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Original Research

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Comparison of Thick Biolimus A9-Eluting Stent and Thin Zotarolimus-Eluting Stent in Multi-Vessel Percutaneous Coronary Intervention

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AUTHOR'S SUMMARY

This study compared the clinical outcomes of 2 drug-eluting stent (DES) types in patients undergoing multi-vessel percutaneous coronary intervention (PCI). In total, 936 patients were randomly assigned to receive either a biodegradable polymer-based biolimus A9-eluting stent (BES) or a durable polymer-based zotarolimus-eluting stent (ZES). No significant difference between the 2 groups was found in 2-year major cardiac adverse event rates (11.2% for BES vs. 10.9% for ZES). Both types of DES showed favorable clinical outcomes in multi-vessel PCI. However, thinner ZES has a lower device failure rate, leading to using other stents.

ABSTRACT

Background and Objectives: There are limited randomized studies on patients undergoing multi-vessel percutaneous coronary intervention (PCI) comparing the outcomes between stent thickness and polymer types. To compare the clinical outcomes of thick biodegradable

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

Data Sharing Statement
The data generated in this study is available from the corresponding author upon reasonable request.

Author Contributions
Conceptualization: Nam CW, Lee CH; Data curation: Nam CW, Lee CH, Koo BK; Formal analysis: Nam CW, Chung TW, Hwang J, Kim IC, Cho YK, Yoon HJ, Hur SH; Funding acquisition: Nam CW; Investigation: Nam CW, Lee CH, Lee HJ, Lee S, Kim IC, Cho YK, Yoon HJ, Hur SH, Kim JY, Kim YS, Jang WS, Lee JH, Kim W, Lee JB, Hong YJ, Heo JH, Lee BR, Doh JH, Shin ES, Koo BK; Methodology: Nam CW, Lee CH, Cho YK; Project administration: Nam CW, Cho YK; Resources: Nam CW, Lee HJ,

polymer-based biolimus A9-eluting stents (BESs) and thin durable polymer-based zotarolimus-eluting stents (ZESs) in patients undergoing multi-vessel PCI.

Methods: A total of 936 patients who underwent multi-vessel coronary artery stenting were randomly assigned to the BES (n=472) or ZES (n=464) groups. The primary endpoint was 2-year major adverse cardiac events (MACEs), a composite of all-cause death, myocardial infarction (MI), and any revascularization at the 2-year follow-up.

Results: Fifty-two (11.2%) of 472 patients in BES group and 50 (10.9%) of the 464 patients in ZES group met the 2-year primary endpoint of MACE (hazard ratio, 1.00; 90% confidence interval, 0.72, 1.38; p=0.994). All-cause death (BES vs. ZES: 2.8% vs. 2.7%, p=0.758), MI (2.1% vs. 2.6%, p=0.483), and repeat revascularization (6.7% vs. 6.9%, p=0.876) were not significantly different between the 2 groups. Although there was no significant outcome difference in any subgroup analysis, the technical failure rate leading to the use of other stents was higher in BES than in ZES (3.2% vs. 0.9%, p=0.023).

Conclusions: In patients who underwent multi-vessel PCI, BES and ZES showed comparable 2-year clinical outcomes. However, BES was not established to demonstrate non-inferiority to ZES in terms of the incidence of the primary endpoint at the 2-year. The technical success rate of the index PCI with the assigned stent was higher for thinner ZES.

Trial Registration: ClinicalTrials.gov Identifier: NCT01947439

Keywords: Drug-eluting stent; Percutaneous coronary intervention; Polymer

INTRODUCTION

In the management of patients with multi-vessel coronary artery disease (MVD), multi-vessel percutaneous coronary intervention (PCI) continues to be challenging compared to coronary artery bypass surgery (CABG).[1] With considerable advancements in interventional techniques and devices to improve the clinical outcomes of PCI, the development of drug-eluting stents (DESs) has significantly contributed to the increased use of PCI in MVD cases.[2-4] DES was initially designed to inhibit excessive neointimal growth by releasing anti-proliferative drugs from a polymer coating around the stent strut. However, earlier generations of DESs were associated with several issues, including adverse events such as late stent thrombosis, which could be attributed to the components of the DES.[5] Consequently, continuous efforts have been made to develop newer-generation DESs with different drugs, polymers, and stent strut thicknesses.[6][7] Although many types of DESs are being developed with improved efficacy and safety, there have been limited randomized studies on MVD in clinical practice. Therefore, this study aimed to compare the clinical outcomes of thicker biodegradable polymer-based biolimus A9-eluting stents (BESs) and thinner durable polymer-based zotarolimus-eluting stents (ZESs) in patients who underwent multi-vessel PCI.

