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Comparison of long-term clinical outcomes among zotarolimus-, everolimus-, and biolimus-eluting stents in acute myocardial infarction patients with renal impairment

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Abstract

Background: *It is important to determine the best drug-eluting stent (DES) for acute myocardial infarction (AMI) in patients with renal impairment. In this studythe outcomes of everolimus-eluting stents (EESs), zotarolimus-eluting stents (ZESs) and biolimus-eluting stents (BESs) were evaluated.*

Methods: *From the Korea Acute Myocardial Infarction-National Institutes of Health registry, a total of 1,470 AMI patients with renal impairment undergoing percutaneous coronary intervention (PCI) were enrolled (816 with EES, 345 with ZES, and 309 with BES). Renal impairment was defined as creatinine clearance < 60 mL/min/1.73 m^2 estimated by the Cockcroft-Gault method. Major adverse cardiac and cerebrovascular events were determined as the composite of all-cause death, non-fatal myocardial infarction (MI), cerebrovascular accident, any revascularization, rehospitalization and stent thrombosis. All clinical outcomes were analyzed.*

Results: *The baseline characteristics of the patients revealed no significant difference between the three groups, except for Killip classification > 2, beta-blockers, lesion type, vascular approach, staged PCI, left main coronary artery (LMCA) complex lesions, LMCA PCI, and the number and length of implanted stents. In the Kaplan-Meier analysis, similar clinical outcomes were derived from the unadjusted data between the three DES groups. However, after the inverse probability of treatment weighting, a statistically significant difference was found in non-fatal MI, which implied a higher incidence of non-fatal MI in the ZES group than in the other two DES groups.*

Conclusions: *In AMI patients with renal impairment, there was no significant difference between the three stent groups in terms of long-term clinical outcomes, except for non-fatal MI.* (Cardiol J)

Key words: myocardial infarction, renal insufficiency, drug-eluting stents, zotarolimus, everolimus, biolimus

Introduction

The incidence of acute coronary syndrome (ACS) with concomitant acute myocardial infarction (AMI), is gradually rising, leading to serious socioeconomic problems. Risk factors for coronary artery disease (CAD) such as diabetes, hypertension, and chronic kidney disease (CKD) are similarly increasing. Among these risk factors, CKD is an independent risk factor for cardiovascular disease [1, 2]. In patients with end-stage kidney disease (ESKD), the incidence of cardiovascular diseases is 8.8–10 times higher than the general population [3, 4].

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Acute myocardial infarction, a medical emergency, is a type of ACS that requires rapid revascularization. The advent of coronary stents, utilized for the treatment of coronary stenosis, has contributed to a decrease in both, restenosis and the likelihood of emergency coronary artery bypass grafting (CABG) [5, 6]. After 2002, the emergence of drug-eluting stents (DESs), including the sirolimus-eluting stents (SESs) and paclitaxel-eluting stents significantly reduced the incidence of restenosis and the need for repeat revascularization compared with balloon angioplasty. The use of first-generation DES (1G-DES) has reduced the rate of target lesion revascularization (TLR) and CABG as a treatment option after stent implantation [7, 8]. However, there is an increasing concern about stent thrombosis, one of the most catastrophic phenomena of percutaneous coronary intervention (PCI), which manifests as ST-segment elevation myocardial infarction (STEMI) and/or sudden cardiac arrest requiring repeat revascularization [9]. Newer generation durable polymer-coated DESs using zotarolimus or everolimus, called second-generation drug-eluting stents (2G-DESs), were developed to ameliorate polymer biocompatibility, leading to a significant reduction in in-stent restenosis, stent thrombosis, the duration of dual antiplatelet therapy (DAPT), and bleeding complications [10, 11]. In addition, biolimus-eluting stents (BESs), which use a biodegradable polymer, have been developed to treat long-term vascular complications related to durable polymers. Studies have shown that BES reduce late stent thrombosis compared with 1G-DES [12]. In addition, it exhibited similar safety and efficacy characteristics compared with those of other 2G-DESs [13, 14].

It has been established that cardiovascular disease is a leading cause of morbidity and mortality among CKD patients. CKD progresses through supply-demand mismatch, ischemic preconditioning, collateralization of blood vessels, and a high prevalence of left ventricular hypertrophy, leading to the development of CAD [2, 15].

In this study, the focus was on the differences in clinical outcomes between DESs in AMI patients. There is a paucity of clinical data on the difference in the outcomes between the three stent groups (zotarolimus-eluting stents [ZESs], everolimus-eluting stents [EESs], and BESs) in patients with AMI and renal impairment (AMI-RI). This clinical study aimed to elucidate the clinical differences between these three types of stents in patients with AMI and concomitant renal impairment undergoing PCI.

