Comparison of 3-year clinical outcomes between Endeavor Resolute® and Resolute Integrity® zotarolimus-eluting stents in an Asian population

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Abstract

Objective: There is a scarcity of comparative studies between Endeavor Resolute®-zotarolimus-eluting stent (R-ZES) and Resolute Integrity®-ZES (I-ZES) during long-term follow-up periods. Although the stent alloy and the polymer of these two ZESs are similar, the platform and the design of these two stents are different. This study was conducted to compare the efficacy and safety of these two different ZESs in the all-comer Korean patients who underwent percutaneous coronary intervention (PCI) during a 3-year follow-up period.

Methods: This study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. In this single-center, retrospective, and all-comer patients' cohort study, a total of 889 patients who underwent PCI with R-ZES (n=394) or I-ZES (n=495) were enrolled. The primary endpoint was the occurrence of major adverse cardiac events (MACEs) defined as all-cause death, nonfatal myocardial infarction (MI), any repeat revascularization including target lesion revascularization (TLR), target vessel revascularization (TVR), and non-TVR, and the secondary endpoint was stent thrombosis (ST) at 3 years.

Results: To adjust for any potential confounders, the propensity score-adjusted multivariable analysis was performed using the logistic regression model (C-statistics=0.689). The cumulative incidence rates of MACEs [adjusted hazard ratio (aHR), 1.341; 95% confidence interval (CI), 0.615–2.922; p=0.461], all-cause death, nonfatal MI, any repeat revascularization, and ST (aHR, 2.090; 95% CI, 0.163–26.77; p=0.571) were similar between the two groups during the 3-year follow-up period.

Conclusion: R-ZES and I-ZES demonstrated comparable efficacy and safety after PCI during a 3-year follow-up period. However, these results can perhaps be more precisely defined by other large and long-term follow-up studies in the future. *(Anatol J Cardiol 2020; 23: 268-76)*

Keywords: zotarolimus, drug-eluting stent, outcomes

Introduction

After the approval of the U.S. Food and Drug Administration (FDA) for the sirolimus-eluting stent (SES, Cypher®, Cordis Corp., Miami Lakes, Florida, USA) in April 2003, and for the paclitaxel-eluting stent (PES, Taxus®, Boston Scientific, Natick, Massachusetts, USA) in March 2004 (1), the zotarolimus-eluting stent (ZES) received FDA's approval approximately 4 years later and has been widely used in clinical practice (2). Zotarolimus has similar antiproliferative capacity and is more lipophilic compared with sirolimus (3). The Endeavor Resolute®-ZES (R-ZES, Medtronic Cardiovascular, Santa Rosa, California, USA) and the Resolute Integrity®-ZES (I-ZES, Medtronic Cardiovascular, Santa Rosa, California, USA) are cobalt-based alloy stents with a thin biocompatible BioLinx-polymer coating system (4-6). Compared with phosphorylcholine polymer, the BioLinx-polymer coating system is composed of three different components such as hydrophilic C19, hydrophobic C10, and a water-soluble polyvinyl pyrrolidinone component and offers potentially improved biocompatibility and extended release of zotarolimus, with 85% of the drug being released within 60 days and the remainder up to 180 days (7, 8). Therefore, this BioLinx-polymer system de-

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creased restenosis and maintained low stent thrombosis (ST) rates through sustained longer duration of zotarolimus release (7). Although the stent alloy and the polymer of these two ZESs are similar, the platform and the design of these two stents are different. R-ZES used Driver® bare-metal stent (BMS) and modular technology, whereas I-ZER used Integrity® BMS and continuous sinusoidal technology. This enhanced sinusoidal technology offers improved flexibility, tracking, and deliverability (9). However, the thickness of the platform of these two stents was similar at 91 μm. Compared with the first-generation drug-eluting stents (DESs), ZESs have more advanced strut design, polymer system, and antiproliferative material to reduce the risk of in-stent restenosis (ISR) (10).

However, it is unclear whether the advanced stent platform and design can improve long-term clinical outcomes, especially in the same class of ZESs. Although Di Santo et al. (7) reported that the clinical performance and safety were similar between R-ZES and I-ZES, several previous studies have compared the efficacy and safety among different classes of DESs (7, 8, 10). Therefore, there are limited long-term clinical outcome data comparing the clinical outcomes among the same class of DESs, especially according to the different stent platform, stent design, and identical polymer in all-comer patients who have undergone successful percutaneous coronary intervention (PCI). Therefore, we investigated the efficacy and safety of these two different ZESs in patients after PCI during a 3-year follow-up period.

In Korea, a more recently developed ZES, Resolute Onyx®-ZES, was launched by Medtronic Korea in March 2015. Due to the short follow-up period after Resolute Onyx®-ZES deployment, we excluded those patients. Regarding this launching time, R-ZES and I-ZES are the latest ZESs in Korea. Therefore, we compared the clinical outcomes between these two stents in this study.

Methods

Study population

This study was a single-center, retrospective, all-comer patients' registry designed to reflect the "real-world" practice since 2004. Data were collected by trained study coordinators using a standardized case report form. This study has been examined and approved by the Local Ethics Committee, and the subjects provided informed written consent. This study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. A total of 4041 patients who underwent PCI between January 2004 and December 2014 at the Cardiovascular Center of Korea University Guro Hospital, Seoul, South Korea, were enrolled. Exclusion criteria were cardiogenic shock or cardiopulmonary resuscitation (n=38), other types of DES (except for R-ZES or I-ZES) implantation (n=3072), and lost to follow-up or did not participate (n=42). Finally, 889 patients who were treated with R-ZES (n=394) or I-ZES (n=495) were eligible for this study (Fig. 1).