METHODS

Ethical statement

This study was approved by the Institutional Review Board or ethics committee at each enrollment site (Keimyung University Dongsan Hospital IRB No. 2012-12-506). Consecutive eligible patients provided written informed consent prior to the interventional procedure.

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Study design and population

BATTLE IN MULTI (ClinicalTrials.gov, NCT01947439) was a prospective, open-label, randomized, multicenter trial comparing BES (BioMatrixTM or BioMatrixFlexTM; Biosensors Inc., Newport Beach, CA, USA) and ZES (Resolute integrityTM or Resolute OnyxTM; Medtronic Inc., Santa Rosa, CA, USA) in patients undergoing multi-vessel PCI at 10 hospitals in South Korea. The enrollment criteria were those who planned to have stents implanted in 2 or more coronary arteries and who agreed to provide informed consent. Patients with contraindications to the use of antiplatelet agents, heparin, contrast agents, biolimus, or zotarolimus, planned major operations requiring discontinuation of antiplatelet agents within 12 months, lactation or pregnancy, cardiogenic shock, or life expectancy within 2 years were excluded (**Supplementary Table 1**). Patients were randomly assigned (1:1) to receive either the BES or ZES. The study used randomization stratified into randomization blocks, considering the study site, diabetes, number of diseased vessel and clinical diagnosis to ensure unbiased allocation. After confirming the inclusion and exclusion criteria, patients were randomly assigned to treatment groups via a central web-based data capture system. The number of enrolled patients was determined based on eligibility confirmation and randomization.

Percutaneous coronary intervention procedure

Coronary interventions were performed per relevant standard guidelines during each procedure. All patients received loading doses of aspirin (300 mg) and P2Y12 inhibitors (clopidogrel 300–600 mg, prasugrel 60 mg, or ticagrelor 180 mg) before PCI unless they had previously received these antiplatelet medications. Anticoagulation was performed using low-molecular-weight or unfractionated heparin to achieve an activated clotting time of 250–300 seconds during PCI. Treatment strategies, such as access site, use of glycoprotein IIb/IIIa inhibitors, and intravascular imaging or invasive physiologic assessment, were all left to the operators' discretion. Lesion preparation with balloon predilation was mandated, and using a rotablator, cutting balloon, or noncompliant balloon was left to the operators' discretion. After the procedure, 100 mg aspirin was continued indefinitely, and the maintenance duration of clopidogrel (75 mg/day), prasugrel (10 mg/day), and ticagrelor (90 mg twice daily) were at the discretion of the operators.

Study outcomes and definitions

The primary clinical outcome was a major adverse cardiac event (MACE), a composite endpoint of death from any cause, myocardial infarction (MI), or repeat revascularization. Various secondary clinical outcomes were also assessed, including death (any cause, cardiac cause, or non-cardiac cause), a MI (any cause or target-vessel MI), target-vessel revascularization, target-lesion revascularization (TLR), definite or probable stent thrombosis according to Academic Research Consortium (ARC) criteria[8)9)] and target-lesion failure (TLF; all-cause death, target-lesion related MI or ischemic-driven TLR), the individual components of the composite endpoints at 2 years.

Death was considered a cardiac cause unless an unequivocal non-cardiac cause could be established. Peri-procedural MI was defined according to the modified ARC criteria specified in the protocol. It included a creatine kinase myocardial band (CK-MB) measurement, if available, or troponin levels measured within 48 hours of the interventional procedure, showing an elevation greater than 3 times the upper limit of normal (ULN). Patients with baseline CK-MB (or troponin) values greater than the ULN also needed a confirmed increase of 50% or higher than the baseline value, with evidence that the cardiac biomarker values decreased before the suspected MI. Spontaneous MI was defined as any elevation

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of CK-MB or troponin levels above the ULN accompanied by ischemic symptoms, new electrocardiographic abnormalities suggestive of ischemia, or the emergence of imaging evidence or regional wall motion abnormalities indicating infarction. Ischemia-driven revascularization was defined as any repeat revascularization of the target-lesion or target-vessel associated with ischemic symptoms, abnormal functional study results, or both, along with coronary stenosis of 50% or higher on quantitative angiography or any revascularization of a 70% or greater diameter stenosis. TLR was defined as repeat revascularization with PCI or coronary artery graft bypass for restenosis of the entire segment involving the implanted stent and within 5 mm of the distal and proximal margins. Device failure was defined as the failure of successful revascularization with the randomized stent.

