Observational Study

Medicine®

OPEN

Three-year major clinical outcomes of phosphorylcholine polymer- vs biolinx polymer-zotarolimus-eluting stents

A propensity score matching study

Yong Hoon Kim, MD, PhD[a], Ae-Young Her, MD, PhD[a], Seung-Woon Rha, MD, PhD[b,*], Byoung Geol Choi, PhD[b], Se Yeon Choi, PhD[c], Jae Kyeong Byun, BS[c], Yoonjee Park, MD[b], Dong Oh Kang, MD[b], Won Young Jang, MD[b], Woohyeun Kim, MD[b], Woong Gil Choi, MD, PhD[d], Tae Soo Kang, MD, PhD[e], Jihun Ahn, MD, PhD[f], Sang-Ho Park, MD, PhD[g], Ji Young Park, MD, PhD[h], Min-Ho Lee, MD, PhD[i], Cheol Ung Choi, PhD[b], Chang Gyu Park, MD, PhD[b], Hong Seog Seo, MD, PhD[b]

Abstract

There are limited long-term outcome data comparing BioLinx polymer (B)-zotarolimus-eluting stents (ZES) with phosphorylcholine polymer (P)-ZES. The aim of this study was to compare the efficacy and safety of B-ZES with P-ZES in patients who underwent percutaneous coronary intervention (PCI) during a 3-year follow-up period.

One thousand two hundred fifty four patients who underwent PCI with P-ZES (Endeavor [ZES-E] or Endeavor sprint [ZES-S], n = 356) or B-ZES (Endeavor resolute [ZES-R] or Resolute Integrity [ZES-I], n = 889) were enrolled. The primary endpoint was major adverse cardiac events (MACE); the composite of total death, non-fatal myocardial infarction (MI), target lesion revascularization (TLR), target vessel revascularization (TVR), non-target vessel revascularization (Non-TVR), and the secondary endpoint was stent thrombosis (ST).

After PSM, 2 propensity-matched (PSM) groups (275 pairs, n = 550, C-statistic = 0.730) were generated. During the 3-year follow-up period, the cumulative incidence of MACE (hazard ratio [HR], 1.525; 95% confidence interval [CI], 0.920–2.526; $P = .101$) and ST (HR, 1.248; 95% CI, 0.335–4.4649; $P = .741$) were similar between P-ZES and B-ZES after PSM. However, TLR rate was significantly higher in ZES-S than ZES-I (11.3% vs 3.8%, log rank $P = .029$) and TVR rate was higher in ZES-S than ZES-R (14.1% vs 4.8%, log rank $P = .025$).

In this single-center, all-comer registry, despite different polymers, P-ZES, and B-ZES showed comparable safety and efficacy during a 3-year follow-up period after PCI.

Abbreviations: ACEI = angiotensin converting enzyme inhibitors, ARB = angiotensin receptor blockers, B = BioLinx, BB = beta blockers, BMS = bare-metal stent, B-ZES = ZES-R and ZES-I, CAG = coronary angiography, CCB = calcium channel blockers, CTO = chronic total occlusive lesion, HF = heart failure, LVEF = left ventricular ejection fraction, LVEF = left ventricular ejection fraction, MACE = major adverse cardiac events, MI = myocardial infarction, NSTEMI = non-ST-segment elevation myocardial infarction, P = phosphorylcholine, PCI = percutaneous coronary intervention, P-ZES = ZES-E and ZES-S, STEMI = ST-segment elevation myocardial infarction, TIMI = thrombolysis in myocardial infarction, TLR = target lesion revascularization, TVR = target vessel revascularization, ZES = zotarolimus-eluting stent, ZES-E = Endeavor, ZES-I = resolute integrity, ZES-R = Endeavor resolute, ZES-S = Endeavor sprint.

Keywords: BioLinx, clinical outcomes, drug-eluting stent, phoshorylcholine, Polymer, Zotarolimus

Editor: Leonardo Roever.

YHK and A-YH contributed equally to the writing of this article.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

[a] Division of Cardiology, Department of Internal Medicine, Kangwon National University School of Medicine, Chuncheon, [b] Cardiovascular Center, Korea University Guro Hospital, [c] Department of Medicine, Korea University Graduate School, Seoul, [d] Cardiology Department, Konkuk University Chungju Hospital, Chungju, [e] Department of Internal Medicine, Cardiovascular Division, Dankook University Hospital, Cheonan, [f] Department of Cardiology, Soonchunhyang University Gumi Hospital, Gumi, [g] Cardiology Department, Soonchunhyang University Cheonan Hospital, Cheonan, [h] Division of Cardiology, Department of Internal Medicine, Cardiovascular Center, Nowon Eulji Medical Center, Eulji University, [i] Department of Cardiology, Soonchunhyang University College of Medicine, Seoul, South Korea.

[*] Correspondence: Seung-Woon Rha, Cardiovascular Center, Korea University Guro Hospital, 148, Gurodong-ro, Guro-gu, Seoul 08308, South Korea (e-mail: swrha617@yahoo.co.kr).

Medicine (2019) 98:32(e16767)

Received: 4 January 2019 / Received in final form: 18 June 2019 / Accepted: 17 July 2019

http://dx.doi.org/10.1097/MD.0000000000016767

1. Introduction

Compared to bare-metal stents (BMS), drug-eluting stents (DES) have reduced target lesion revascularization (TLR) by inhibition of neointimal hyperplasia but increased the risk of fatal stent thrombosis which a major concern.[1,2] Medtronic Vascular (Santa Rosa, CA., USA) and Abbott Laboratories (Abbott Park, Chicago, IL, USA) has developed a new stent, the zotarolimus-eluting stent (ZES; Endeavor), combining the approved Driver chromium-cobalt-nickel alloy coronary stent system with an antiproliferative agent, zotarolimus, and a biomimetic phoshorylcholine (P)-polymer.[3]

Zotarolimus is equivalent to sirolimus in terms of antiproliferative power but is more lipophilic compared with sirolimus.[4,5] This P-polymer system induced a 75% zotarolimus release within 2 days. In contrast, BioLinx (B)-polymer with more delayed zotarolimus release (50% and 85% released at 7 and 60 days, respectively) and over approximately 180 days after percutaneous coronary intervention (PCI).[6,7] The B-polymer system was developed to decrease restenosis and maintain low stent thrombosis (ST) rates by means of sustained longer duration zotarolimus release.[8] The Endeavor sprint (ZES-S) and the everolimus-eluting stent (Xience stent V; EES) showed similar good results in the treatment of coronary artery disease (CAD).[9,10] The Endeavour Resolute (ZES-R) and the Resolute Integrity (ZES-I) ZES utilize identical polymers (B polymer) and anti-proliferative agents and differ only in their respective strut design, and the clinical performance and safety were similar between ZES-R and ZES-I.[11]

Many previous studies compared the efficacy and safety among different classes of DES.[12,13] However, there are limited long-term clinical outcome data comparing the clinical outcomes among the same class of DESs, especially according to different type of polymer system in patients who underwent successful PCI. The aim of this study was to compare the efficacy and safety of B-ZES with P-ZES in patients who underwent PCI during 3-year clinical follow-up periods.