Methods

Study population

The study population was extracted from the Korea Acute Myocardial Infarction Registry-National Institutes of Health (KAMIR-NIH), a nationwide, multicenter, online observational cohort study. The KAMIR-NIH consecutively enrolled AMI patients at 20 major cardiovascular institutes between 2011 and 2015. Among 13,104 AMI patients, a total of 4,692 AMI-RI patients were initially screened. The exclusion criteria included patients who: (a) had a prior myocardial infarction (MI); (b) died during index hospitalization; (c) underwent no PCI or unsuccessful and/or partial revascularization during the index PCI; (d) underwent PCI without stent implantation or with stents other than the EES, ZES, or BES; (e) underwent CABG as a revascularization strategy; (f) underwent thrombolysis; and (g) received overlap implantations of two or three types of EES, ZES, or BES. After excluding 3,222 patients, a total of 1,470 patients were included in the study. These patients were classified into three groups as follows: (a) AMI-RI patients undergoing PCI with EES implantation (n = 816), (b) AMI-RI patients undergoing PCI with ZES implantation (n = 345), and (c) AMI-RI patients undergoing PCI with BES implantation (n = 309) (Fig. 1). Follow-up data of these patients were obtained mainly through regularly scheduled outpatient visits. The present study was conducted according to the ethical principles of the Declaration of Helsinki, the best-known policy statement of the World Medical Association, which was revised in 2013 [16]. Similarly, the study protocol of the KAMIR-NIH registry was also approved by the ethics committee of each participating center [17]. Written informed consent was secured from all participants.

Definition and clinical endpoints

Kidney function was determined by the creatinine clearance (CrCl) calculated using the Cockcroft-Gault formula [18], and it was based on the serum creatinine level upon admission. In this study, renal impairment was determined as CrCl < 60 mL/min/1.73 m^2 based on the serum creatinine level at the time of admission.

Acute myocardial infarction was defined according to current guidelines [19, 20], which include the typical rise and/or fall of biochemical markers of myocardial necrosis with at least one of the following: (a) clinical symptoms indicative of myocardial ischemia, (b) development of pathological Q-waves

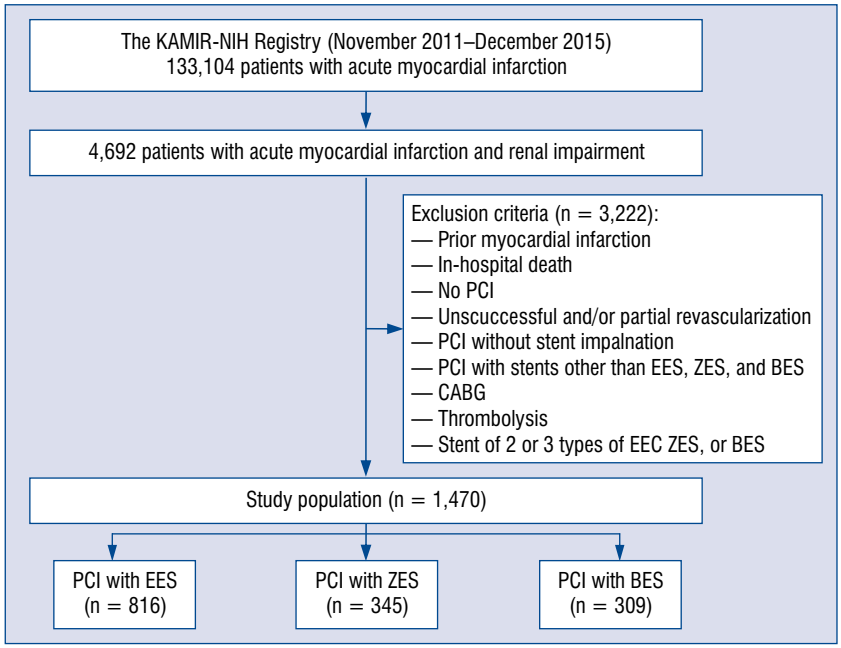

Figure 1. Flow chart for the selection of study participants; BES — biolimus-eluting stent; CABG — coronary artery bypass graft; EES — everolimus-eluting stent; KAMIR-NIH — Korea Acute Myocardial Infarction Registry-National Institutes of Health; PCI — percutaneous coronary intervention; ZES — zotarolimus-eluting stent.

in the 12-lead electrocardiogram (ECG) results, (c) ECG changes indicative of ischemia (elevation or depression of the ST-segment), and (d) imaging modalities suggesting MI (i.e., new loss of viable myocardium or new-onset regional wall motion abnormality). STEMI was defined as AMI with new-onset ST-segment elevation of at least 1 mm (0.1 mV) in 2 or more contiguous leads, or new-onset left bundle branch block observed on ECG [21]. To quantitatively evaluate the left ventricle, left ventricular ejection fraction (LVEF) was examined using 2-dimensional echocardiography. The Killip classification, introduced in 1967, is defined as follows: Killip class I, no chronic heart failure; Killip class II, third heart sound and rales; Killip class III, overt pulmonary edema; and Killip class IV, cardiogenic shock [22]. Significant stenosis of the left main coronary artery (LMCA) was defined as an — at least — 50% reduction in the intraluminal diameter of the LMCA. Unprotected left main disease was defined as the presence of significant stenosis in the LMCA with no patent bypass graft to the left anterior descending coronary artery or left circumflex coronary artery. LMCA complex lesions were defined as the presence of significant stenosis in the LMCA with the presence of added epicardial coronary artery stenosis. Significant stenosis of other epicardial coronary arteries was defined as a reduction of at least 70% in the intraluminal diameter of the epicardial coronary artery. The degree of coronary flow was quantitatively classified according to the Thrombolysis In Myocardial Infarction (TIMI) flow grade.