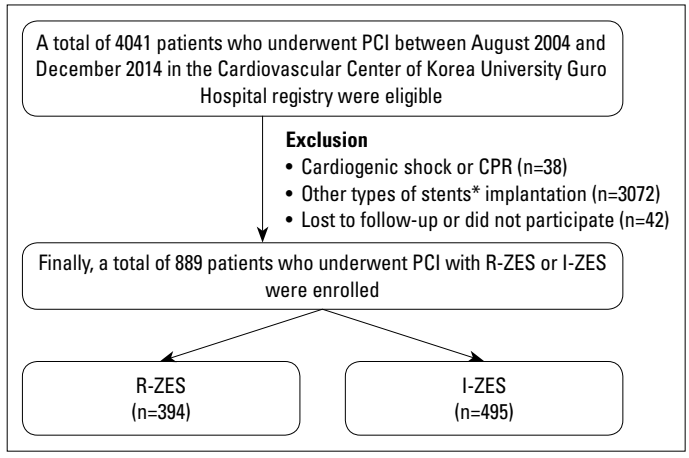

Figure 1. Flow chart

PCI - percutaneous coronary intervention, CPR - cardiopulmonary resuscitation, R - Endeavor Resolute®, I - Resolute Integrity®, ZES - zotarolimus-eluting stent, * - other type of stents except for R-ZES and I-ZES

PCI procedure and medical treatment

A diagnostic coronary angiography (CAG) and PCI were performed 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 at >250 s during the procedure. All patients received a loading dose of 200–300 mg aspirin and 300–600 mg clopidogrel as the dual antiplatelet therapy (DAPT) and were maintained with 100 mg aspirin and 75 mg 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 (100mg daily aspirin and 75 mg daily clopidogrel) was prescribed at least for 12 months. During hospitalization, the enrolled patients had taken cardiovascular beneficial medications, including all types of antiplatelet agents (aspirin, clopidogrel), beta-blockers (BBs), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and lipid-lowering agents. After discharge, the patients were recommended to stay on the same medications they received during hospitalization.

Study definitions and clinical follow-up

All the cardiovascular risk factors and past medical histories were based on patients' self-report. The primary endpoint was the occurrence of major adverse cardiac events (MACEs) defined as all-cause death, nonfatal myocardial infarction (MI), any repeat revascularization including target lesion revascularization (TLR), target vessel revascularization (TVR), and non-TVR, and the secondary endpoint was ST at 3 years.

All-cause deaths were defined as cardiac (CD) or non-CD. Nonfatal 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 (CK-MB) above the upper normal limits or an increase in troponin-T/troponin-I to greater than the 99th

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percentile of the upper normal limit (4). TLR was defined as a revascularization of the target lesion due to restenosis or reocclusion 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 nontarget coronary artery. ST was defined as acute (0–24 h), subacute (24 h to 30 days), late (30 days to 1 year), and very late (>1 year) according to the onset time of ST (11). The participants were required to visit the outpatient department of cardiology at the end of the first month and then every 3–6 months after the index PCI procedure, and we were able to follow-up on the clinical data of all the enrolled patients through face-to-face interviews at regular outpatient clinic, medical chart reviews, and telephone contacts. Therefore, all the enrolled patients had completed their follow-up program.

Statistical analysis

All data were processed with SPSS 20 (SPSS Inc., Chicago, IL, USA). For continuous variables, differences between the two groups were evaluated using the unpaired t-test or the Mann–Whitney U rank test. Data are expressed as mean±standard deviation or median (quartile 1 to quartile 3). For discrete variables, differences are expressed as counts and percentages and analyzed using χ^2 or Fisher's exact test between the groups as appropriate. To adjust for any potential confounders, the propensity score (PS)-adjusted multivariable analysis was performed using the logistic regression model. We included all meaningful confounding covariates ($p<0.005$) or those having predictive values in the multivariable Cox proportional hazard regression analysis. These covariates included men, age, ST-segment elevation MI (STEMI), non-NSTEMI, previous cerebrovascular accidents, peripheral vascular disease, chronic kidney disease, routine angiographic follow-up, CK-MB, total cholesterol, low-density lipoprotein-cholesterol, treated chronic total occlusive lesion, diffuse long lesion (>30 mm), small vessel disease (≤2.25 mm), bifurcation, mean total stent length, mean stent diameter, number of stents/patient, and post-PCI medications (aspirin, clopidogrel, BBs, ACEIs, and ARBs). The PS was estimated using the C-statistics for the logistic regression model, and the PS for the two groups was 0.689 in this study. For all analyses, a 2-sided $p<0.05$ was considered as statistically significant.

Results

Baseline characteristics and angiographic characteristics

Table 1 shows the baseline clinical and angiographic characteristics. Before PSM adjustment, the mean age (62.9±10.9 vs. 64.0±11.2 years, p=0.124) and gender distribution (men, 70.8% vs. 69.9%, p=0.767) were similar between the two groups. The number of patients with STEMI, serum level of CK-MB, total cholesterol, low-density lipoprotein-cholesterol, diffuse long lesion, bifurcation lesion, and mean total stent length were significantly higher in the R-ZES group than in the I-ZES group. In contrast, the number of previous cerebrovascular accidents, peripheral vascular disease, chronic kidney disease, small vessel disease, mean stent diameter, and number of stents for each patient were significantly higher in the I-ZES group than in the R-ZES group. Furthermore, the total procedure time was similar between the two groups.

Post-PCI medications

Table 1 shows the post-PCI medications between the two groups. The prescription rates of aspirin (98.2% vs. 93.1%, p=0.047), clopidogrel (96.2% vs. 90.3%, p=0.001), BBs (60.9% vs. 47.3%, p<0.001), and ACEIs (37.8% vs. 27.5%, p=0.001) were significantly higher in the R-ZES group. However, ARBs (33.2% vs. 41.0%, p=0.018) was much more frequently prescribed in the I-ZES group than in the R-ZES group.