2. Methods

2.1. Study design and population

This study is a single-center, retrospective, all-comers registry designed to reflect the "real world" practice since 2004. Data were collected by a trained study-coordinator with a standardized case report form. This study has been examined and approved by the local ethics committee insuring that the subjects gave informed written consent. This study has been performed in accordance with the ethical standards laid down in the 1964 declaration of Helsinki. From January 2004 to December 2014, a total of 4041 patients underwent PCI (Fig. 1). Among above 4 kinds of ZES (Table 1), 2 kinds of ZES (ZES-E and ZES-S) had the same polymer system (P-polymer) and the same stent platform (Driver BMS) but different stent delivery balloon catheter system (TrueStream vs Sprinter). The other 2 kinds of ZES (ZES-R, ZES-I) had the same polymer system (BioLinx, B-polymer) and different stent platforms (Driver BMS vs Integrity) and different stent delivery balloon catheter system (Sprinter vs Micro-Trac). In this study, we classified the above 4 ZES according to the types of polymer system such as P-ZES (ZES-E and ZES-S) and B-ZES (ZES-R, ZES-I). The exclusion criteria are shown in Figure 1. Finally, a total of 1245 eligible patients who treated with P-ZES (ZES-E, n = 272, ZES-S, n = 84, total n = 356) or B-ZES (ZES-R, n = 394, ZES-I, n = 495, total n = 889) were enrolled. After a propensity score matched (PSM) analysis, 2 propensity-matched groups (275 pairs, n = 550) were generated (P-ZES; ZES-E, n = 203, ZES-S, n = 72, vs B-ZES; ZES-R, n = 126, ZES-I, n = 149).

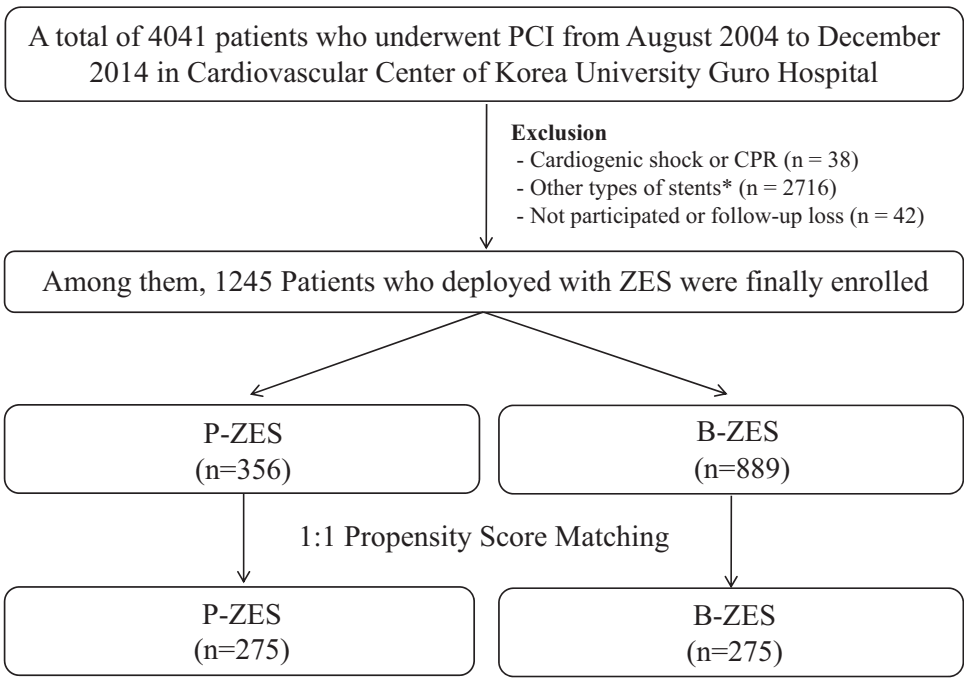

Figure 1. Flow chart. *, other types of stents except for P-ZES (Endeavor and Endeavor sprint) or B-ZES (Endeavor resolute and Resolute integrity).

Table 1

Characteristics of 4 kinds of zotarolimus-eluting stents.

	ZES-E	ZES-S	ZES-R	ZES-I
Stent platform	Driver BMS	Driver BMS	Driver BMS	Integrity BMS
Stent design	Modular technology	Modular technology	Modular technology	Continuous sinusoid technology
Alloy	Chromium–cobalt-nickel	Chromium–cobalt-nickel	Chromium–cobalt–nickel	Chromium–cobalt–nickel
Delivery system	TrueStream balloon	Sprinter balloon	Sprinter balloon	Micro-Trac balloon
Drug	Zotarolimus	Zotarolimus	Zotarolimus	Zotarolimus
Polymer	Phosphorylcholine	Phosphorylcholine	BioLinx	BioLinx

BMS = bare-metal stent, ZES = zotarolimus-eluting stent, ZES-E = Endeavor, ZES-I = Resolute integrity, ZES-R = Endeavor resolute, ZES-S = Endeavor sprint.

2.2. PCI procedure and medical treatment

A diagnostic coronary angiography (CAG) and PCI were done through either the femoral or the radial artery after an administration of unfractionated heparin (70–100 IU/kg). Patient's activated clotting time was maintained above 250 seconds during the procedure. All patients received a loading dose of 200 to 300 mg aspirin and 300 to 600 mg of clopidogrel as dual antiplatelet therapy (DAPT) and were maintained with 100 mg of aspirin and 75 mg of clopidogrel. The use of cilostazol (Pletaal, Otsuka Pharmaceutical Co., Tokyo, Japan) or platelet glycoprotein IIb/IIIa receptor blockers was left to the discretion of the individual operators. After stent implantation, DAPT (100-mg daily aspirin and 75 mg daily clopidogrel) was prescribed for at least 12 months. During hospitalization, the enrolled patients had taken cardiovascular beneficial medications, including aspirin, clopidogrel, cilostazole, beta-blockers (BB), angiotensin converting enzyme inhibitors (ACEI), or angiotensin receptor blockers (ARB), calcium channel blockers (CCB), diuretics, and lipid lowering agents. After discharge, the patients were encouraged to stay on the same medications that they received during hospitalization.

2.3. Study definitions and clinical follow-up

The recording of cardiovascular risk factors and past medical histories were based on the patients' self-report. The primary endpoint was the occurrence of major adverse cardiac events (MACE) defined as total death, non-fatal myocardial infarction (MI), TLR, target vessel revascularization (TVR), non-TVR, and the secondary endpoint was ST. All deaths were classified as cardiac or non-cardiac death. Non-fatal MI was defined as the presence of clinical symptoms, electrocardiographic changes, or abnormal imaging findings of MI, combined with an increase in the creatine kinase myocardial band fraction above the upper normal limits or an increase in troponin-T/troponin-I to greater than the 99th percentile of the upper normal limit.[14] TLR was defined as a revascularization of the target lesion due to restenosis or re-occlusion within the stent or 5 mm in and adjacent of the distal or proximal segment. TVR was defined as a revascularization of the target vessel or any segment of the coronary artery containing the target lesion. Non-TVR was defined as a revascularization of any segment of the non-target coronary artery. Multivessel disease was defined as the presence of a lesion with >50% diameter stenosis in a non-target vessel by visual estimation. ST was defined as acute (0–24 hours), subacute (24 hours–30 days), late (30 days–1 year) and very late (>1 year) according to the onset time of stent thrombosis.[15] The participants were required to visit the outpatient department of cardiology at the end of the first month and then every 3 to 6 months after the index PCI procedure and we followed-up on the clinical data of all enrolled patients through face-to-face interviews at regular outpatient clinic, medical chart reviews, and telephone contacts. Therefore, all enrolled patients finished their follow-up program.