Clinical follow-up was performed after the commencement of the study. The primary endpoint was major adverse cardiac and cerebrovascular events (MACCE), defined as the composite of all-cause death (cardiac and non-cardiac death), non-fatal MI, cerebrovascular accident (CVA), any revascularization using PCI or CABG, rehospitalization, and stent thrombosis. The secondary endpoints were net adverse clinical events (NACE), all-cause mortality, non-fatal MI, any revascularization, CVA, rehospitalization, and stent thrombosis. NACE was defined as a composite of all-cause death, non-fatal MI, and any revascularization. Any revascularization was defined as any repeat PCI or CABG of any part of the epicardial coronary arteries overall. Rehospitalization was defined as post-index admission due to angina and/ /or heart failure.

Statistical analysis

All data analysis was performed using both STATA version 15.0 (StataCorp, College Station, Texas, United States of America) and SPSS ver-

sion 25.0 (SPSS Inc., Armonk, New York, USA). Continuous variables were expressed as means ± standard deviation and analyzed using the Student t-test and the analysis of variance test. Discrete (categorical) variables were represented as percentages with numbers and analyzed using the Pearson chi-squared test, the Fisher two-by--two exact test, or linear by linear association. All results were considered statistically significant at $p < 0.05$.

To control for differences in baseline characteristics and potential confounding factors, the propensity score weighting method, called the inverse probability of treatment weighting (IPTW), was applied [23]. The propensity score was constructed by a multiple logistic regression model using a total of 41 covariates. Participants with missing data in these covariates or whose follow-up period after hospital discharge was estimated as 0 days were excluded from IPTW adjustment.

Unadjusted and IPTW-adjusted survival analyses were performed using the Kaplan-Meier analysis to determine the incidence of clinical outcomes, and log-rank (Mantel-Cox) tests were performed to evaluate differences among the treatment groups (i.e., EES, ZES, and BES groups).

Results

Baseline clinical and procedural characteristics

Baseline clinical characteristics are summarized in Table 1. Before IPTW adjustment, a significant baseline difference was observed between the three groups in terms of the Killip classification at admission. Although the proportion of Killip classification > 2 in the ZES group was similar to that in the EES group, the BES group had a lower Killip classification than the other two groups. For discharge medications, there was a significant difference in the use of beta-blockers. The BES group received a relatively low prescription of this medication compared with the EES group. Although the EES group had a higher proportion of patients with DAPT ≥ 12 months than the ZES group, the net difference was similar between the three groups.

In coronary angiography and procedural characteristics (Table 2), some differences were observed between the three groups. The BES group had a relatively lower incidence of pre-procedural TIMI flow grade 0–I and stent number ≥ 3. The incidence of thrombus aspiration was higher in the ZES group than in the EES group. The incidence of RCA PCI was higher in the ZES group than in the other two groups. The ZES group had a higher proportion of STEMI patients compared to the EES group. Nonetheless, the net difference between the three groups was similar for these variables. Meanwhile, the overall difference was found in terms of the American Heart Association and the American College of Cardiology lesion type, vascular approach, staged PCI, LMCA complex lesions, LMCA PCI, stent number, total stent length, and total stent length > 60 mm.

After IPTW adjustment, baseline clinical and procedural characteristics were balanced between the three DES groups (**Suppl. Tables 1, 2**).

Long-term follow-up clinical outcomes

After hospital discharge, follow-up was conducted with a median delay of 1,088 days. Clinical outcomes of MACCE, NACE, all-cause mortality, non-fatal MI, any revascularization, CVA, rehospitalization and stent thrombosis were determined. Kaplan-Meier analysis was performed to describe the crude (unadjusted) and IPTW-adjusted survival curves, and the pair-wise log-rank test results for these comparisons are shown in Figures 2 and 3. Before IPTW adjustment, there were no significant differences in any clinical outcomes between the three DES groups. However, after IPTW, a significant difference was found between these groups in terms of non-fatal MI. In the ZES group, the incidence of non-fatal MI was higher than in the other two groups. The number of patients at risk is shown in Table 3.

Discussion

This study demonstrates that except for non--fatal MI, there was no significant difference among the three stent groups concerning long-term MACCE, NACE, all-cause mortality, any revascularization, CVA, rehospitalization and stent thrombosis. Regarding non-fatal MI, despite the significant difference not derived from unadjusted raw data analysis, IPTW-adjusted analysis showed that the ZES group had a higher incidence of non-fatal MI than the other two groups ($p = 0.005$).

Chronic kidney disease is a major health issue, with an increasing prevalence worldwide [24]; similarly, it is a debilitating medical condition, culminating in ESKD requiring dialysis or kidney transplantation, and is recognized as an independent cardiovascular risk factor [2, 25]. Among patients with renal impairment, cardiovascular events such as CAD, are the main cause of mortality [25, 26]. CKD

Table 1. Baseline clinical characteristics.