Clinical outcomes

Table 2 shows the clinical outcomes at 30 days, 1 year, and 3 years for the two groups. During 1 month after the index PCI, the incidence of MACEs was not significantly different between the two groups (1.3% vs. 1.4%, p=0.852). At 1 year, the incidence rates of MACEs and ST were similar between the two groups. At 3 years, the incidence rates of MACEs (8.6% vs. 9.7%, p=0.585) and ST (1.0% vs. 0.6%, p=0.706) were also comparable between the two groups. The results of the PS-adjusted multivariable analysis of MACEs [adjusted hazard ratio (aHR), 1.341; 95% confidence interval (CI), 0.615–2.922; p=0.461, Fig. 2a], ST (aHR, 2.090; 95% CI, 0.163–26.77, p=0.571, Fig. 2b), all-cause death (aHR, 1.843; 95% CI, 0.401–8.480; p=0.432), cardiac death (aHR, 4.805; 95% CI, 0.500–46.17; p=0.174), nonfatal MI (aHR, 1.429; 95% CI, 0.280–7.301; p=0.668), any repeat revascularization (aHR, 1.238; 95% CI, 0.496–3.094; p=0.548), TLR (aHR, 2.284; 95% CI, 0.699–5.470: p=0.172), TVR (aHR, 1.895; 95% CI, 1.102–3.402; p=0.451), and non-TVR (aHR, 1.834; 95% CI, 0.439–7.672; p=0.406) were also similar between the two groups (Table 3). The subgroup analysis showed that in case of the non-diabetes group, the choice of I-ZES may be preferable rather than R-ZES to reduce MACEs after PCI (Fig. 3).

Discussion

The primary finding of this "real-world" all-comer patients' PS-adjusted multivariable analysis study is that the cumulative incidence rates of MACEs, all-cause death, cardiac death, nonfatal MI, any repeat revascularization, TLR, TVR, and non-TVR were comparable between R-ZES and I-ZES, and the cumulative incidence of ST was not significantly different between the two groups during the 3-year follow-up period. Therefore, R-ZES and I-ZES demonstrate comparable efficacy and safety for treating

Table 1. Baseline, angiographic characteristics, and post-PCI medications

Variables	Total (n=889)	R-ZES (n=394)	I-ZES (n=495)	*P* value
Men, n (%)	625 (70.3)	279 (70.8)	346 (69.9)	0.767
Age (years)	63.5±11.1	62.9±10.9	64.0±11.2	0.124
LVEF (%)	55.1±8.6	55.1±8.6	55.0±8.6	0.855
Stable angina, n (%)	227 (25.5)	94 (23.9)	133 (26.9)	0.306
Unstable angina, n (%)	308 (34.6)	140 (35.5)	168 (33.9)	0.620
STEMI, n (%)	161 (18.1)	105 (26.6)	56 (11.3)	<0.001
NSTEMI, n (%)	155 (17.4)	52 (13.2)	103 (20.8)	0.003
Hypertension, n (%)	580 (65.2)	254 (64.5)	326 (65.9)	0.665
Diabetes mellitus, n (%)	326 (36.7)	138 (35.0)	188 (38.0)	0.364
Dyslipidemia, n (%)	158 (17.7)	66 (16.8)	92 (18.6)	0.477
Previous CVA, n (%)	50 (5.6)	14 (3.6)	36 (7.3)	0.017
Previous MI, n (%)	1 (0.1)	0 (0.0)	1 (0.2)	0.372
Previous PCI, n (%)	2 (0.2)	2 (0.5)	0 (0.0)	0.133
Peripheral vascular disease, n (%)	34 (3.8)	9 (2.3)	25 (5.1)	0.033
Chronic kidney disease, n (%)	44 (4.9)	10 (2.5)	34 (6.9)	0.003
Routine angiographic follow-up	359 (40.4)	183 (46.4)	176 (35.6)	<0.001
CK-MB (mg/dL), initial	3.6 (2.1-34.8)	3.8 (2.4-43.8)	3.5 (1.9-36.7)	0.016
Troponin-T (ng/dL), initial	0.019 (0.010-0.210)	0.018 (0.010-0.150)	0.020 (0.010-0.270)	0.622
High-sensitivity CRP (mg/dL)	1.4 (0.6-4.6)	1.5 (0.6-4.8)	1.3 (0.7-4.4)	0.290
Total cholesterol (mg/L)	175.4±29.3	179.1±41.8	171.7±45.8	0.019
Triglyceride (mg/L)	145.7±112.3	143.5±99.8	147.9±125.0	0.621
HDL cholesterol (mg/L)	43.9±10.6	43.5±10.5	44.2±11.0	0.429
LDL cholesterol (mg/L)	111.5±32.3	113.7±34.9	109.4±30.8	0.048
Serum creatinine (mg/L)	0.99±0.99	0.91±0.60	1.06±1.36	0.057
Serum glucose (mg/dL)	127.1±56.4	129.6±59.9	124.6±52.9	0.232
Hemoglobin A1C (%)	6.1 (5.6-6.9)	6.1 (5.7-6.8)	6.1 (5.6-7.0)	0.195
Angiographic characteristics				
Targeted vessel				
Left anterior descending, n (%)	564 (63.4)	254 (64.5)	310 (62.6)	0.571
Left circumflex, n (%)	303 (34.1)	122 (31.0)	181 (36.6)	0.080
Right coronary artery, n (%)	307 (34.5)	135 (34.3)	172 (34.7)	0.880
Left main, n (%)	19 (2.1)	5 (1.3)	14 (2.8)	0.110
Ramus, n (%)	10 (1.1)	2 (0.5)	8 (1.6)	0.119
Number of MVD (≥2 vessels)	263 (29.6)	107 (27.2)	156 (31.5)	0.157
ACC/AHA lesion type				
Type B1, n (%)	50 (5.6)	20 (5.1)	30 (6.1)	0.527
Type B2, n (%)	217 (24.4)	93 (23.6)	124 (25.1)	0.618
Type C, n (%)	621 (69.9)	281 (71.3)	340 (68.7)	0.395
Extent of CAD, n (%)				
1-vessel	624 (70.2)	287 (72.8)	337 (68.1)	0.123
2-vessel	213 (24.0)	90 (22.8)	123 (24.8)	0.486
3-vessel	52 (5.8)	17 (4.3)	35 (7.1)	0.082