2.4. Statistical analysis

All statistical analyses were performed using SPSS 20 (SPSS Inc., Chicago, IL, USA). For continuous variables, differences between the 2 groups were evaluated with the unpaired t test or Mann–Whitney rank test. Data were expressed as mean ± standard deviations. For discrete variables, differences were expressed as counts and percentages and analyzed with χ^2 or Fisher exact test between the groups as appropriate. To adjust for any potential confounders, propensity score matching (PSM) analysis was performed using the logistic regression model. We tested all available variables that could be of potential relevance; gender (men), age, left ventricular ejection fraction (LVEF), stable angina, unstable angina, STEMI, NSTEMI, coronary artery disease (CAD) risk factors, chronic kidney disease, laboratory findings, and post-PCI medications. Angiographic and procedural characteristics were also considered as covariate, such as target vessel, American College of Cardiology (ACC) /American Heart Association (AHA) B1/B2/C lesions, extent of CAD, ostial lesion, bifurcation lesion, heavy calcified lesion, diffuse long lesion (>30 mm), small vessel disease (≤2.25 mm), mean total stent length, mean stent diameter, number of stents/patient, total procedure time. The logistic model by which the propensity score was estimated showed a good predictive value (C statistic = 0.730). Subjects were matched with a caliper width equal to 0.01. Various clinical outcomes were estimated with the Kaplan–Meier method, and differences between the 2 groups were compared with the log-rank test. Proportional hazard models were used to assess the hazard ratio of the P-ZES compared with B-ZES adjusted PS. For all analyses, a 2-sided $P < .05$ was considered statistically significant.

3. Results

3.1. Baseline clinical and angiographic characteristics

Table 2 shows baseline clinical and angiographic characteristics. Before PSM adjustment, the mean age and gender distribution was also similar between the 2 groups. The level of LVEF (55.1 ± 8.6% vs 51.3 ± 10.5%, $P < .001$), the number of diabetic patients, ACC/AHA type B2 lesion, 3-vessel disease, and stents per each patient were significantly higher in the B-ZES compared

Table 2

Baseline clinical and angiographic characteristics.

Variables	Entire patients			Propensity-matched patients		
	P-ZES (n=356)	B-ZES (n=889)	*P*	P-ZES (n=275)	B-ZES (n=275)	*P*
Men, n (%)	249 (69.9)	625 (70.3)	.900	194 (70.5)	199 (72.4)	.637
Age (years)	62.6±10.8	63.5±11.1	.175	62.3±10.9	62.9±11.3	.499
LVEF (%)	51.3±10.5	55.1±8.6	<.001	53.3±9.3	53.9±9.4	.440
Stable angina, n (%)	93 (26.1)	227 (25.5)	.830	78 (28.4)	66 (24.0)	.244
Unstable angina, n (%)	122 (34.3)	308 (34.6)	.900	97 (35.3)	90 (32.7)	.529
ST segment elevation MI, n (%)	68 (19.1)	161 (18.1)	.683	43 (15.6)	46 (16.7)	.595
Non-ST segment elevation MI, n (%)	50 (14.0)	155 (17.4)	.145	37 (13.5)	37 (13.5)	1.000
Hypertension, n (%)	229 (61.3)	580 (65.2)	.759	172 (62.5)	166 (60.4)	.599
Diabetes mellitus, n (%)	106 (29.8)	326 (36.7)	.021	84 (30.5)	81 (29.5)	.780
Dyslipidemia, n (%)	126 (35.4)	158 (17.8)	<.001	69 (25.1)	75 (27.3)	.561
Previous MI, n (%)	1 (0.3)	1 (0.1)	.480	1 (0.4)	1 (0.4)	1.000
Previous PCI, n (%)	9 (2.5)	2 (0.2)	<.001	2 (0.7)	1 (0.4)	.636
Routine angiographic follow-up, n (%)	242 (68.0)	359 (40.4)	<.001	138 (50.2)	125 (45.5)	.267
CK-MB (mg/dl), initial	35.7±99.2	38.6±92.8	.636	33.1±97.2	50.1±111.4	.066
Troponin T (ng/dl), initial	0.46±1.90	0.58±1.89	.380	0.46±2.12	0.79±2.44	.163
High sensitivity CRP (mg/dl)	10.2±22.4	7.8±20.9	.095	9.1±20.9	6.5±16.1	.175
Total cholesterol (mg/L)8	172.2±40.5	175.2±44.1	.283	171.6±40.0	175.2±42.6	.322
Triglyceride (mg/L)	141.1±82.3	145.7±112.9	.572	141.4±83.6	143.7±97.8	.809
HDL cholesterol (mg/L)	45.4±12.2	43.8±10.8	.062	45.8±12.4	44.0±10.3	.126
LDL cholesterol (mg/L)	113.5±36.2	111.3±38.1	.460	112.6±37.2	112.0±37.5	.851
Serum creatinine (mg/L)	0.99±0.85	0.98±1.01	.870	0.92±0.27	0.89±0.36	.413
Serum glucose (mg/dL)	121.9±47.4	127.0±56.5	.147	121.7±48.1	124.6±49.6	.515
Angiographic characteristics						
Target vessel						
Left anterior descending, n (%)	202 (56.7)	564 (63.4)	.028	159 (57.8)	153 (55.6)	.606
Left circumflex, n (%)	84 (23.6)	303 (34.1)	<.001	69 (25.1)	74 (26.9)	.627
Right coronary artery, n (%)	143 (40.2)	307 (34.5)	.061	107 (38.9)	110 (40.0)	.794
Left main, n (%)	11 (3.1)	19 (2.1)	.322	10 (3.6)	6 (2.2)	.310
Ramus, n (%)	3 (0.8)	10 (1.1)	.658	3 (1.1)	1 (0.4)	.316
ACC/AHA Lesion type						
Type B1, n (%)	20 (5.6)	50 (5.6)	.997	16 (5.8)	16 (5.8)	1.000
Type B2, n (%)	62 (17.4)	217 (24.4)	.007	54 (19.6)	58 (21.1)	.672
Type C, n (%)	273 (76.7)	621 (69.9)	.015	205 (74.5)	201 (73.1)	.698
Extent of coronary artery disease, n (%)						
1-vessel	277 (77.8)	624 (70.2)	.007	209 (76.0)	210 (76.4)	.920
2-vessel	70 (19.7)	213 (24.0)	.102	58 (21.1)	57 (20.7)	.916
3-vessel	9 (2.5)	52 (5.8)	.014	8 (2.9)	8 (2.9)	1.000
Mean total stent length (mm)	23.5±6.0	22.9±6.6	.136	23.5±6.0	23.7±6.8	.613
Mean stent diameter (mm)	3.08±0.44	2.95±0.42	<.001	3.05±0.43	3.06±0.43	.693
Number of stents/patient	1.31±0.59	1.63±0.97	<.001	1.36±0.63	1.35±0.67	.896
Total procedure time (minutes)	39.9±30.8	43.2±44.0	.197	40.2±30.4	38.3±26.3	.432

Values are mean±SD or n (%). The *P* values for continuous data were obtained from analysis of variance. The *P* values for categorical data were obtained from chi-square test. ACC/AHA=American college of cardiology/American heart association, B=BioLinx, CK-MB=creatine kinase myocardial band, CRP=C-reactive protein, HDL=high-density lipoprotein, LDL=low-density lipoprotein, LVEF=left ventricular ejection fraction, MI=myocardial infarction, P=phosphorylcholine, PCI=percutaneous coronary intervention, ZES=zotarolimus-eluting stents.

with P-ZES. In contrast, the number of previous PCI, ACC/AHA type C lesion, 1-vessel disease, and mean total stent diameter were significantly higher in the P-ZES group than B-ZES. However, all of these differences disappeared after PSM analysis.