Statistical analysis

Continuous variables were compared between the groups using a Student's t-test and are presented as the mean ± standard deviation. Categorical data were compared between groups using the χ^2 test and are presented as numbers and relative frequencies. The cumulative incidence of clinical events was presented as a Kaplan–Meier estimate, and the significance level was assessed using a log-rank test. Hazard ratios (HRs) and 90% confidence intervals (CIs) were calculated using Cox proportional hazard models, and the proportional hazard assumptions of the HRs in the Cox proportional hazard models were graphically inspected in the "log minus log" plot and also tested by Schoenfeld residuals.

This trial was designed to establish the non-inferiority of BES compared to ZES for the primary endpoint of MACE at 2 years. In the SYNTAX trial,[3] which compared PCI and CABG using a first-generation paclitaxel-eluting stent for the treatment of MVD, the incidence of major cardiac events at 2 years after PCI was approximately 24%. Second-generation stents are expected to have a lower event rate. In the case of RESOLUTE ALL Comers using second-generation stents for various coronary lesions, the incidence of major cardiac events at 2 years was approximately 20%.[10] Therefore, in the current study, BES and ZES were randomly assigned to patients who needed multi-vessel PCI, assuming a 2-year MACE rate of around 20% for BES approximately 24% for ZES. Considering that the MACE rate of second-generation stents will not exceed 24% of the first-generation DES, we aimed to confirm that the BES is non-inferior to the ZES. For the sample size calculation, the assignment of 932 patients in a 1:1 ratio to the BES vs. ZES group and a power of 80% showed non-inferiority, with a 1-sided α-level of 0.05, a non-inferiority margin of 3% and an estimated 2% procedural failure and 5% loss to follow-up. All primary and secondary analyses were performed in the intention-to-treat (ITT) population, which consisted of all randomly assigned patients regardless of the treatment received. All probability values were 2-sided, and p values <0.05 were considered statistically significant. Statistical analyses were performed using the R Statistical Software (version 3.6.0; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Characteristics of the study patients and lesions

A total of 936 patients were enrolled and randomly assigned to either the BES (n=472) or ZES (n=464) groups (**Figure 1**). Approximately one-third of the patients had been medically treated for diabetes mellitus, and 60% presented with acute coronary syndromes (**Table 1**). The number of 3-vessel disease was 16%, and the mean SYNTAX score was 20. The left anterior descending and right coronary arteries were the most commonly treated vessels,

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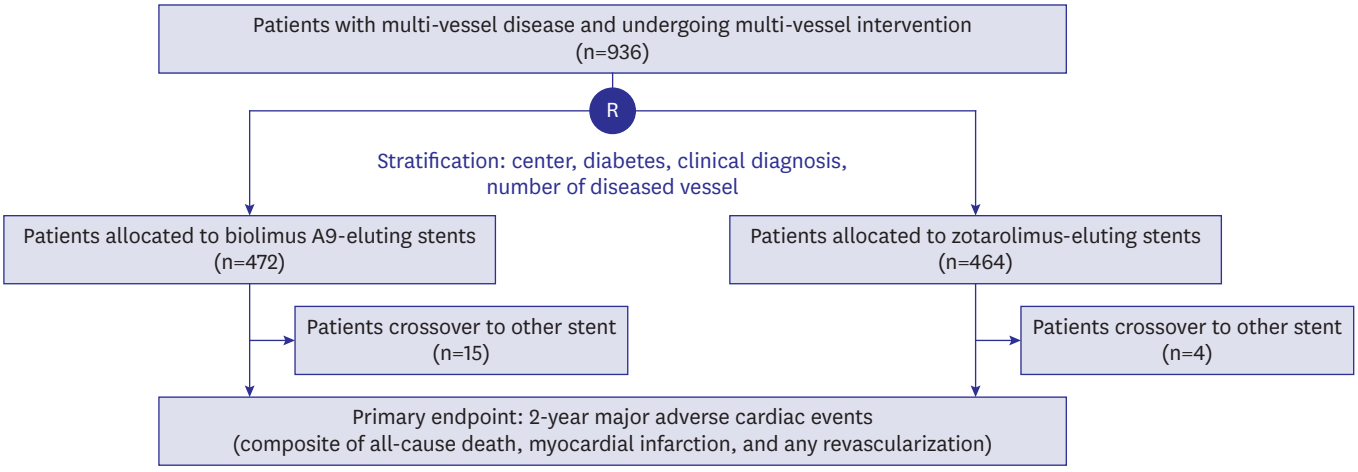

Figure 1. Study flow.