Characteristics	EES group (n = 816)	ZES group (n = 345)	BES group (n = 309)	P (EES vs. ZES)	P (EES vs. BES)	P (ZES vs. BES)	P
Male gender	467 (57.2%)	194 (56.2%)	174 (56.3%)	0.754	0.781	0.984	0.744
Age [years]	72.90 ± 9.33	72.86 ± 8.37	73.81 ± 8.41	0.951	0.136	0.152	0.275
Age ≥ 65 years	674 (82.6%)	294 (85.2%)	268 (86.7%)	0.273	0.094	0.578	0.076
Killip classification > 2	155 (19.0%)	68 (19.7%)	39 (12.6%)	0.777	**0.012**	**0.014**	**0.031**
BMI [kg/m^2]	22.44 ± 3.15	22.86 ± 3.13	22.38 ± 3.19	**0.036**	0.761	0.050	0.073
BMI ≥ 25 [kg/m^2]	144 (17.7%)	76 (22.0%)	59 (19.1%)	0.083	0.579	0.355	0.363
Previous history:							
Hypertension	524 (64.2%)	209 (60.6%)	196 (63.4%)	0.241	0.807	0.454	0.614
Diabetes mellitus	274 (33.6%)	119 (34.5%)	112 (36.2%)	0.764	0.400	0.640	0.413
Dyslipidemia	78 (9.6%)	31 (9.0%)	31 (10.0%)	0.760	0.811	0.648	0.912
Prior heart failure	12 (1.5%)	7 (2.0%)	9 (2.9%)	0.493	0.111	0.465	0.123
Prior CVA	74 (9.1%)	29 (8.4%)	29 (9.4%)	0.717	0.870	0.660	0.955
Smoking	343 (43.1%)	147 (44.0%)	134 (44.4%)	0.775	0.702	0.927	0.691
Family history of CAD	29 (3.6%)	12 (3.5%)	7 (2.4%)	0.943	0.298	0.385	0.362
CrCl [mL/min/1.73 m^2]	41.84 ± 13.88	43.19 ± 13.27	43.55 ± 12.83	0.126	0.060	0.722	0.095
LVEF < 40% (%)	128 (16.1%)	46 (13.9%)	35 (11.8%)	0.351	0.078	0.440	0.067
Discharge medications:							
Acetylsalicylic acid	815 (99.9%)	345 (100.0%)	309 (100.0%)	1.000	1.000	–	0.765
P2Y12 inhibitors	814 (99.8%)	344 (99.7%)	309 (100.0%)	1.000	1.000	1.000	0.714
Calcium channel blockers	58 (7.1%)	21 (6.1%)	21 (6.8%)	0.528	0.855	0.712	0.749
Beta-blockers	690 (84.6%)	280 (81.2%)	245 (79.3%)	0.153	**0.035**	0.548	**0.029**
ACEI or ARBs	653 (80.0%)	267 (77.4%)	247 (79.9%)	0.312	0.973	0.428	0.779
Statins	758 (92.9%)	315 (91.3%)	284 (91.9%)	0.350	0.574	0.781	0.504
Fibrates	2 (0.2%)	2 (0.6%)	1 (0.3%)	0.587	1.000	1.000	0.791
Oral anticoagulants	37 (4.5%)	13 (3.8%)	9 (2.9%)	0.557	0.220	0.545	0.217
Duration of DAPT:				**0.004**	0.832	**0.013**	0.609
< 12 months	312 (38.2%)	163 (47.2%)	124 (40.1%)				
12–24 months	140 (17.2%)	62 (18.0%)	50 (16.2%)				
24–36 months	114 (14.0%)	30 (8.7%)	26 (8.4%)				
≥ 36 months	250 (30.6%)	90 (26.1%)	109 (35.3%)				
Duration of DAPT (< 12 vs. ≥ 12 months):				**0.004**	0.561	0.067	0.220
< 12 months	312 (38.2%)	163 (47.2%)	124 (40.1%)				
≥ 12 months	504 (61.8%)	182 (52.8%)	185 (59.9%)				

Values are presented as mean ± standard deviation or number (%). ACEI — angiotensin-converting enzyme inhibitors; ARB — angiotensin II receptor blocker; BES — biolimus-eluting stent; BMI — body mass index; CAD — coronary artery disease; CrCl — creatinine clearance; CVA — cerebrovascular accident; DAPT — dual antiplatelet therapy; EES — everolimus-eluting stent; LVEF — left ventricular ejection fraction; ZES — zotarolimus-eluting stents

Table 2. Coronary angiography and procedural characteristics.