3.2. Post-PCI medications

Supplemental Table 1, http://links.lww.com/MD/D162 shows post-PCI medications between the 2 groups. Before and after PSM analysis, the description rates of all drugs (aspirin, clopidogrel, cilostazole, BB, ACEI, ARB, CCB, diuretics, lipid lowering agents) were similar between the 2 groups.

3.3. Clinical outcomes

Table 3 shows clinical outcomes at 30 days, 1 year and 3 years for the 2 groups. During month 1, the incidences of MACE and ST were not significantly different between the 2 groups. At 1 year, although the incidence of MACE was significantly higher in the P-ZES group before PSM, the incidence of MACE was similar between the 2 groups after PSM. The incidence of ST was not significantly different between the 2 groups before and after PSM. The incidences of TLR and TVR were significantly higher in the P-ZES group compared with the B-ZES group before PSM. However, these differences in TLR and TVR were also similar after PSM. At 3 years, the cumulative incidences of MACE

Table 3

Clinical outcomes at 30 days, 1 year and 3 years.

Outcomes	Entire patients				Propensity-matched patients		
	Total (n = 1245)	P-ZES (n = 356)	B-ZES (n = 889)	*P*	P-ZES (n = 275)	B-ZES (n = 275)	*P*
30 days							
MACE	17 (1.4)	5 (1.4)	12 (1.3)	.940	3 (1.1)	5 (1.8)	.476
All death, n (%)	10 (0.8)	2 (0.6)	8 (0.9)	.733	1 (0.4)	3 (1.1)	.316
Cardiac death, n (%)	9 (3.7)	2 (0.6)	7 (0.8)	.671	1 (0.4)	3 (1.1)	.316
Non-fatal MI, n (%)	11 (0.9)	4 (1.1)	7 (0.8)	.521	3 (1.1)	3 (1.1)	1.000
Total revascularization, n (%)	10 (0.8)	3 (0.8)	7 (0.8)	1.000	2 (0.7)	4 (1.5)	.412
TLR, n (%)	8 (0.6)	3 (0.8)	5 (0.6)	.696	2 (0.7)	2 (0.7)	1.000
TVR, n (%)	10 (0.8)	3 (0.8)	7 (0.8)	1.000	2 (0.7)	4 (1.5)	.412
Non-TVR, n (%)	2 (0.2)	1 (0.3)	1 (0.1)	.490	0 (0.0)	0 (0.0)	-
Stent thrombosis (definite, probable), n (%)							
Acute, n (%)	4 (0.3)	1 (0.3)	3 (0.3)	1.000	0 (0.0)	3 (1.1)	.082
Subacute, n (%)	5 (0.4)	3 (0.8)	2 (0.2)	.119	3 (1.1)	0 (0.0)	.082
Total, n (%)	9 (0.7)	4 (1.1)	5 (0.6)	.291	3 (1.1)	3 (1.1)	1.000
1 year							
MACE, n (%)	95 (7.6)	38 (10.7)	57 (6.4)	.010	27 (9.9)	22 (8.0)	.454
All death, n (%)	29 (2.3)	11 (3.1)	18 (2.0)	.298	9 (3.3)	8 (2.9)	.805
Cardiac death, n (%)	20 (1.6)	8 (2.2)	12 (1.3)	.317	6 (2.2)	5 (1.8)	.761
Non-fatal MI, n (%)	17 (1.4)	8 (2.2)	9 (1.0)	.106	7 (2.5)	3 (1.1)	.339
Total revascularization, n (%)	72 (5.8)	29 (8.1)	43 (4.8)	.024	20 (7.3)	17 (6.2)	.610
TLR, n (%)	47 (3.8)	23 (6.5)	24 (2.7)	.002	16 (5.8)	7 (2.5)	.086
TVR, n (%)	59 (4.7)	28 (7.9)	31 (3.5)	.001	20 (7.3)	12 (4.4)	.145
Non-TVR, n (%)	19 (1.5)	6 (1.7)	13 (1.5)	.799	2 (0.7)	4 (1.5)	.686
Stent thrombosis (definite, probable), n (%)							
Late (31 - 365 days)	2 (0.2)	2 (0.6)	0 (0.0)	.025	2 (0.7)	0 (0.0)	.157
Total (1 - 365 days)	11 (0.9)	6 (1.7)	5 (0.6)	.056	5 (1.8)	3 (1.1)	.476
3 years							
MACE, n (%)	137 (11.0)	55 (15.4)	82 (9.2)	.003	38 (13.8)	25 (9.1)	.108
All death, n (%)	41 (3.3)	19 (5.3)	22 (2.5)	.014	13 (4.7)	8 (2.9)	.266
Cardiac death, n (%)	23 (1.8)	11 (3.1)	12 (1.3)	.059	6 (2.2)	5 (1.8)	.761
Non-fatal MI, n (%)	34 (2.7)	15 (4.2)	19 (2.1)	.053	10 (3.6)	4 (1.5)	.104
Total revascularization, n (%)	94 (7.6)	35 (9.8)	59 (6.8)	.058	25 (9.1)	20 (7.3)	.534
TLR, n (%)	62 (5.0)	27 (7.6)	35 (3.9)	.009	20 (7.3)	10 (3.6)	.090
TVR, n (%)	83 (6.7)	34 (9.6)	49 (5.5)	.012	25 (9.1)	16 (5.8)	.194
Non-TVR, n (%)	22 (1.8)	6 (1.7)	16 (1.8)	.890	2 (0.7)	4 (1.5)	.412
Stent thrombosis (definite, probable), n (%)							
Very late (366–1095 days)	3 (0.2)	1 (1.3)	2 (0.2)	.856	0 (0.0)	1 (0.4)	.317
Total (1–1095 days)	14 (1.1)	7 (2.0)	7 (0.8)	.075	5 (1.8)	4 (1.5)	.737

Values are numbers and percentages. The *P* value for categorical data from Chi-Squared test. B = BioLinx, ACE = major adverse cardiac events, MI = myocardial infarction, P = phosphorylcholine, TLR = target lesion revascularization, TVR = target vessel revascularization, ZES = zotarolimus-eluting stents.

(hazard ratio [HR], 1.525; 95% confidence interval [CI], 0.920–2.526; $P = .101$) and ST (HR, 1.248; 95% CI, 0.335–4.4649; $P = .741$) were similar between the 2 groups after PSM (Table 4). The incidences of TLR and TVR were also higher in the P-ZES group compared with the B-ZES group before PSM. After PSM, the 3-year cumulative incidences of TLR and TVR were similar between the 2 groups. Figure 2 shows Kaplan–Meier curved analysis of MACE-free survival, TLR, TVR, and ST at 3-year according to the kinds of polymers (P-polymer vs B-polymer). Figure 3 shows subgroup analysis for MACE up to 3 years. In the cases of male, hypertension, no history of dyslipidemia, not long stent (mean length < 30 mm), ACC/AHA lesion type C, the choice of B-ZES may be preferred rather than P-ZES to reduce MACE after index PCI.