Table 1. Baseline characteristics of patients

Characteristics	BES (n=472)	ZES (n=464)	p value
Age (years)	65.6±10.3	65.5±10.3	0.82
Body mass index	24.6±3.2	24.8±3.2	0.31
Male	346 (73.3)	315 (67.9)	0.08
Hypertension	280 (59.3)	266 (57.3)	0.58
Diabetes mellitus	176 (37.3)	166 (35.8)	0.68
Dyslipidemia	212 (44.9)	218 (47.0)	0.56
Current smoker	138 (29.2)	121 (26.1)	0.31
Previous MI	16 (3.4)	17 (3.7)	0.96
Previous PCI	15 (3.2)	17 (3.7)	0.81
Previous stroke	45 (9.5)	40 (8.6)	0.71
Renal failure	25 (5.3)	13 (2.8)	0.08
Ejection fraction (%)	57.6±11.6	58.4±11.9	0.31
Clinical presentation			0.93
Stable angina	183 (38.8)	183 (39.4)	
Unstable angina	101 (21.4)	104 (22.4)	
NSTEMI	146 (30.9)	140 (30.2)	
STEMI	42 (8.9)	37 (8.0)	
Acute coronary syndrome	289 (61.2)	281 (60.6)	0.88
Number of disease vessel			0.99
2-vessel disease	396 (83.9)	389 (83.8)	
3-vessel disease	76 (16.1)	75 (16.2)	
Syntax score	20.8±9.7	20.8±9.9	0.96
Discharge medications			
Aspirin	465 (98.5)	459 (98.9)	0.79
P2Y12 inhibitor	452 (95.8)	453 (97.6)	0.15
β-blocker	318 (67.4)	313 (67.5)	>0.99
Calcium channel blocker	98 (20.8)	96 (20.7)	>0.99
ACE inhibitor or ARB	282 (59.7)	257 (55.4)	0.20
Statin	449 (95.1)	431 (92.9)	0.19

Data are shown as the mean ± standard deviation for continuous variables and absolute numbers (percentage) for dichotomous variables.
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BES = biolimus A9-eluting stent; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; ZES = zotarolimus-eluting stent.

and 70% of lesions were characterized by type B2 or C complexity. The mean number of lesions treated per patient was 2.6, and the mean total stent length per patient was 64.6 mm (**Table 2**). In the BES group, the device failure rate of assigned stents was considerably higher than that of the ZES group (BES vs. ZES: 3.2% vs. 0.9%, p=0.023). There was no in-hospital

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Table 2. Baseline lesion and procedural characteristics

Characteristics	BES (n=1,049)	ZES (n=1,044)	p value
Location			0.99
LM	24 (2.3)	25 (2.4)	
LAD	406 (38.7)	403 (38.6)	
LCX	281 (26.8)	283 (27.1)	
RCA	338 (32.2)	333 (31.9)	
ACC/AHA class B2/C	735 (70.1)	739 (70.8)	0.75
In-stent restenosis	5 (0.5)	5 (0.5)	0.99
Total occlusion	87 (8.3)	107 (10.2)	0.14
Moderate to severe calcification	130 (12.4)	101 (9.7)	0.056
Thrombus present	49 (4.7)	40 (3.8)	0.39
Bifurcation lesion	140 (13.3)	158 (15.1)	0.26
Ostial lesion	36 (3.4)	44 (4.2)	0.41
Number of stents			
Per lesion	1.2±0.4	1.2±0.4	0.095
Per patient	2.7±0.9	2.6±0.9	0.31
Mean stent diameter	3.0±0.4	3.0±0.4	0.96
Total stent length			
Per lesion	29.0±15.1	28.9±15.0	0.88
Per patient	64.5±26.8	64.8±28.5	0.89
Pre-procedure QCA			
Reference diameter (mm)	3.0±0.4	2.9±0.4	0.93
MLD (mm)	0.6±0.3	0.6±0.4	0.40
Diameter stenosis (%)	80.9±9.8	80.3±10.3	0.21
Lesion length (mm)	26.0±14.1	25.2±14.1	0.32
Post-procedure			
MLD (mm)	2.7±0.4	2.7±0.4	0.83
Diameter stenosis (%)	10.6±6.8	10.7±6.7	0.93

Data are shown as the mean ± standard deviation for continuous variables and absolute numbers (percentage) for dichotomous variables. Number, length, and diameter of the stents were all calculated per lesion.
ACC = American College of Cardiology; AHA = American Heart Association; BES = biolimus A9-eluting stent; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; LM = left main coronary artery; MLD = minimal luminal diameter; QCA = quantitative coronary angiography; RCA = right coronary artery; ZES = zotarolimus-eluting stent.

mortality, and peri-procedural MI was no significant difference between the 2 groups (1.25% vs. 1.9%, p=0.418).