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Table 1. Cont.

Variables	Total (n=889)	R-ZES (n=394)	I-ZES (n=495)	*P* value
Treated CTO	85 (9.6)	48 (12.2)	37 (7.5)	0.018
Ostial lesion (≤5 mm), n (%)	162 (18.2)	62 (15.7)	100 (20.2)	0.087
Diffuse long lesion (>30 mm), n (%)	417 (46.9)	206 (52.3)	211 (42.6)	0.004
Small vessel disease (≤2.25 mm), n (%)	110 (12.4)	33 (8.4)	77 (15.6)	0.001
Bifurcation, n (%)	342 (38.5)	171 (43.4)	171 (34.5)	0.007
Heavy calcification	149 (16.8)	69 (17.5)	80 (16.2)	0.592
Mean total stent length (mm)	23.1±6.5	23.8±6.5	22.2±6.6	<0.001
Mean stent diameter (mm)	2.95±0.42	2.92±0.39	2.98±0.46	0.032
Number of stents/patient	1.62±0.93	1.50±0.83	1.74±1.05	<0.001
Total procedure time (min)	43.1±43.4	41.3±57.2	44.7±29.5	0.262
Post-PCI medications				
Aspirin, n (%)	840 (94.5)	379 (98.2)	461 (93.1)	0.047
Clopidogrel, n (%)	826 (92.1)	379 (96.2)	447 (90.3)	0.001
Cilostazol, n (%)	178 (20.0)	87 (22.1)	91 (18.4)	0.171
Beta-blockers, n (%)	474 (53.3)	240 (60.9)	234 (47.3)	<0.001
Calcium channel blockers, n (%)	311 (35.0)	124 (31.5)	187 (37.8)	0.050
ACEIs, n (%)	285 (32.1)	149 (37.8)	136 (27.5)	0.001
ARBs, n (%)	334 (37.6)	131 (33.2)	203 (41.0)	0.018
Diuretics, n (%)	179 (20.1)	89 (22.6)	90 (18.2)	0.104
Lipid-lowering agents, n (%)	786 (88.4)	351 (89.1)	435 (87.9)	0.576

Values are expressed as numbers (percentage), mean±SD, or median (quartile 1- quartile 3). For continuous variables, differences were analyzed using the unpaired t-test or the Mann–Whitney U rank test. For discrete variables, differences were analyzed using χ^2 or Fisher's exact test. R - Endeavor Resolute®, I - Resolute Integrity®, ZES - zotarolimus-eluting stent, LVEF - left ventricular ejection fraction, STEMI - ST-segment elevation myocardial infarction, NSTEMI - non-STEMI, CVA - cerebrovascular accidents, CK - creatine kinase myocardial band, CRP - C-reactive protein, HDL - high-density lipoprotein, LDL - low-density lipoprotein, MVD -multivessel disease, ACC/AHA - American College of Cardiology/American Heart Association, CAD - coronary artery disease, CTO - chronic total occlusive lesion, PCI - percutaneous coronary intervention, ACEIs - angiotensin-converting enzyme inhibitors, ARBs - angiotensin receptor blockers

CAD in the all-comer patients despite the different stent platform and stent design.

Although stent platforms, stent design, delivery system, and polymers have rapidly evolved (11), the safety and efficacy results between R-ZES and I-ZES have not been completely illuminated. In general, we expect that newer generation stents may have several advantages rather than those previously used or currently being used. Hence, it is necessary to estimate the safety and efficacy of these two ZESs in the "real-world" routine clinical practice. There is a high scarcity of comparative studies between R-ZES and I-ZES. Di Santo et al. (7) reported the comparative safety and efficacy of R-ZES versus I-ZES during a 1-year follow-up period. They reported that the unadjusted rates of MACEs [R-ZES (3.2%) vs. I-ZES (5.0%), p=0.43, odds ratio, 1.37; 95% CI, 0.46–4.07, p=0.57], mortality [R-ZES (0.9%) vs. I-ZES (1.9%), p=0.59], and nonfatal MI [R-ZES (2.3%) vs. I-ZES (3.1), p=0.75] were similar between the two groups. In our study, the rates of MACEs in all patients were 6.3% in the R-ZES group and 6.5% in the I-ZES group (p=0.942) during the 1-year follow-up period. The primary cause of this difference between our study and the study of Di Santo et al. (7) was the definition of MACEs. In the study of Di Santo et al. (7), MACEs were defined as the composite of all-cause death, nonfatal MI, and CVA not including TLR, TVR, and non-TVR. Regardless of the definition of MACEs and the number of study population, our study demonstrated a similar pattern of major outcomes as those reported in the study of Di Santo et al. (7) between the R-ZES and I-ZES groups. Therefore, based on the results of the study of Di Santo et al. (7) and those of our study, the modifications in the stent platform design do not likely translate into differences in the clinical outcomes. Because of the deficit of a randomized direct comparison of these stents, more potential advantages of this newer I-ZES stent platform remain unrevealed.