4. Discussion

This "real-world" all-comers analysis study showed

1. the cumulative incidences of MACE, total death, MI, and total revascularization were similar between P-ZES and B-ZES after PSM during a 3-year follow-up period; and
2. the incidences of ST also were not significantly different between the 2 groups.

These results suggest these P-ZES and B-ZES are equally effective in the treatment of CAD in all-comers regarding the kinds of polymer.

4.1. Zotarolimus-eluting stent (ZES)

In April 2003, the sirolimus-eluting stent (SES, Cypher, Cordis Corp., Miami Lakes, Florida) and in March 2004, paclitaxel-eluting stents (PES, Taxus, Boston Scientific, Natick, Massachusetts) were approved by the U.S. Food and Drug Administration (FDA).[16] Four years later, ZES-E received FDA's approval and was used widely in clinical practice.[17] Until recently, a total of 5 kinds (ZES-E, ZES-S, ZES-R, ZES-I, and ZES-Resolute Onyx) of

Table 4

Three-year clinical outcomes by Kaplan–Meier Curved analysis and cox-proportional Hazard ratio model analysis.

Outcomes	Cumulative events at 3 years (%)				
	P-ZES	B-ZES	Log rank	Hazard ratio (95% CI)	*P*
Entire patients					
MACE	55 (15.6)	82 (9.5)	.002	1.687 (1.199–2.375)	.003
All death	19 (5.3)	22 (2.5)	.015	2.112 (1.143–3.903)	.017
Cardiac death	11 (3.1)	12 (1.4)	.045	2.260 (0.997–5.123)	.051
Non-fatal myocardial infarction	15 (4.3)	19 (2.3)	.061	1.888 (0.959–3.717)	.066
Total revascularization	35 (10.1)	59 (6.9)	.056	1.500 (0.988–2.280)	.057
Target lesion revascularization	27 (7.7)	35 (4.1)	.008	1.946 (1.178–3.216)	.009
Target vessel revascularization	34 (9.7)	49 (5.8)	.012	1.744 (1.126–2.702)	.013
Non-target vessel revascularization	6 (1.7)	16 (1.9)	.879	0.930 (0.364–2.377)	.879
Stent thrombosis	7 (2.0)	7 (0.8)	.074	2.511 (0.881–7.158)	.085
Propensity-matched patients					
MACE	38 (13.9)	25 (9.1)	.099	1.525 (0.920–2.526)	.101
All death	13 (4.7)	8 (2.9)	.283	1.612 (0.668–3.890)	.288
Cardiac death	6 (2.2)	5 (1.8)	.771	1.193 (0.364–3.908)	.771
Non-fatal myocardial infarction	10 (3.8)	4 (1.5)	.123	2.435 (0.763–7.767)	.133
Total revascularization	25 (9.3)	20 (7.4)	.451	1.253 (0.696–2.257)	.452
Target lesion revascularization	20 (7.4)	10 (3.8)	.067	2.002 (0.937–4.279)	.073
Target vessel revascularization	25 (9.3)	16 (6.0)	.158	1.566 (0.836–2.934)	.161
Non-target vessel revascularization	2 (0.7)	4 (1.5)	.411	0.498 (0.091–2.716)	.420
Stent thrombosis	5 (1.8)	4 (1.5)	.740	1.248 (0.335–4.649)	.741

B = BioLinx, CI = confidence interval, MACE = major adverse cardiac events, P = phosphorylcholine, ZES = zotarolimus-eluting stents.

ZES were developed by Medtronic Vascular (Santa Rosa, CA., USA) and Abbott Laboratories (Abbott Park, Chicago, IL, USA). Because we wanted to evaluate long-term major clinical outcome in all-comers, among these 5 kinds of ZES, ZES-Resolute Onyx was excluded due to the launching date (April, 2015) was so late in Korea. The Endeavor stent is a cobalt-based alloy stent with a P-polymer loaded with zotarolimus at dose a concentration of 10 μg/mm stent length. P-polymer is a durable polymer composed of hydrophilic monomers is similar to the outer membrane of a red blood cell (90% of phospholipids in the outer membrane of a red blood cell including the phosphorylcholine head group).[5] The B-polymer coating system is composed of 3 different components such as a hydrophilic C19 component, hydrophobic C19 components, and a water soluble polyvinyl pyrrolidinone component which offers potentially improved biocompatibility and extended release of zotarolimus with 85% of drug being released within 60 days and the remainder up to 180 days.[18] In this study, we could not precisely explain the reason for the differences of TLR and TVR rates between ZES-S and ZES-I or ZES-S and ZES-R, the possible mechanisms may be the differences in the types of polymer or stent platform as shown in Table 1. Therefore in this aspect, we can suggest that B-polymer may be more beneficial than P-polymer to reduce TVR.

4.2. Studies concerned with P-ZES

In the ENDEAVOR II study,[19] ZES-E showed improved clinical outcomes and sustained safety compared with Driver BMS in the aspects of target vessel failure (TVF, 15.4% vs 24.4%), TLR (7.5% vs 16.3%), TVR (10.7% vs 20.1%), and MACE (15.4% vs 24.6%). In the ENDEAVOR II study, 1-year TLR rate of ZES-E was 5.9% and TVR rate of ZES-E was 7.5% these rates were comparable with the results of our study. One-year TLR rate of P-ZES was 5.8% and TVR rate of P-ZES was 7.3% in our study after PSM (Table 3). Eisenstein et al[20] reported 3-year comparative results between ZES-E and SES from the ENDEAVOR III trial. In their study, ZES-E showed reduced 3-year rates/100 subjects of death or MI (3.9 vs 10.8; difference, −6.9; 95% CI: −13.0 to 0.8; $P = .028$) but similar TVR rates compared with SES. (17.9 vs 12.2; difference, 5.7; 95% CI: −3.7 to 15.1; $P = .23$). Although ZES-E showed better outcomes compared with SES in the ENDEAVOR III study, in the SORT OUT III study,[21] the MACE rate was higher in patients treated with ZES-S than in patients treated with SES (148 [12.9%] vs 116 [10.1%]; HR,1.33; 95% CI, 1.04–1.69; $P = .022$) and the TVR rate was also higher in the ZES-S group compared with the SES group (103 [9.1%] vs 76 [6.7%]; HR, 1.40; 95% CI, 1.04–1.89; $P = .025$). In our study, 3-year the MACE rate of P-ZES was 13.8% and TVR rate of P-ZES was 9.1% after PSM. These results of our study also are comparable with the results of the SORT OUT III study.

4.3. Studies concerned with B-ZES

Di et al[11] reported the comparative safety and efficacy of ZES-R vs ZES-I. In their report, the rate of MACE (ZES-R [3.2%] vs ZES-I [5.0%], $P = .43$, HR, 1.37; 95% CI, 0.46–4.07, $P = .57$), mortality rate, non-fatal MI were similar between the 2 groups during 3-year follow-up period. In TWENTE II trial,[22] ZES-I showed similar clinical outcomes compared with PROMUS Element EES (TVR, 6.0% vs 6.2%, Log-rank $P = .87$; TVF, 10.7% vs 10.3%, Log-rank $P = .77$). Piccolo et al[23] also reported that ZES-R and EES provide similar safety and efficacy in patients undergoing PCI (TVR, risk ratio [RR], 1.06; 95% CI, 0.90–1.24; $P = .50$).