Comparison of clinical outcome between zotarolimus-eluting stent and biolimus A9-eluting stent

The proportion of patients who completed 2-year follow-up monitoring was 98.2%. The 2-year observed primary endpoint was not statistically different between the 2 groups, and obtained results exceeded the predefined non-inferiority margin (11.2% vs. 10.9%; HR, 1.00; 90% CI, 0.72, 1.38; p=0.994, non-inferiority margin, 3.0%; absolute risk difference 90% CI, −3.12, 3.77%). In the secondary endpoint, the incidence of a 2-year cardiac death (1.5% vs. 2.2%; HR, 0.77; 90% CI, 0.35, 1.69; p=0.588), spontaneous MI (0.9% vs. 0.7%; HR, 0.95; 90% CI, 0.30, 3.04; p=0.940), and TLR (4.1% vs. 4.7%; HR, 0.87; 90% CI, 0.52, 1.46; p=0.656) did not differ between the 2 groups (**Table 3**, **Figure 2**). Technical failure occurred in 15 patients with the BES and 4 patients with the ZES (p=0.023). Specifically, delivery failure occurred in 11 patients with the BES and 2 patients with the ZES, showing a statistically significant difference (p=0.028). The remaining technical failures were due to stent length mismatches. **Figure 3** shows the subgroup analyses of the primary endpoint. There was no statistically significant difference between the 2 groups. Multivariable regression analysis for the predictors of the MACE showed chronic renal failure (HR, 2.19; 95% CI, 1.1, 4.35; p=0.026), SYNTAX score (HR, 1.03; 95% CI, 1.01, 1.05; p=0.006), and

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body mass index (HR, 0.93; 95% CI, 0.88, 0.99; p=0.036) as the independent predictors (**Supplementary Table 2**).

DISCUSSION

The major findings from the present study, which compared BES and ZES after multi-vessel PCI, are as follows: 1) in the contemporary DES era, the 2-year clinical outcome of multi-vessel PCI was favorable; 2) biodegradable polymer-based BES showed similar clinical outcomes to durable polymer-based ZES in multi-vessel PCI patients. However, BES was not showed to be