Ishikawa et al. (12) reported the results of a comparative study on the clinical outcomes between Taxus Liberte® (TAXUS-Lib; Boston Scientific, Natick, MA, USA) and Taxus Express® (TAXUS-Exp; Boston Scientific). They also reported a similar result that the only difference between these two Taxus stents is the stent design, which implies that the Taxus Liberte® stent has a thinner strut and greater space to improve uniform drug distribution. The dose of delivering drug and the release pharmacokinetics are identical between these two Taxus stents. The

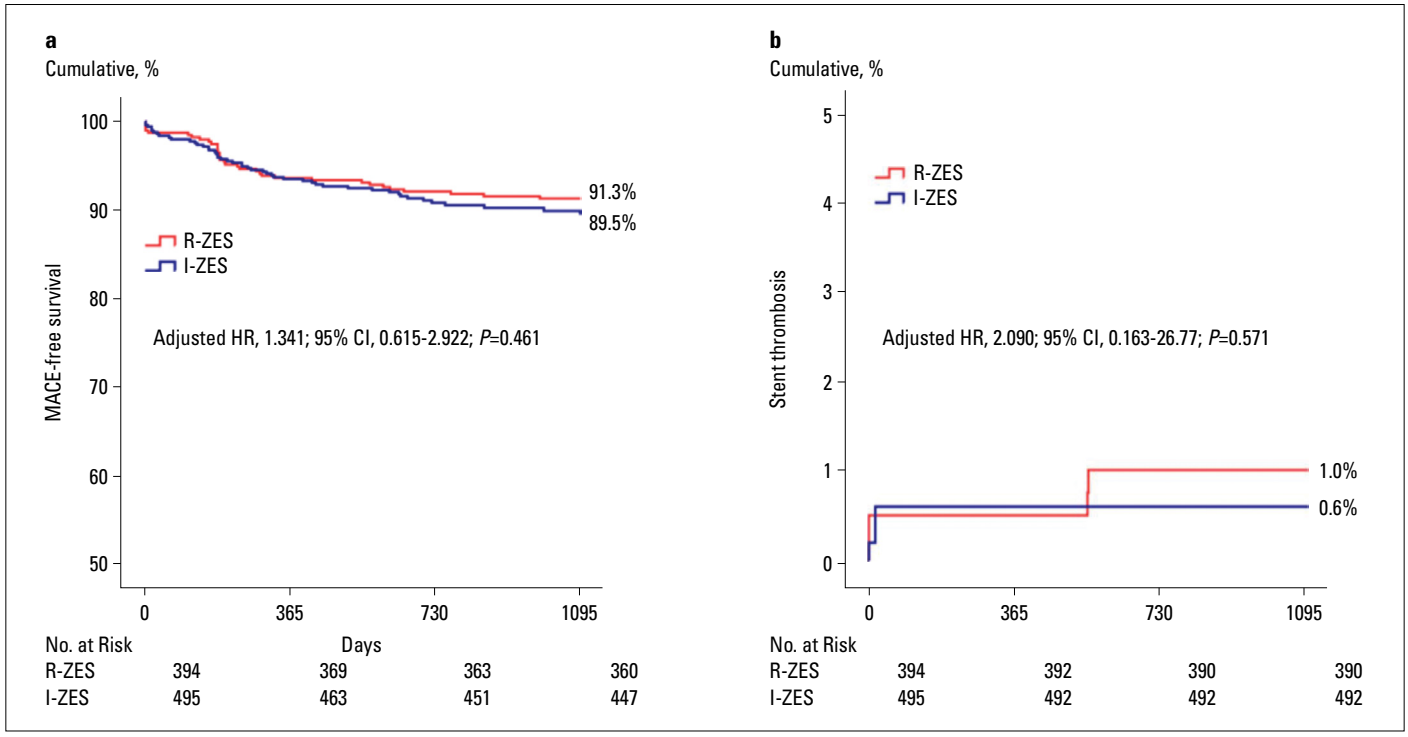

Figure 2. Kaplan–Meier curved analysis of MACE-free survival (a) and stent thrombosis (b) between the R-ZES and I-ZES groups at 3 years

R - Endeavor Resolute®, I - Resolute Integrity®, ZES - zotarolimus-eluting stent, HR - hazard ratio, CI - confidence interval

clinical outcomes (cardiac death, nonfatal MI, and definite ST) were not significantly different between these stents during a 700-day follow-up period. These results also suggest that the new advanced stent design could not demonstrate improved clinical outcomes compared with the old stent design in case of the Taxus stents.

To estimate the beneficial effects of sinusoidal technology, we performed a subgroup analysis of MACEs using the PS-adjusted multivariable analysis (Fig. 3). In cases of ACC/AHA type C lesion (adjusted HR, 1.27; 95% CI, 0.57–2.84; p=0.567), diffuse long lesion (>30 mm, adjusted HR, 1.18; 95% CI, 0.44–3.19; p=0.745), and heavy calcified lesion (adjusted HR, 1.50; 95% CI, 0.44–5.13; p=0.518), the adjusted HRs were not significantly different between the two groups. Therefore, unlike our expectations, the sinusoidal technology did not show beneficial effects in this study.

ST is another debatable issue in the DES era. In the first 1 month after DES implantation, the polymer plays an important role to inhibit neointimal hyperplasia by controlling drug-release kinetics (13, 14). We can expect that the B-polymer system can exhibited a decreased ST rate due to its sustained longer duration of zotarolimus release (8). In the TWENTE II trial (13), the incidence of definite or probable ST of I-ZES was 1.4% during the 3-year follow-up. In our study, the 3-year overall definite/probable ST rates of ST were 1.0% in the R-ZES group and 0.6% in the I-ZES group (p=0.706). The RESOLUTE US trial (5) reported an ST rate of 0.0% in the R-ZES group during a 1-year follow-up period. Moreover, Cassese et al. (15) suggested that first- and second-generation ZESs have similar thrombogenicity compared with other limus-eluting stents. However, this issue is debatable, and further large-scale, randomized, well-controlled trials with longer follow-up would be required to verify these findings.