4.4. Comparative studies between P-ZES and B-ZES

Tada et al[24] demonstrated comparable 2-year clinical outcome results between ZES-R and ZES-E. In their study, the incidence of

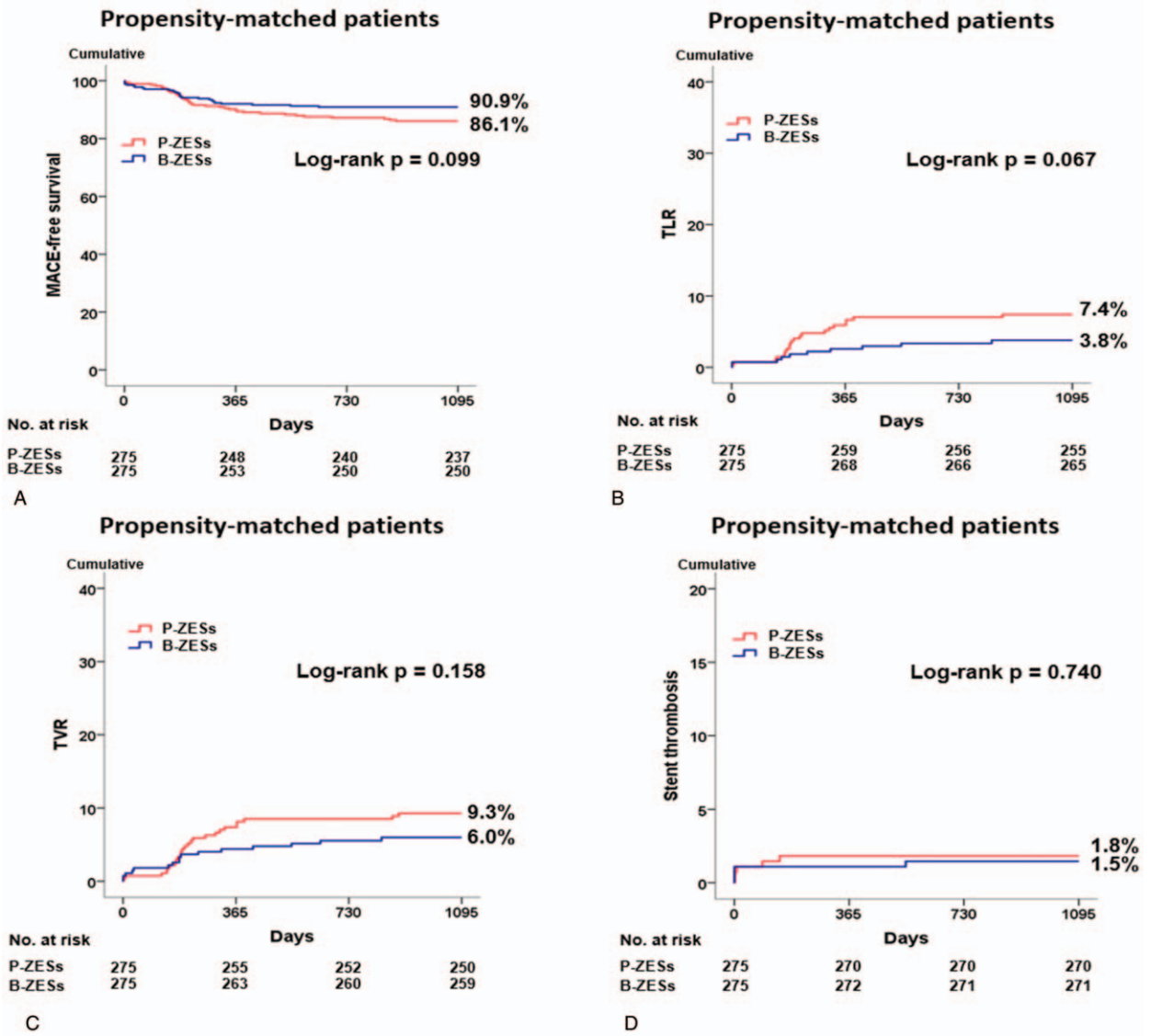

Figure 2. Kaplan–Meier curved analysis of MACEs-free survival (A), TLR (B), TVR (C), and stent thrombosis (D) at 3 year according to the types of polymer.

TLR was 12.0% in the ZES-R group and 16.0% in the ZES-E (HR, 0.72; 95% CI, 0.52–1.00; $P = .052$). Also, the incidence of cardiac death or MI was not different between the 2 groups (5.5% vs 4.8% [HR, 1.15; 95% CI, 0.66–2.02; $P = .62$]). More recently, Nishimoto et al[25] reported that ZES-E had better neointimal coverage and more stable than ZES-I by angioscopic comparisons. Sim et al[26] suggested that there were similar cumulative incidence of MACE between the ZES-S and ZES-R during 1-year follow-up period. In our study, the cumulative incidence of MACE between P-ZES and B-ZES was also similar before and after PSM during a 3-year follow-up period.

4.5. Stent thrombosis

ST is another debatable issue in the DES era. In the ENDEAVOR II study, definite and probable very late ST rate of ZES-E was 0.2% during 5-year follow-up period.[19] In the SORT OUT III[21] study, the incidence of very late ST was 0% in ZES-S. In the TWENTE II trial,[22] the incidence of definite or probable ST of ZES-I was 1.4% during a 3-year follow-up. According to 5-year follow-up result from the ENDEAVOR IV trial,[27] the overall definite/probable ST rate of ZES-E was 1.3% and very late stent thrombosis of ZES-E was 0.4%. In this study, the 3-year overall definite/probable ST rate of P-ZES was 1.8% and very late ST rate of P-ZES was 0%. The very late ST rate of P-ZES in this study was similar with the result of SORT OUT III study.

4.6. Others

There are limited long-term clinical outcome data comparing the clinical outcomes among the same class of DES, especially according to different types of polymer systems and the kinds of DES in patients who underwent successful PCI. Therefore, we think that our results provide useful clinical outcome information and trends between P-ZES and B-ZES in patients who underwent PCI during very long-term follow-up periods in the DES era.