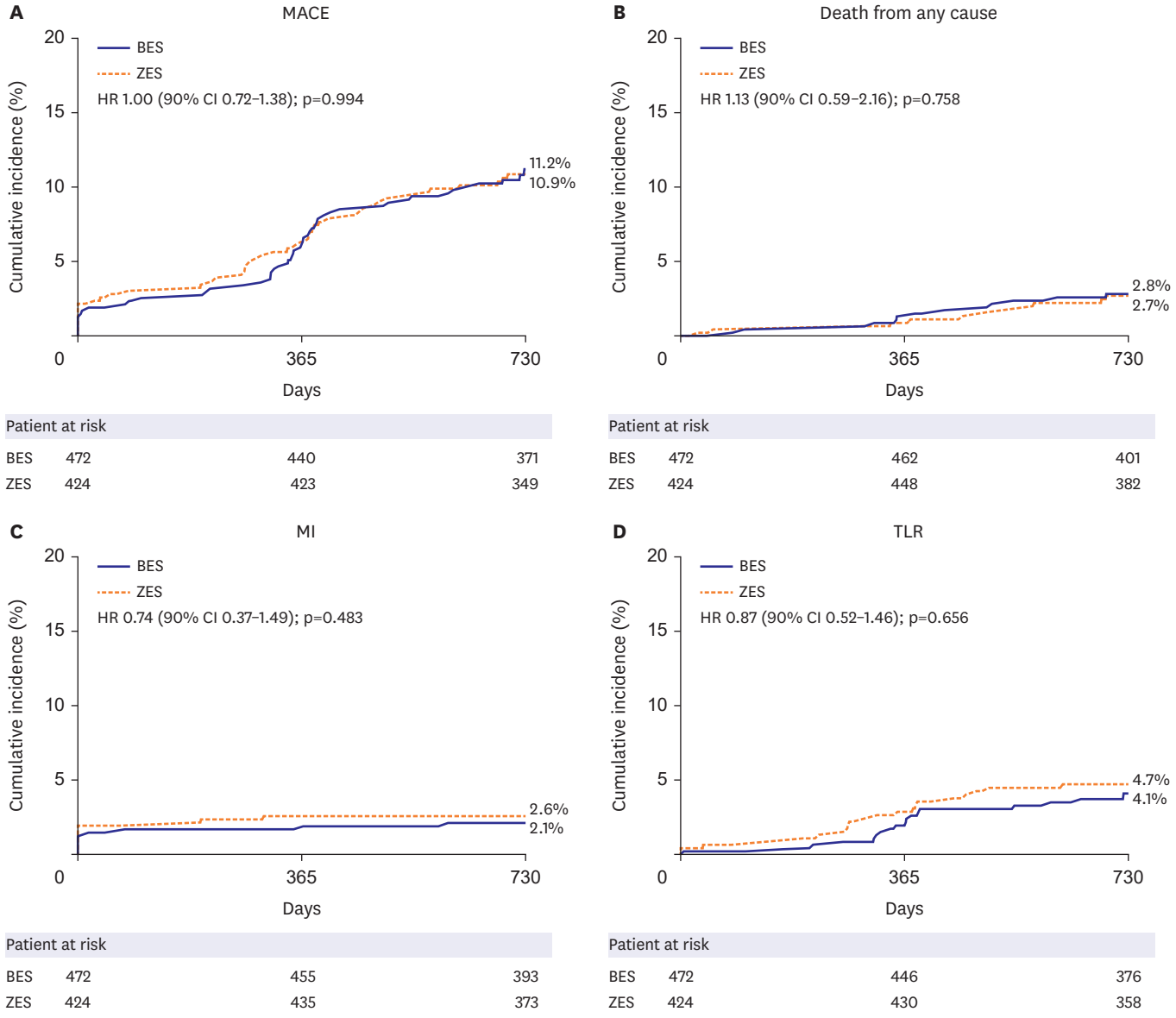

Figure 2. Cumulative 2-year event rate according to type of DES. Each figure shows the 2-year cumulative incidence curves for major adverse cardiovascular events according to the DES type of DES. MACE was defined as a composite of death from any cause, MI, or any repeat revascularization (A), death from any cause (B), MI (C), or TLR (D).
BES = biolimus A9-eluting stent; CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio; MACE = major adverse cardiac event; MI = myocardial infarction; TLR = target-lesion revascularization; ZES = zotarolimus-eluting stent.

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Table 3. Two-year clinical outcomes according to type of drug-eluting stent

Outcomes	BES (n=472)	ZES (n=464)	Absolute difference (90% CI)	Hazard ratio (90% CI)	p value
Primary outcome					
MACE	52 (11.2)	50 (10.9)	0.33 (−3.12, 3.77)	1.00 (0.72, 1.38)	0.994
Secondary outcomes					
Death from any cause	14 (2.8)	12 (2.7)	0.11 (−1.67, 1.90)	1.13 (0.59, 2.16)	0.758
Cardiac	8 (1.5)	10 (2.2)	−0.70 (−2.19, 0.79)	0.77 (0.35, 1.69)	0.588
Non-cardiac	6 (1.3)	2 (0.5)	0.82 (−0.20, 1.84)	2.91 (0.76, 11.13)	0.191
Myocardial infarction	10 (2.1)	13 (2.6)	−0.47 (−2.11, 1.17)	0.74 (0.37, 1.49)	0.483
Peri-procedure MI	6 (1.2)	9 (1.9)	−0.67 (−2.02, 0.68)	0.65 (0.27, 1.55)	0.418
Spontaneous MI	4 (0.9)	4 (0.7)	0.20 (−0.76, 1.16)	0.95 (0.30, 3.04)	0.940
Any revascularization	31 (6.7)	31 (6.9)	−0.31 (−3.08, 2.47)	0.96 (0.63, 1.46)	0.876
Target-vessel	31 (6.7)	31 (6.9)	−0.31 (−3.08, 2.47)	0.96 (0.63, 1.46)	0.876
Target-lesion	19 (4.1)	21 (4.7)	−0.63 (−2.98, 1.75)	0.87 (0.52, 1.46)	0.656
Definite stent thrombosis	1 (0.2)	0 (0.0)	-	-	0.301
Target-vessel failure	46 (10.0)	48 (10.4)	−0.43 (−3.85, 2.88)	0.92 (0.66, 1.29)	0.687
Target-lesion failure	35 (7.7)	38 (8.3)	−0.55 (−3.46, 2.45)	0.88 (0.60, 1.30)	0.600

Values are number of events, percentages (Kaplan–Meier estimates), and hazard ratio (90% CI). Target-vessel failure was defined as a composite of death from cardiac causes, target-vessel MI, or target-vessel revascularization.
BES = biolimus A9-eluting stent; CI = confidence interval; MACE = major adverse cardiovascular events; MI = myocardial infarction; ZES = zotarolimus-eluting stent.