Characteristics	EES group (n = 816)	ZES group (n = 345)	BES group (n = 309)	P (EES vs. ZES)	P (EES vs. BES	P (ZES vs. BES)	P
AHA/ACC lesion type:				0.429	**< 0.001**	**0.005**	**< 0.001**
Type A	3 (0.4%)	10 (2.9%)	6 (1.9%)				
Type B1	103 (12.6%)	46 (13.3%)	54 (17.5%)				
Type B2	346 (42.4%)	128 (37.1%)	151 (48.9%)				
Type C	364 (44.6%)	161 (46.7%)	98 (31.7%)				
AHA/ACC type B2 or C	710 (87.0%)	289 (83.8%)	249 (80.6%)	0.145	**0.007**	0.287	**0.006**
Vascular approach:				0.930	**0.006**	**0.017**	**0.014**
Femoral approach	594 (72.8%)	252 (73.0%)	199 (64.4%)				
Non-femoral approach	222 (27.2%)	93 (27.0%)	110 (35.6%)				
Significant coronary stenosis	798 (97.8%)	340 (98.6%)	298 (96.4%)	0.398	0.201	0.081	0.308
GPIIb/IIIa inhibitor use	101 (12.4%)	44 (12.8%)	37 (12.0%)	0.859	0.854	0.763	0.922
Thrombus aspiration	157 (19.3%)	90 (26.2%)	62 (20.1%)	**0.009**	0.762	0.066	0.360
Image-guided PCI:	143 (17.5%)	61 (17.7%)	59 (19.1%)	0.949	0.540	0.641	0.582
IVUS use	138 (16.9%)	58 (16.8%)	55 (17.8%)	0.967	0.724	0.739	0.763
OCT use	7 (0.9%)	4 (1.2%)	6 (1.9%)	0.741	0.129	0.529	0.172
Pre-procedural TIMI 0–I	460 (56.4%)	225 (65.2%)	149 (48.2%)	**0.005**	**0.014**	**< 0.001**	0.126
Infarct-related artery:				0.085	0.347	0.533	0.204
LMCA	22 (2.7%)	7 (2.0%)	2 (0.6%)				
LAD	395 (48.4%)	159 (46.1%)	146 (47.2%)				
LCX	124 (15.2%)	39 (11.3%)	55 (17.8%)				
RCA	275 (33.7%)	140 (40.6%)	106 (34.3%)				
Multivessel PCI (not IRA-only PCI):	193 (23.7%)	74 (21.4%)	60 (19.4%)	0.415	0.129	0.520	0.115
Staged PCI	85 (10.4%)	26 (7.5%)	18 (5.8%)	0.127	**0.017**	0.383	**0.010**
LMCA complex lesions (multivessel lesion or ULMD)	32 (3.9%)	9 (2.6%)	5 (1.6%)	0.268	0.053	0.382	**0.038**
Territories of revascularization:							
LMCA PCI	36 (4.4%)	12 (3.5%)	5 (1.6%)	0.465	**0.026**	0.136	**0.027**
LAD PCI	519 (63.6%)	221 (64.1%)	189 (61.2%)	0.883	0.450	0.445	0.519
LCX PCI	247 (30.3%)	94 (27.2%)	102 (33.0%)	0.301	0.375	0.108	0.582
RCA PCI	368 (45.1%)	179 (51.9%)	133 (43.0%)	**0.034**	0.536	**0.024**	0.976
Multivessel disease	275 (33.7%)	116 (33.6%)	96 (31.1%)	0.980	0.402	0.486	0.447
STEMI diagnosis	397 (48.7%)	184 (53.3%)	141 (45.6%)	0.145	0.365	**0.049**	0.651
Stent profiles:							
Stent number	1.57 ± 0.84	1.61 ± 0.89	1.42 ± 0.75	0.472	**0.006**	**0.005**	**0.012**
Stent number ≥ 3	109 (13.4%)	54 (15.7%)	27 (8.7%)	0.304	**0.034**	**0.007**	0.111
Total stent length [mm]	32.04 ± 15.92	30.45 ± 15.72	25.68 ± 11.61	0.119	**< 0.001**	**< 0.001**	**< 0.001**
Total stent length > 60 mm	68 (8.3%)	16 (4.6%)	6 (1.9%)	**0.026**	**< 0.001**	0.056	**< 0.001**
Mean stent diameter [mm]	3.08 ± 0.41	3.09 ± 0.39	3.05 ± 0.39	0.646	0.282	0.186	0.417

Values are presented as mean ± standard deviation or number (%). AHA/ACC — The American Heart Association and the American College of Cardiology; BES — biolimus-eluting stent; EES — everolimus--eluting stent; GPIIb/IIIa — glycoprotein IIb/IIIa complex; IRA — infarct-related artery; IVUS — intravascular ultrasound; LAD — left anterior descending coronary artery; LCX — left circumflex coronary artery; LMCA — left main coronary artery; PCI — percutaneous coronary intervention; RCA — right coronary artery; STEMI — ST-segment elevation myocardial infarction; OCT — optical computed tomography; TIMI — Thrombolysis In Myocardial Infarction; ZES — zotarolimus-eluting stent; ULMD — unprotected left main disease