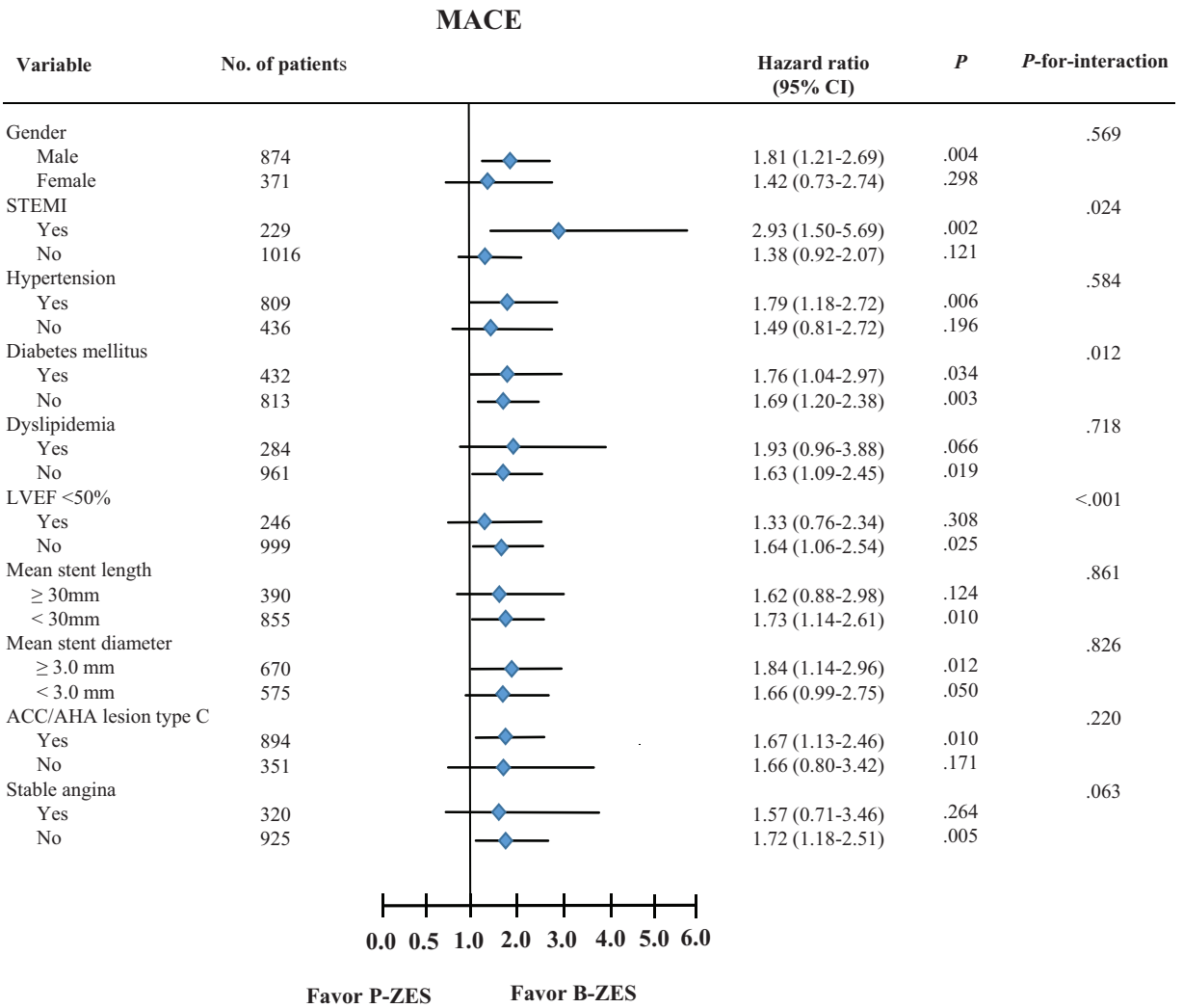

Figure 3. Subgroup analyses for MACE.

Finally, findings of this study support the notion that modern DES platforms are nowadays very similar in terms of their efficacy and safety, and further improvements in PCI care will depend on the operator experience, more use of advanced intravascular imaging and patient-oriented individualized approach with post-PCI pharmacotherapy.

4.7. Limitations

This study has some limitations. First, because it is a non-randomized registry design and single center study, several confounding factors such as under-reporting and/or missing value and selection bias may have affected the end results. Second, although PSM analysis and subgroup analysis was done, the proportion of each stents in both groups were not evenly distributed and this method also have some limitations to select appropriate population. Third, the strategy of antiplatelet therapy (e.g., DAPT or triple antiplatelet therapy [TAPT]) was left to the physician's discretion, which may have influenced the major clinical outcomes. Fourth, because the selection of specific type of ZES was depends on physicians' discretion, this may can be a bias of this study. Fifth, this study enrolled only Korean patients; the present results may not be generalizable to all other ethnicities in different parts of the world. Sixth, 9 operators were participated in this study. However, the operators' skills and experiences for PCI were mostly similar but may be different to some degree in particular complex patients and complicated lesion subset such as chronic total occlusion (CTO) lesion. Therefore, these operators' factor may act as bias. Seventh, in this study, the use of intravascular ultrasound (IVUS), optical coherence tomography (OCT), and fractional flow reserve (FFR) in addition to CAG to improve post-PCI outcomes were very low (<10%) due to cost issue. In Korea, currently there is no reimbursement program for IVUS or OCT and FFR is partially available under very limited indications during PCI. Only left main bifurcation or CTO PCI was mainly recommended to use image-guided (IVUS or OCT) or functional study-guided (FFR) for stent optimization. Therefore most physicians' decision for PCI was depend on angiographic findings and clinical information under "real-world clinical practices." Hence, this inter-rater variability could be an important limitation of this study. Although relatively lower rates of imaging or functional studies,

non-randomized design and single center study, this study may be meaningful because we tried to reflect "real world" clinical practice with longer follow-up duration.

4.8. Future directions

Although P-ZES and B-ZES showed comparable safety and efficacy, this result may be more precisely defined by future randomized controlled trials or large scale registry studies with long-term follow-up to get final conclusion.

In conclusion, in this single-center, all-comer registry, despite different polymers, P-ZES, and B-ZES showed comparable safety and efficacy during a 3-year follow-up period after PCI.

Author contributions

Conceptualization: Yong Hoon Kim, Ae-Young, Seung-Woon Rha, Tae Soo Kang, Jihun Ahn, Sang-Ho Park, Ji Young Park, Min-Ho Lee, Cheol Ung Choi, Chang Gyu Park, Hong Seog Seo.
Data curation: Yong Hoon Kim, Ae-Young Her, Seung-Woon Rha, Byoung Geol Choi, Se Yeon Choi, Jae Kyeong Byun, Yoonjee Park, Dong Oh Kang, Won Young Jang, Woohyeun Kim, Woong Gil Choi, Tae Soo Kang, Jihun Ahn, Sang-Ho Park, Ji Young Park, Min-Ho Lee, Cheol Ung Choi.
Formal analysis: Yong Hoon Kim, Ae-Young Her, Seung-Woon Rha, Byoung Geol Choi, Se Yeon Choi, Jae Kyeong Byun, Sang-Ho Park, Ji Young Park, Min-Ho Lee, Cheol Ung Choi.
Investigation: Yong Hoon Kim, Ae-Young Her, Seung-Woon Rha, Byoung Geol Choi, Se Yeon Choi, Jae Kyeong Byun, Woong Gil Choi, Jihun Ahn, Sang-Ho Park, Ji Young Park, Min-Ho Lee, Cheol Ung Choi, Hong Seog Seo.
Methodology: Yong Hoon Kim, Ae-Young Her, Seung-Woon Rha, Byoung Geol Choi, Se Yeon Choi, Jae Kyeong Byun, Woong Gil Choi, Jihun Ahn, Sang-Ho Park, Ji Young Park, Min-Ho Lee, Cheol Ung Choi.
Project administration: Seung-Woon Rha, Chang Gyu Park.
Resources: Seung-Woon Rha, Yoonjee Park, Dong Oh Kang, Won Young Jang, Woohyeun Kim, Cheol Ung Choi, Hong Seog Seo.
Software: Yong Hoon Kim, Ae-Young Her, Seung-Woon Rha, Byoung Geol Choi, Jae Kyeong Byun, Yoonjee Park, Dong Oh Kang, Won Young Jang, Woohyeun Kim, Woong Gil Choi, Tae Soo Kang, Jihun Ahn, Sang-Ho Park, Min-Ho Lee, Cheol Ung Choi.
Supervision: Seung-Woon Rha, Chang Gyu Park, Hong Seog Seo.
Validation: Yong Hoon Kim, Ae-Young Her, Seung-Woon Rha, Byoung Geol Choi.
Visualization: Yong Hoon Kim, Ae-Young Her, Seung-Woon Rha, Byoung Geol Choi.
Writing – original draft: Yong Hoon Kim, Ae-Young Her.
Writing – review & editing: Yong Hoon Kim, Ae-Young Her, Seung-Woon Rha.