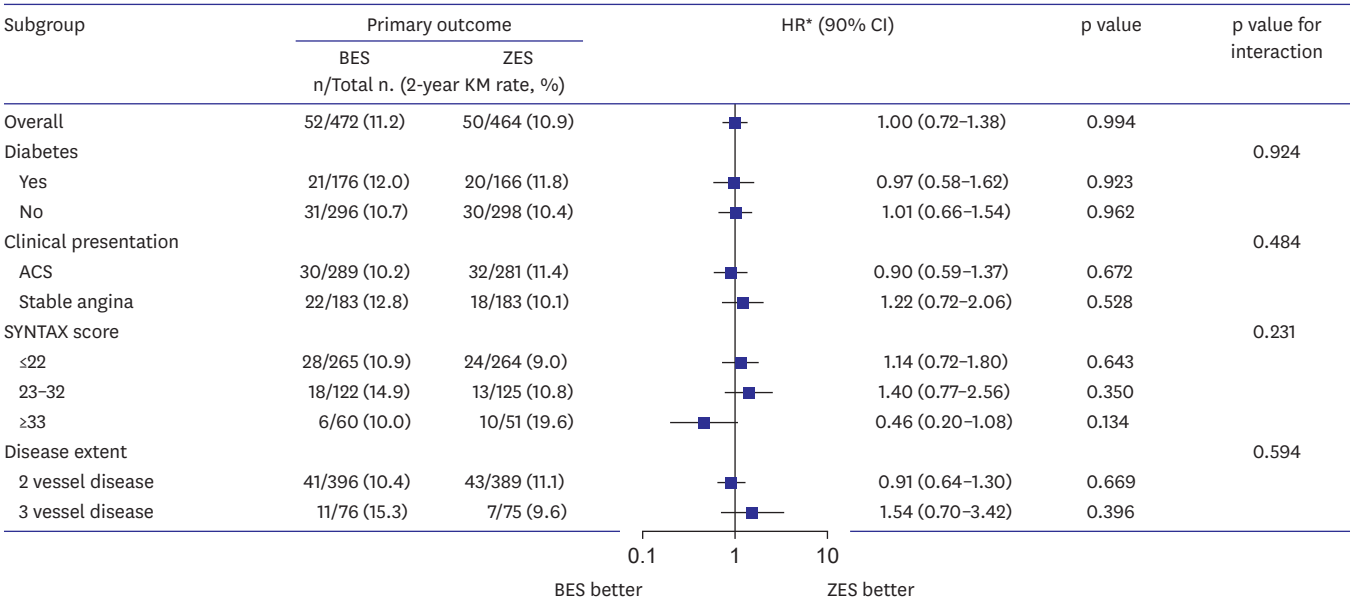

Figure 3. Subgroup analysis.
ACS = acute coronary syndrome; BES = biolimus A9-eluting stent; CI = confidence interval; HR = hazard ratio; KM = Kaplan–Meier; ZES = zotarolimus-eluting stent.
*HRs are for the BES, as compared to the ZES.

noninferior to ZES with respect to incidence of primary endpoint at 2-year; 3) Thinner ZES showed a lower device failure rate than that of thicker BES, leading to the use of other stents.

DESs have been developed continuously over the past decade. Major changes in contemporary DES can be seen in the type of drug, polymer, and strut thickness used. The stent's delivery drug and polymer type used in the current study were the biocompatible polymer zotarolimus and the biodegradable polymer biololimus A9. The RESOLUTE ALL trial had a mean SYNTAX score of approximately 14, and MVD was approximately 27%. In contrast, the all-comer LEADERS trial had an average SYNTAX score of approximately 12, and MVD was approximately 20%, showing a favorable clinical outcome for all-comer patients.[10][11] Accordingly, both contemporary stents showed results similar to those of the standard stent in a randomized

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trial. However, the current study enrolled only patients with multi-vessel coronary lesions, and the mean SYNTAX score was 20, indicating more anatomically complex lesions. Considering the disease burden and lesion complexity, this study included patients in the borderline zone for CABG and PCI treatment decisions. The 2-year MACE was approximately 11%, and it was possible to confirm how a contemporary DES is applied to anatomically complex coronary lesions.

In studies comparing CABG and PCI, the BEST trial comparing PCI and CABG using second-generation durable polymer DES had a mean SYNTAX score of 24 and the number of 3-vessel disease was 75%, showing more complex PCI than in the current study.[4] The 2-year MACE rate in the BEST trial was 15%, which showed the same clinical outcome as a high syntax score. Another recent study, the FAME 3 trial, is a randomized trial that showed the clinical outcome of physiologically guided multi-vessel PCI to be most similar to modern PCI strategies.[12] This study using ZES was one of the trials that performed PCI on the most complex lesions with a mean SYNTAX score of 26 and a mean number of 3.7 stents; the 1-year MACE rate was reported to be 10%. In summary, when comparing several trials, contemporary DES show acceptable clinical outcomes according to the lesion complexity, regardless of the drug or polymer. Subgroup analysis showed no differences between the groups according to acute coronary syndrome, diabetes mellitus, SYNTAX score, and extent of disease, which is similar to previous studies that did not show changes in clinical outcomes according to the drug and polymer type of contemporary DES.[13][14]