The results of this study may be considered as important for several reasons. First, although I-ZES was more recently developed than R-ZES using the enhanced sinusoidal technology, these modifications in the stent platform design were not associated with improved clinical outcomes in this study. To our knowledge, any other randomized or comparative study did not deal with clinical outcomes (more than 3 years) between R-ZES and I-ZES. Regarding limited long-term clinical outcome data comparing the clinical outcomes among the same class of DESs, especially under the circumstance of different types of stent platform and stent design with the same polymer system, we speculate that our study may provide a valuable message to interventional cardiologists in the era of new-generation DESs. Second, the study population consisted of all-comer patients, not confining to a specific population, except for patients who were complicated with cardiogenic shock or those who had cardiopulmonary resuscitation on admission. In this regard, this study may have merit reflecting the "real-world" routine clinical practice.

Study limitations

This study has some limitations. First, because it is a non-randomized registry design and single-center study, several confounding factors such as underreporting and/or missing values and selection bias may have affected the end results. Second,

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Table 2. Clinical outcomes at 30 days, 1 year, and 3 years

Outcomes	Total (n=889)	R-ZESs (n=394)	I-ZESs (n=495)	*P* value
30 days				
MACEs	12 (1.3)	5 (1.3)	7 (1.4)	0.852
All-cause death, n (%)	8 (0.9)	3 (0.8)	5 (1.0)	0.697
Cardiac death, n (%)	7 (0.8)	3 (0.8)	4 (0.8)	0.938
Nonfatal MI, n (%)	7 (0.8)	4 (1.0)	3 (0.6)	0.493
Any repeat revascularization, n (%)	7 (0.8)	3 (0.8)	4 (0.8)	0.938
TLR, n (%)	5 (0.6)	2 (0.5)	3 (0.6)	0.845
TVR, n (%)	7 (0.8)	3 (0.8)	4 (0.8)	0.938
Non-TVR, n (%)	1 (0.1)	1 (0.3)	0 (0.0)	0.443
ST (definite, probable), n (%)				
Acute, n (%)	3 (0.3)	2 (0.5)	1 (0.2)	0.587
Subacute, n (%)	2 (0.2)	0 (0.0)	2 (0.4)	0.506
Total, n (%)	5 (0.6)	2 (0.5)	3 (0.6)	0.845
1 year				
MACEs, n (%)	57 (6.4)	25 (6.3)	32 (6.5)	0.942
All-cause death, n (%)	18 (2.0)	6 (1.5)	12 (2.4)	0.473
Cardiac death, n (%)	12 (1.3)	3 (0.8)	9 (1.8)	0.245
Nonfatal MI, n (%)	9 (1.0)	5 (1.3)	4 (0.8)	0.520
Any repeat revascularization, n (%)	43 (4.8)	19 (4.8)	24 (4.8)	0.986
TLR, n (%)	24 (2.7)	11 (2.8)	13 (2.6)	0.880
TVR, n (%)	31 (3.5)	13 (3.3)	18 (3.6)	0.855
Non-TVR, n (%)	13 (1.5)	9 (2.3)	4 (0.8)	0.091
ST (definite, probable), n (%)				
Late (31–365 days)	0 (0.0)	0 (0.0)	0 (0.0)	-
Total (1–365 days)	5 (0.6)	2 (0.5)	3 (0.6)	0.845
3 years				
MACEs, n (%)	82 (9.2)	34 (8.6)	48 (9.7)	0.585
All-cause death, n (%)	22 (2.5)	8 (2.0)	14 (2.8)	0.519
Cardiac death, n (%)	12 (1.3)	3 (0.8)	9 (1.8)	0.245
Nonfatal MI, n (%)	19 (2.1)	10 (2.5)	9 (1.8)	0.491
Any repeat revascularization, n (%)	59 (6.6)	25 (6.3)	34 (6.9)	0.755
TLR, n (%)	35 (3.9)	16 (4.1)	19 (3.8)	0.846
TVR, n (%)	49 (5.5)	19 (4.8)	30 (6.1)	0.422
Non-TVR, n (%)	16 (1.8)	10 (2.5)	6 (1.2)	0.203
ST (definite, probable), n (%)				
Very late (366–1095 days)	2 (0.2)	2 (0.5)	0 (0.0)	0.196
Total (1–1095 days)	7 (0.8)	4 (1.0)	3 (0.6)	0.706

Values are numbers and percentages. The p values for categorical data were obtained from the chi-square test. R - Endeavor Resolute®, I -Resolute Integrity®, ZES -zotarolimus-eluting stent, MI - myocardial infarction, TLR - target lesion revascularization, TVR - target vessel revascularization, MACEs - major adverse cardiac events, ST - stent thrombosis

imaging modality-guided [e.g., intravascular ultrasound (IVUS), optical coherence tomography (OCT)] PCI can improve the clinical outcomes in terms of optimal stent expansion, minimizing geographic miss, and directing appropriate stent sizing to maximize the final stent area (16). Fractional flow reserve (FFR)-guided PCI is associated with a significantly lower rate of MACEs

Table 3. Three-year clinical outcomes by multivariable Cox regression analysis and PS-adjusted multivariable Cox regression analysis