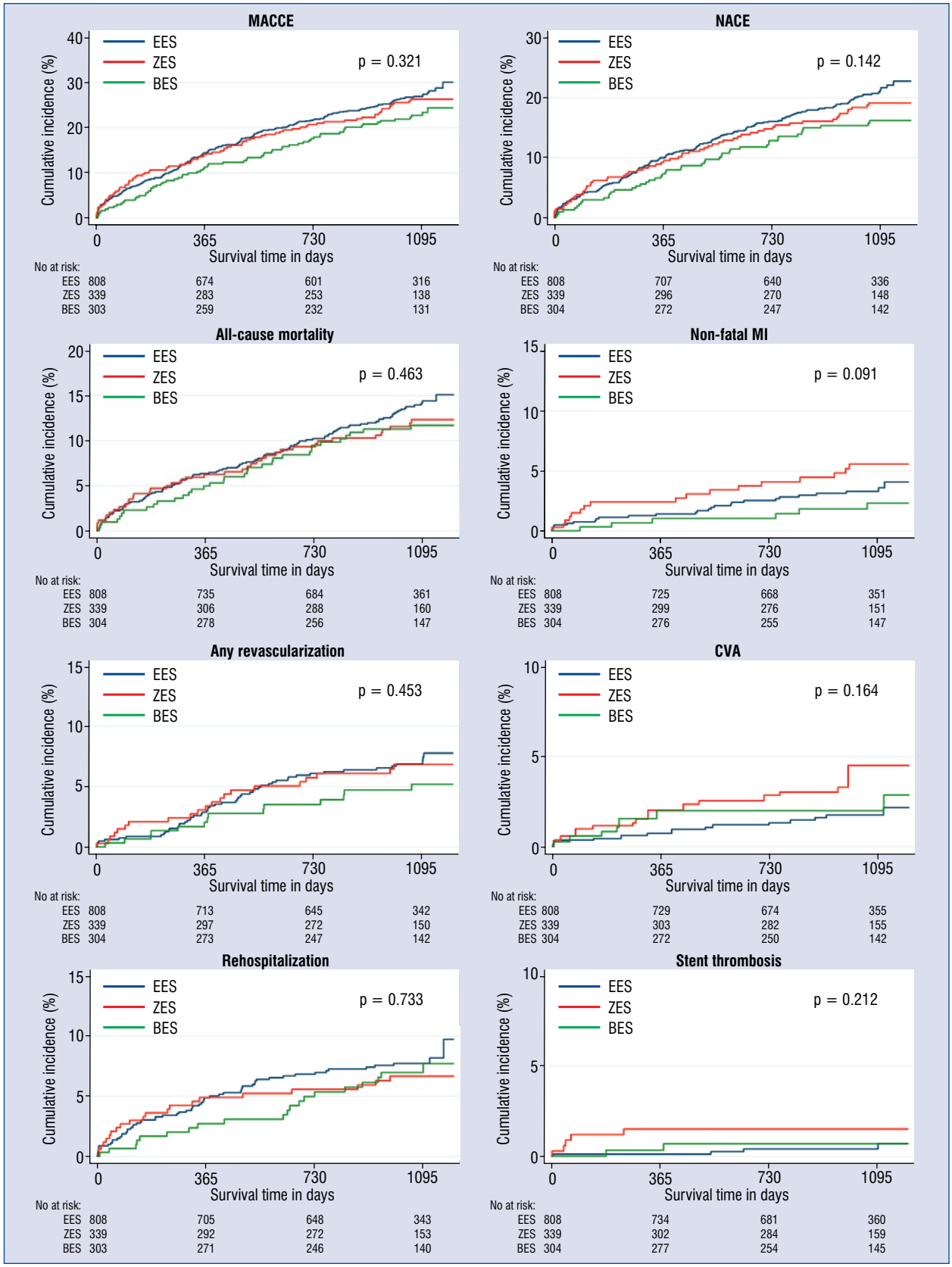

Figure 2. Kaplan-Meier survival analyses of long-term follow-up clinical outcomes (MACCE, NACE, and all-cause mortality, non-fatal MI, any revascularization, CVA, rehospitalization, and stent thrombosis), stratified according to stent types (before inverse probability of treatment weighting); CVA — cerebrovascular accident; MACCE — major adverse cardiac and cerebrovascular events; MI — myocardial infarction; NACE — net adverse clinical events.