To enhance the performance of durable polymer-based second-generation DES, multiple versions have been introduced, such as bioresorbable polymer-based DES, polymer-free DES, and bioresorbable scaffolds. Nevertheless, the clinical results achieved with these novel systems have shown non-inferiority compared to their durable polymer counterparts.[15][16] However, recent studies based on large registries using national data have reported that clinical outcomes differ after 2 years depending on the polymer type.[17] As many previous randomized trials have only investigated midterm data, there is a need to focus on long-term outcomes using national registries. The current study focused on complex PCI, excluding simple coronary lesions, making it more suitable for observing differences in clinical outcomes based on polymer type. While no significant difference was observed between the groups for up to 2 years, it is important to note the potential changes in this difference beyond the 2-year landmark in the future.

Another important issue with multi-vessel PCI is that most lesions are long, and many situations are unsuitable for stent delivery, such as heavily calcified lesions, chronic total occlusion, and angled lesions. The strut thickness of the stent used in the current study is 90 μm for ZES and 120 μm for BES, and there is a difference in strut thickness on both sides. ITT analysis confirmed no difference in the 2-year clinical outcomes between the 2 groups after successful PCI. However, the device failure rate of the assigned stent, which was changed to another stent during the PCI procedure after being randomly assigned, was significantly high in the BES with thick struts. Strut thickness, as in BIOFLOW V, reduces MI in ultrathin struts and improves clinical outcomes[18][19]; however, it can also affect stent delivery at PCI, which can also affect procedural success.[20] Contemporary DES was mainly developed with a 60–90 μm strut thickness. BES, which had a strut thickness of 120 μm in the current study, was recently developed with a strut thickness of 80 μm, showing favorable data.[21] Strut thickening may not be a problem with sufficient lesion preparation in simple coronary lesions. However, there may be problems with stent delivery or optimization in

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multi-vessel and complex lesions. These findings, which showed differences in device failure rates based on strut thickness, could inform physicians regarding stent selection in routine practice. Given these results, the direction in stent development should be to develop strut thickness as a thinner strut within a range where the radial force does not significantly decrease.

Using thinner struts improves flexibility, making the stent easier to deliver and decreasing the extent of arterial injury and inflammation caused by the stent, leading to faster endothelialization.[22] Reducing the strut thickness of a stent by approximately 10 μm is expected to result in a modest but consistent 16% relative risk reduction in TLF, as reported in a recent meta-analysis.[23] However, in the current study, the difference in strut thickness only affected the device failure rate of the assigned stent and did not show any difference in the clinical outcomes. Recent data show that the ultrathin strut stent in BIOFLOW V mainly reduced MI during the peri-procedural period while improving TLF but did not show improvement in TLR or TLF in the long-term landmark analysis.[24] Thinner struts did not improve TLR through changes in angiographic lumen loss in several studies.[25][26] In the current study, neither stent was an ultrathin strut stent, and there was no difference in the clinical outcomes based on strut thickness after stent implantation.

This study has several limitations. First, because TLF was not the primary endpoint of the current study, device-related clinical outcomes may not have been demonstrated. However, since it is a multi-vessel coronary disease, when comparing target-vessel failure, there is almost no difference from MACE, which may not be an important issue. Second, compared with the cardiac adverse event rate at the time of the study design, the clinical outcome of the current study was shown to be low, which may have resulted in the study being underpowered. This lower event rate may have been a time lag bias. In addition, it may have contributed to the reduction in cardiac adverse events due to technological advances in coronary interventions, such as intravascular imaging and hemodynamic assessment, between previous studies. For this reason, even though the clinical outcome was similar, the event rate was smaller than expected, and therefore non-inferiority could not be demonstrated. Third, it is estimated that the thicker-strut BES is inferior to the thinner ZES in delivery performance and has a high crossover rate; however, because all information, such as eccentric calcification and angulation of the lesion, is not known, differences in lesion characteristics at baseline cannot be completely ruled out. However, even for thicker-strut BES, a new stent with improved thickness has recently been developed, showing good clinical results, which has a correlation with our research findings. Thinner struts can be considered an important change in stent development in complex lesions.

In this randomized study with multiple uses of BES and ZES, although the procedural success rate with the random stent was higher in thinner ZES, both stents showed comparable clinical outcomes at the 2-year follow-up. However, BES was not founded to be noninferior to ZES with respect to incidence of MACE at 2-year. Further follow-up is required to confirm the clinically meaningful differences between these devices.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Inclusion and exclusion criteria

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Supplementary Table 2

Univariate and multivariate Cox proportional hazard analyses for MACE in enrolled patients

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