furthermore, the stents with an abluminal bioabsorbable polymer, effectively paired with the potent anti-proliferative agent, everolimus. Additionally, the advantage of a biodegradable polymer stent is that the polymer is fully absorbed after completion of drug release. The SYNERGY™ stent is uniquely designed for concurrent drug elution and polymer absorption. The polymer is absorbed shortly after the completion of drug elution, which occurs at 3 months. Such a feature promotes early vascular healing and eliminates prolonged exposure to the polymer.³¹

Two cases of stent thrombosis occurred within the first month. All instances of MI were attributed to stent thrombosis. In addition, most cardiac death (4 of 5 cases) occurred within the second month after stent implantation, with one exception. Fatal cases, such as stent thrombosis, MI, or cardiac death, which are considered to be associated with the BP-EES, did not appear to occur 3–4 months after PCI. This trend might be related to the polymer resorption characteristics of the BP-EES. On the other hand, subgroup analysis indicated a low risk of clinical event in patients with ACS or DM. However, caution is warranted when interpreting these subgroup analyses, given that the limited number of patients in each subgroup may constrain the statistical power needed to detect differences.

Among the patients who experienced TLF, ISR and total stent length were significant predictors in both univariable and multivariable analysis. The presence of left main disease was a significant predictor in the univariable analysis. Other clinical factors such as age, gender, diagnosis of MI, previous history of PCI, HTN, DM, dyslipidemia, and heart failure did not demonstrate a significant association with TLF. This suggests that angiographic complexity is an important factor in clinical outcomes for the patient population with MVD, although caution is required when interpreting these findings owing to the low event rate observed in our study. Our findings also indicate an association between the combination of lesion locations and clinical outcomes. Patients with left main involvement or three-vessel disease experienced higher rates of adverse events, suggesting greater myocardial jeopardy in these patient subsets. In contrast, we observed no adverse events among the patients with disease limited to LCX and RCA, suggesting that this group may represent a lower-risk profile. Therefore, the lesion location combinations would be relevant consideration in clinical practice for comprehensive risk assessment, optimized revascularization planning, patient management, and counseling in multivessel CAD.

The present study demonstrated favorable clinical outcomes, with a low 1-year TLF rate, despite a relatively modest imaging-guided PCI rate (37%). This lower rate would

be attributed to observational, real-world design of our registry, in which the use of intracoronary imaging was entirely at the discretion of the physician. However, recently published data suggest that intravascular imaging-guided PCI could further improve clinical outcomes, particularly in patients with complex coronary anatomy, such as MVD. The RENOVATE-COMPLEX-PCI Study (Randomized Controlled Trial of IVI Guidance versus Angiography-Guidance on Clinical Outcomes after Complex Percutaneous Coronary Intervention) showed a 34% lower risk of the primary endpoint (a composite of cardiac death, MI, and TVR) at 2.1 years in the intravascular imaging group compared to the angiography guidance group.³² Similarly, the OCCUPI (optical coherence tomography-guided versus angiography-guided PCI for patients with complex lesions) trial demonstrated a 38% lower risk of MACE at 1 year with optical coherence tomography (OCT)-guided PCI.³³ In addition, the prospective Japanese registry including exclusively patients who undergoing multivessel PCI including a target lesion in LAD reported a 10.3% incidence of major adverse cardiac and cerebrovascular events at 1 year, which is a numerically lower than predefined CABG performance.³⁴ Indeed, our subgroup analysis revealed that most adverse events occurred in patients with left main involvement or three-vessel disease, who might particularly benefit from intravascular imaging guidance, suggesting potential for further outcome improvement.

While current guidelines for coronary revascularization recommend CABG as a class I indication for patients with MVD, ongoing advancement in stent technology promotes research on the use of current stent use in this patient group. The 2018 European Society of Cardiology guideline have updated the recommendation for PCI, elevating it from a class IIa to a class I treatment (level of evidence A) for those with MVD and SYNTAX (SYNergy between percutaneous intervention with TAXus and cardiac surgery) score of 22 or lower.^{35,36} However, regarding stent type, there is still insufficient evidence about the efficacy and safety of PCI in treating MVD. Therefore, this study could inform physicians in guiding decision-making for MVD revascularization strategy in modern DES era. The everolimus-eluting stents (BP-EES) SYNERGY™ stent could be a reasonable option for patients with MVD and relatively low anatomical complexity. Future research is required for a head-to-head comparison of the different stent in these patients.

The strength of this study is its focus on evaluating the clinical outcomes of using exclusive BP-EES in selected patients with MVD in a real-world clinical setting. This includes patients with ACS, DM, and angiographic risk factors such as CTO, ISR or left main artery disease. The study was conducted as an all-comer analysis, without significant exclusion except for cases of cardiogenic shock. Although our study provides valuable insights, it has several limitations. First, this study has typical constraints of an observational analysis despite having acceptable number of patients with a high follow-up rate. Adverse clinical events may have been underreported, which is a prevalent issue in registry studies. Additionally, our database did not contain specific data on functional testing or the use of atherectomy devices. Furthermore, we were unable to use the SYNTAX score for assessing angiographic complexity owing to the unavailability of this data. Second, the absence of a direct comparison with a durable polymer DES cohort restricts the comprehensive interpretation of our findings. Thus, we could not ascertain the superiority of BP-EES or any specific type of stent to other counterparts. Third, our study did not include peri-procedural MI, which may lead to an underestimation of the risks associated with this event compared to previous studies. Fourth, this analysis was constrained to a 1-year follow-up, thus precluding the assessment of long-term outcomes. Fifth, the data were exclusively sourced from Korean

centers, limiting the generalizability to other ethnic populations. Sixth, one limitation of our subgroup analyses was the low event rates and limited sample sizes across all analyzed subgroups, precluding precise estimation of HRs or definitive conclusions. Thus, all subgroup results should be interpreted cautiously and validated through larger-scale studies. Finally, the use of intravascular imaging device was relatively low (37%) in this study. The use of imaging guided PCI in patients with MVD could have potentially modified the risk of cardiovascular events associated with multivessel PCI.³²

In conclusion, the data from real-world registry showed the favorable outcomes for patient population with MVD following multivessel PCI using biodegradable-polymer coated everolimus-eluting stents (BP-EES). The study reported a remarkably low 1-year incidence of TLF. In addition, the occurrence of MACE, cardiac death, MI, stent thrombosis, and repeat revascularization was minimal. This outstanding performance was consistent across patients with ACS and DM.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Inclusion and exclusion criteria

Supplementary Table 2

Subgroup analysis of target lesion failure at 1 year

Supplementary Fig. 1

Medications at discharge and at 1, 6, and 12 months.

Supplementary Fig. 2

Kaplan-Meier curves for target lesion failure according to disease artery combination. Kaplan-Meier curve for patients with left main disease was depicted separately (dashed line) due to overlapping classification.

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