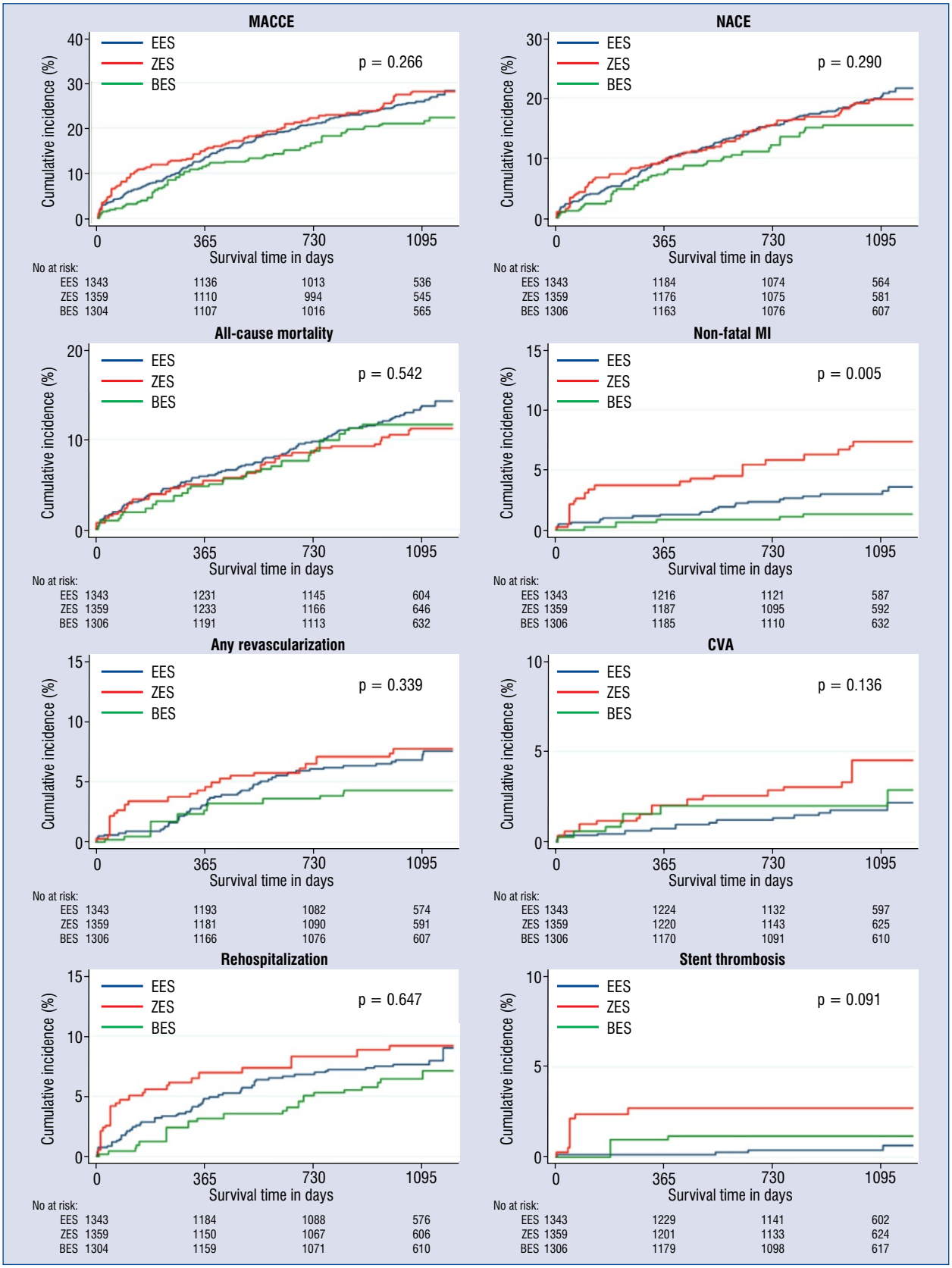

Figure 3. Kaplan-Meier survival analyses of long-term follow-up clinical outcomes (MACCE, NACE, and all-cause mortality, non-fatal MI, any revascularization, CVA, rehospitalization, and stent thrombosis), stratified according to stent types (after inverse probability of treatment weighting); CVA — cerebrovascular accident; MACCE — major adverse cardiac and cerebrovascular events; MI — myocardial infarction; NACE — net adverse clinical events.

patients tend to have a higher risk of experiencing cardiovascular events than patients with normal kidney function [27, 28]. Furthermore, the 2-year mortality rate after AMI is approximately 50% in ESKD patients, which is much higher than the mortality rate after AMI in the general population [29]. Some large-scale studies demonstrated that reduced kidney function was independently associated with an increased risk of mortality and cardiovascular events in patients with reduced LVEF [30, 31]. A similar trend was observed between kidney function and cardiovascular events in an AMI setting [25].

Although the mechanism underlying the development of cardiovascular disorders by renal impairment is still not well understood, it may be explained by several factors related to renal impairment. The progression of renal impairment is closely related to systemic inflammation and oxidative stress, which are responsible for the clinical manifestations of numerous complications, including atherosclerosis, vascular calcification (calciphylaxis), anemia, heart failure, and derangements in calcium-phosphate homeostasis (mineral and bone disorders) [32–34]. Additionally, CKD is associated with an increased risk of thrombosis [35]. In CKD patients, clinically relevant thrombosis often presents as venous thromboembolism, vascular access-associated thrombosis, and right atrial thrombosis [35]. Similarly, thrombosis may occur within arteries, presenting as CAD, CVA, or peripheral artery disease [36]. These factors are directly and/or indirectly associated with cardiovascular disorders and may contribute to the development of cardiovascular events in patients with renal impairment. Meanwhile, the prevalence of coronary risk factors tends to be high in CKD patients [37, 38]. In the present study, the proportion of patients with hypertension and diabetes mellitus increased with the worsening of the CrCl (**Suppl. Table 3**). Because these coronary risk factors, including hypertension and diabetes mellitus, are equally recognized as predictors of renal impairment, they may worsen kidney function, subsequently increasing the influence of such risk factors [25]. This synergistic effect is also reflected in the present study, as lower CrCl caused lower LVEF with increasing incidence of the two aforementioned coronary risk factors (**Suppl. Table 3**).

Several clinical studies have compared the clinical outcomes of implanted coronary stents in patients with AMI who underwent PCI. DES implantation showed better clinical outcomes than the bare-metal stent in reducing MI and mortality after PCI [39, 40]. Some studies compared 2G-DES and BES in AMI patients. Kim et al. [41] compared the 2-year clinical outcomes of 2G-DES with those of BES in AMI patients with dyslipidemia after PCI and found similar results. Choe et al. [42] reported that BES shows clinical outcomes similar to those of new-generation DES. An article about the network meta-analysis of the efficacy and safety of coronary stents in patients with STEMI showed comparable results regarding the risk of primary outcomes between the DES groups, including the ZES, EES, and BES groups [40].