	Cumulative Events at 3 years (%)						
Outcomes	**R-ZES**	**I-ZES**	***P* value**	**Adjusted HR*(95% CI)**	***P* value**	**PS-adjusted HR*(95% CI)**	***P* value**
MACEs	34 (8.6)	48 (9.7)	0.585	1.155 (0.667-2002)	0.606	1.341 (0.615-2.922)	0.461
All-cause death	8 (2.0)	14 (2.8)	0.519	1.467 (0.396-5.437)	0.556	1.843 (0.401-8.480)	0.432
Cardiac death	3 (0.8)	9 (1.8)	0.245	3.709 (0.270-37.26)	0.315	4.805 (0.500-46.17)	0.174
Non-fatal MI	10 (2.5)	9 (1.8)	0.491	1.262 (0.436-3.654)	0.742	1.429 (0.280-7.301)	0.668
Any repeat revascularization	25 (6.3)	34 (6.9)	0.755	1.053 (0.567-1.925)	0.867	1.238 (0.496-3.094)	0.548
TLR	16 (4.1)	19 (3.8)	0.846	1.208 (0.554-2.638)	0.634	2.284 (0.699-5.470)	0.172
TVR	19 (4.8)	30 (6.1)	0.422	2.261 (0.903-4.437)	0.107	1.895 (1.102-3.402)	0.451
Non-TVR	10 (2.5)	6 (1.2)	0.203	1.627 (0.491-5.387)	0.426	1.834 (0.439-7.672)	0.406
Stent thrombosis	4 (1.0)	3 (0.6)	0.706	2.305 (0.240-39.63)	0.209	2.090 (0.163-26.77)	0.571

*Adjusted by men, age, STEMI, NSTEMI, previous CVA, PVD, CKD, RAF, CK-MB, total cholesterol, LDL-cholesterol, treated CTO, diffuse long lesion (>30mm), small vessel disease (≤2.25mm), bifurcation, mean total sent length, mean stent diameter, number of stent/patient, post-PCI medications (aspirin, clopidogrel, BBs, ACEIs, and ARBs).
R - Endeavor Resolute®, I - Resolute Integrity®, ZES - zotarolimus-eluting stent, HR - hazard ratio, CI - confidence interval, PS - propensity-score, MACEs - major adverse cardiac events, MI - myocardial infarction, TLR - target lesion revascularization, TVR - target vessel revascularization, STEMI - ST-segment elevation myocardial infarction, NSTEMI - non-STEMI, CVA - cerebrovascular accidents, PVD - peripheral vascular disease, CKD - chronic kidney disease, RAF - routine angiographic follow-up, CK-MB - creatine kinase myocardial band, LDL - low density lipoprotein, CTO - chronic total occlusive lesion, BBs - beta-blockers, ACEIs - angiotensin converting enzyme inhibitors, ARBs - angiotensin receptor blockers