References

[1] Kastrati A, Mehilli J, Pache J, et al. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med 2007;356:1030–9.
[2] Camenzind E, Steg PG, Wijns W. Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern. Circulation 2007;115:1440–55.
[3] Meredith IT, Ormiston J, Whitbourn R, et al. First-in-human study of the Endeavor ABT-578-eluting phosphorylcholine-encapsulated stent system in de novo native coronary artery lesions: Endeavor I Trial. EuroIntervention 2005;1:157–64.
[4] Marx SO, Marks AR. Bench to bedside: the development of rapamycin and its application to stent restenosis. Circulation 2001;104:852–5.
[5] Valgimigli M, Patialiakas A, Thury A, et al. Randomized comparison of Zotarolimus-Eluting Endeavor Sprint versus bare-metal stent implantation in uncertain drug-eluting stent candidates: rationale, design, and characterization of the patient population for the Zotarolimus-Eluting Endeavor Sprint stent in uncertain DES candidates study. Am Heart J 2013;166:831–8.
[6] Udipi K, Chen M, Cheng P, et al. Development of a novel biocompatible polymer system for extended drug release in a next-generation drug-eluting stent. J Biomed Mater Res A 2008;85:1064–71.
[7] Udipi K, Melder RJ, Chen M, et al. The next generation Endeavor Resolute Stent: role of the BioLinx polymer system. EuroIntervention 2007;3:137–9.
[8] Yeung AC, Leon MB, Jain A, et al. RESOLUTE US InvestigatorsClinical evaluation of the resolute zotarolimus-eluting coronary stent system in the treatment of de novo lesions in native coronary arteries: the RESOLUTE US clinical trial. J Am Coll Cardiol 2011;57:1778–83.
[9] Fajadet J, Wijns W, Laarman GJ, et al. ENDEAVOR II Investigators-Randomized, double-blind, multicenter study of the Endeavor zotarolimus-eluting phosphorylcholine-encapsulated stent for treatment of native coronary artery lesions: clinical and angiographic results of the ENDEAVOR II trial. Circulation 2006;114:798–806.
[10] Gershlick A, Kandzari DE, Leon MB, et al. ENDEAVOR InvestigatorsZotarolimus-eluting stents in patients with native coronary artery disease: clinical and angiographic outcomes in 1,317 patients. Am J Cardiol 2007;100:45m–55m.
[11] Di Santo P, Simard T, Ramirez FD, et al. Does stent strut design impact clinical outcomes: comparative safety and efficacy of Endeavor Resolute versus Resolute Integrity zotarolimus-eluting stents. Clin Invest Med 2015;38:E296–304.
[12] Colmenarez H, Fernández C, Escaned J. Impact of technological developments in drug-eluting stents on patient-focused outcomes: a pooled direct and indirect comparison of randomised trials comparing first- and second-generation drug-eluting stents. EuroIntervention 2014;10:942–52.
[13] Bavishi C, Baber U, Panwar S, et al. Efficacy and safety of everolimus and zotarolimus-eluting stents versus first-generation drug-eluting stents in patients with diabetes: a meta-analysis of randomized trials. Int J Cardiol 2017;230:310–8.
[14] Consensus Document Myocardial infarction redefined–a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. Eur Heart J 2000;21:1502–13.
[15] Bundhun PK, Wu ZJ, Chen MH. Is there any significant difference in stent thrombosis between sirolimus and paclitaxel eluting stents?: a systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore) 2016;95:e2651.
[16] Doostzadeh J, Clark LN, Bezenek S, et al. Recent progress in percutaneous coronary intervention: evolution of the drug-eluting stents, focus on the XIENCE V drug-eluting stent. Coron Artery Dis 2010;21:46–56.
[17] Stefanini GG, Holmes DRJr. Drug-eluting coronary-artery stents. N Engl J Med 2013;368:254–65.
[18] Meredith IT, Worthley S, Whitbourn R, et al. RESOLUTE InvestigatorsClinical and angiographic results with the next-generation resolute stent system: a prospective, multicenter, first-in-human trial. JACC Cardiovasc Interv 2009;2:977–85.
[19] Fajadet J, Wijns W, Laarman GJ, et al. Long-term follow-up of the randomised controlled trial to evaluate the safety and efficacy of the zotarolimus-eluting driver coronary stent in de novo native coronary artery lesions: five year outcomes in the ENDEAVOR II study. EuroIntervention 2010;6:562–7.
[20] Eisenstein EL, Leon MB, Kandzari DE, et al. ENDEAVOR III InvestigatorsLong-term clinical and economic analysis of the Endeavor zotarolimus-eluting stent versus the cypher sirolimus-eluting stent: 3-year results from the ENDEAVOR III trial (Randomized Controlled Trial of the Medtronic Endeavor Drug [ABT-578] Eluting Coronary Stent System Versus the Cypher Sirolimus-Eluting Coronary Stent System in De Novo Native Coronary Artery Lesions). JACC Cardiovasc Interv 2009;2:1199–207.

[21] Maeng M, Tilsted HH, Jensen LO, et al. 3-Year clinical outcomes in the randomized SORT OUT III superiority trial comparing zotarolimus- and sirolimus-eluting coronary stents. JACC Cardiovasc Interv 2012;5: 812–8.
[22] van der Heijden LC, Kok MM, Löwik MM, et al. Three-year safety and efficacy of treating all-comers with newer-generation Resolute Integrity or PROMUS Element stents in the randomised DUTCH PEERS (TWENTE II) trial. EuroIntervention 2017; 12:2128–31.
[23] Piccolo R, Stefanini GG, Franzone A, et al. Safety and efficacy of resolute zotarolimus-eluting stents compared with everolimus-eluting stents: a meta-analysis. Circ Cardiovasc Interv 2015;8: pii: e002223.
[24] Tada T, Byrne RA, Cassese S, et al. Comparative efficacy of 2 zotarolimus-eluting stent generations: resolute versus endeavor stents in patients with coronary artery disease. Am Heart J 2013;165:80–6.
[25] Nishimoto Y, Matsuo K, Ueda Y, et al. Angioscopic comparison of resolute and endeavor zotarolimus-eluting stents. Circ J 2016;80:650–6.
[26] Sim DS, Jeong MH, Hong YJ, et al. Safety and efficacy of the Endeavor Resolute® Stent in patients with multivessel disease: the HEART (Honam EndeAvor ResoluTe) Prospective, Multicenter Trial. Chonnam Med J 2018;54:55–62.
[27] Kirtane AJ, Leon MB, Ball MW, et al. ENDEAVOR IV InvestigatorsThe "final" 5-year follow-up from the ENDEAVOR IV trial comparing a zotarolimus-eluting stent with a paclitaxel-eluting stent. JACC Cardiovasc Interv 2013;6:325–33.