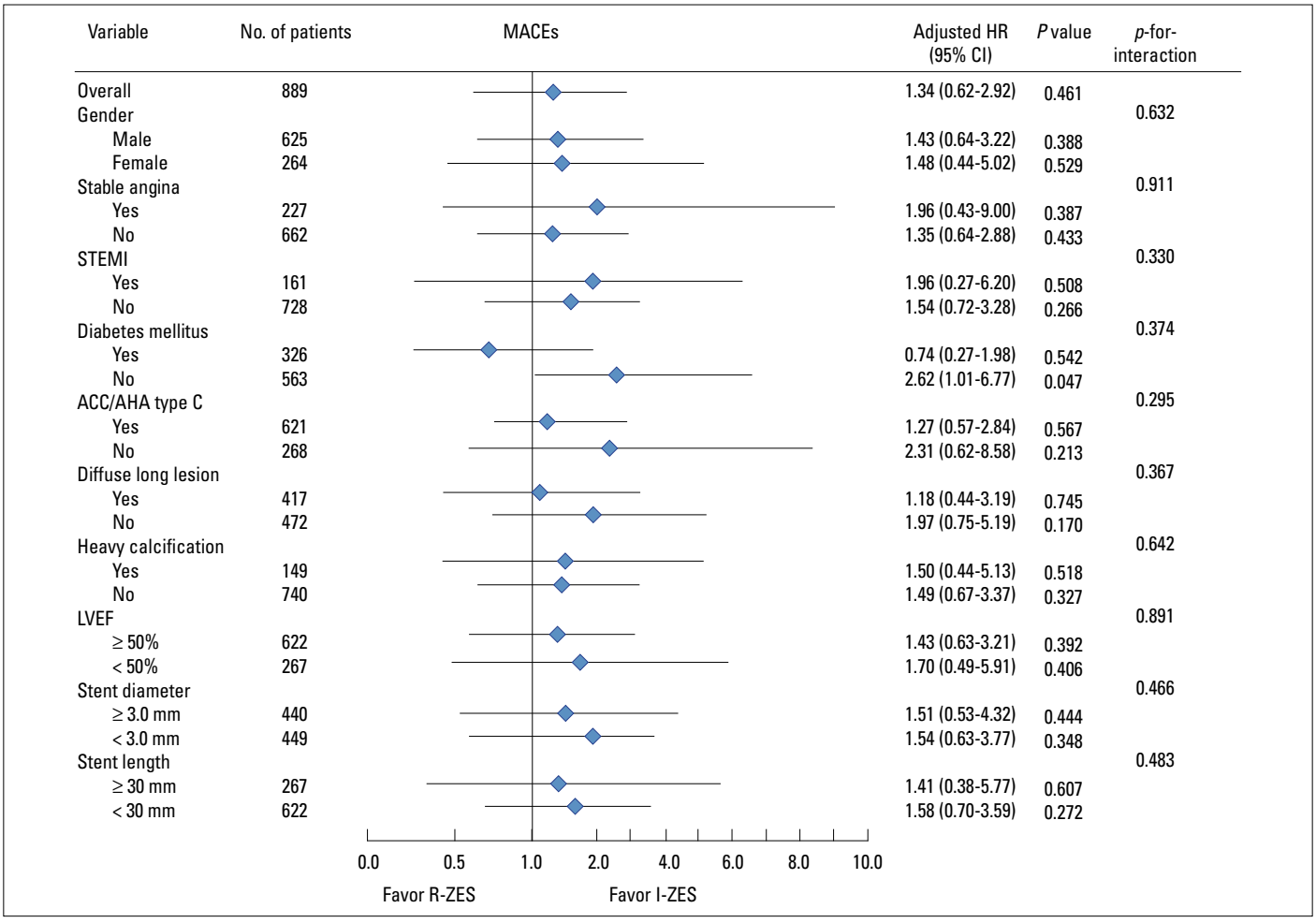

Figure 3. Subgroup analyses of MACEs

MACEs - major adverse cardiac events, R-ZES - Endeavor resolute®-ZES, I-ZES - Resolute integrity®-ZES, STEMI - ST-segment elevation myocardial infarction, ACC/AHA - American College of Cardiology/American Heart Association, LVEF - left ventricular ejection fraction

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(17). Unfortunately, in this study, imaging or functional studies were conducted only for a small number of patients (<10%). In Korea, currently, there is very restricted reimbursement program for FFR, IVUS, OCT, or cardiac computed tomography and magnetic resonance imaging; hence, PCI decision largely depends on clinical decision in real-world clinical practice. Therefore, we could not perform fine analysis for the pattern and amount of neointimal hyperplasia between the two stents. Third, the strategy of antiplatelet therapies (e.g., DAPT or triple antiplatelet therapy) was left to the physician's discretion, which may have influenced the major clinical outcomes. Fourth, even though this study was all-comer patients' registry, the number of patients enrolled in this study was limited and may be underpowered to define major clinical outcome differences between the two groups.

Conclusion

This single-center, retrospective, all-comer patients' cohort study demonstrated comparable efficacy and safety between R-ZES and I-ZES in patients after PCI during a 3-year follow-up period. However, these results can perhaps be more precisely defined by other large and long-term follow-up studies in the future.

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References

1. Doostzadeh J, Clark LN, Bezenek S, Pierson W, Sood PR, Sudhir K. 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. [CrossRef]
2. Stefanini GG, Holmes DR Jr. Drug-eluting coronary-artery stents. N Engl J Med 2013; 368: 254-65. [CrossRef]
3. Gershlick A, Kandzari DE, Leon MB, Wijns W, Meredith IT, Fajadet J, et al. Zotarolimus-eluting stents in patients with native coronary artery disease: clinical and angiographic outcomes in 1,317 patients. Am J Cardiol 2007; 100: 45m-55m. [CrossRef]
4. [No authors listed]. 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. [CrossRef]
5. Yeung AC, Leon MB, Jain A, Tolleson TR, Spriggs DJ, Mc Laurin BT, et al.; RESOLUTE US Investigators. Clinical 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. [CrossRef]
6. Fajadet J, Wijns W, Laarman GJ, Kuck KH, Ormiston J, Münzel T, 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. [CrossRef]
7. Di Santo P, Simard T, Ramirez FD, Pourdjabbar A, Harnett DT, Singh K, 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. [CrossRef]
8. 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. [CrossRef]
9. Turco MA. The Integrity bare-metal stent made by continuous sinusoid technology. Expert Rev Med Devices 2011; 8: 303-6. [CrossRef]
10. Bavishi C, Baber U, Panwar S, Pirrotta S, Dangas GD, Moreno P, 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. [CrossRef]
11. Kolandaivelu K, Swaminathan R, Gibson WJ, Kolachalama VB, Nguyen-Ehrenreich KL, Giddings VL, et al. Stent thrombogenicity early in high-risk interventional settings is driven by stent design and deployment and protected by polymer-drug coatings. Circulation 2011; 123: 1400-9. [CrossRef]
12. Ishikawa T, Nakano Y, Hino S, Suzuki T, Murakami A, Tsutsumi J, et al. Propensity-matched lesion-based comparison of midterm outcomes of TAXUS Express and TAXUS Liberte stents for de novo native coronary stenosis. J Cardiol 2013; 62: 289-95. [CrossRef]
13. Serruys PW, Sianos G, Abizaid A, Aoki J, den Heijer P, Bonnier H, et al. The effect of variable dose and release kinetics on neointimal hyperplasia using a novel paclitaxel-eluting stent platform: the Paclitaxel In-Stent Controlled Elution Study (PISCES). J Am Coll Cardiol 2005; 46: 253-60. [CrossRef]
14. van der Heijden LC, Kok MM, Löwik MM, Danse PW, Jessurun GAJ, Hautvast RWM, 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. [CrossRef]
15. Cassese S, Ndrepepa G, King LA, Tada T, Fusaro M, Kastrati A. Two zotarolimus-eluting stent generations: a meta-analysis of 12 randomised trials versus other limus-eluting stents and an adjusted indirect comparison. Heart 2012; 98: 1632-40. [CrossRef]
16. Maehara A, Matsumura M, Ali ZA, Mintz GS, Stone GW. IVUS-Guided Versus OCT-Guided Coronary Stent Implantation: A Critical Appraisal. JACC Cardiovasc Imaging 2017; 10: 1487-1503. [CrossRef]
17. Xaplanteris P, Fournier S, Pijls NHJ, Fearon WF, Barbato E, Tonino PAL, et al.; FAME 2 Investigators. Five-Year Outcomes with PCI Guided by Fractional Flow Reserve. N Engl J Med 2018: 379: 250-9.