Similarly, there are published papers comparing stents in patients with AMI and renal impairment. Hachinohe et al. [43] reported that ZES results in a higher frequency of major adverse cardiovascular events (MACE) due to the increased TLR rate compared with SES in AMI patients with concomitant CKD. Ahmed et al. [44] compared the ZES and EES in STEMI patients with CKD undergoing PCI, and their results showed similarities with the risk of 12-month MACE and death in patients with STEMI and CKD undergoing PCI.

Unlike these studies comparing two stent groups among AMI-RI patients, the current study is the first to compare clinical outcomes between three DES groups in selected AMI-RI patients undergoing PCI. This study highlights that the use of ZES is associated with the occurrence of non-fatal MI compared with the use of the other two DESs. In addition, clinical findings herein, were based on a longer follow-up period than in previously published articles that were mentioned earlier.

Nonetheless, it is still unclear why this significant result was derived regarding non-fatal MI. It was mainly driven by the difference between ZES and EES groups, or between ZES and EES groups. In a comparative study evaluating 5-year efficacy of both EES and Resolute ZES in PCI-treated ACS patients, Resolute ZES demonstrated worse long-term outcomes than EES [45]. The authors of this study emphasized that the clinical differences between the two stent types were mainly driven by the polymer characteristics, not by the antiproliferative agents. Because the fluoropolymer, a highly fluorinated bilayer copolymer, coated with EES platform has high biocompatibility, reduces platelet adhesion and thrombus formation, these characteristics seems to influence better long-term outcomes in EES compared to Resolute ZES. Meanwhile, unlike both ZES and EES, which have durable polymers, BES has biodegradable polymers. In the BIOSTEMI trial, biodegradable polymer DES was statistically superior to durable polymer DES among STEMI patients [46]. Similarly, in the present study, BES showed relatively

Table 3. Unadjusted and adjusted clinical outcomes.

Clinical outcomes	Overall patients				Inverse probability of treatment weighting analysis			
	EES (n = 808*)	ZES (n = 339*)	BES (n = 304*)	P	EES (n = 1343**)	ZES (n = 1359**)	BES (n = 1306**)	P
MACCE	217 (26.9%)	86 (25.4%)	69 (22.7%)	0.321	344 (25.6%)	367 (27.0%)	274 (21.0%)	0.266
NACE	167 (20.7%)	62 (18.3%)	47 (15.5%)	0.142	266 (19.8%)	257 (18.9%)	194 (14.9%)	0.290
All-cause mortality:	111 (13.7%)	40 (11.8%)	34 (11.2%)	0.463	175 (13.0%)	145 (10.7%)	145 (11.1%)	0.542
Cardiac death	65 (8.0%)	25 (7.4%)	14 (4.6%)	0.151	104 (7.7%)	92 (6.8%)	67 (5.1%)	0.407
Non-cardiac death	46 (5.7%)	15 (4.4%)	20 (6.6%)	0.521	71 (5.3%)	53 (3.9%)	78 (6.0%)	0.516
Non-fatal MI	26 (3.2%)	17 (5.0%)	6 (2.0%)	0.091	39 (2.9%)	92 (6.7%)	16 (1.2%)	**0.005**
Any revascularization	53 (6.6%)	21 (6.2%)	14 (4.6%)	0.453	87 (6.5%)	97 (7.1%)	52 (3.9%)	0.339
Cerebrovascular accident	17 (2.1%)	14 (4.1%)	9 (3.0%)	0.164	23 (1.7%)	55 (4.1%)	28 (2.2%)	0.136
Rehospitalization	60 (7.4%)	21 (6.2%)	21 (6.9%)	0.733	98 (7.3%)	118 (8.7%)	83 (6.4%)	0.647
Stent thrombosis	4 (0.5%)	5 (1.5%)	2 (0.7%)	0.212	6 (0.5%)	36 (2.7%)	15 (1.1%)	0.091

Values are presented as number (%); BES — biolimus-eluting stent; EES — everolimus-eluting stent; MACCE — major adverse cardiac and cerebrovascular events; MI — myocardial infarction; NACE — net adverse clinical events; ZES — zotarolimus-eluting stent

*Number of patients represents the number in the study population excluding those whose follow-up period was 0 days after hospital discharge.

**Number of patients represent the number in the synthetic pseudo-population generated by the inverse probability of treatment weighting. The propensity score was constructed by a multiple logistic regression model using a variety of clinical variables, such as sex, age ≥ 65 years, Killip classification > 2, body mass index, hypertension, diabetes mellitus, dyslipidemia, prior heart failure, prior cerebrovascular accident, smoking, family history of coronary artery disease, creatinine clearance, left ventricular ejection fraction < 40%, discharge medications (acetylsalicylic acid, P2Y12 inhibitors, calcium channel blockers, beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, statins, fibrates, and oral anticoagulants), The American Heart Association and the American College of Cardiology lesion type (type A or B1 versus type B2 or C), vascular approach (femoral vs. non-femoral approach), significant coronary stenosis, glycoprotein IIb/IIIa complex inhibitor use, thrombus aspiration, image-guided percutaneous coronary intervention (PCI), pre-procedural Thrombolysis In Myocardial Infarction 0–I, infarct-related artery, multivessel PCI, staged PCI, left main coronary artery (LMCA) complex lesions, multivessel disease, territories of revascularization (LMCA PCI, left anterior descending coronary artery PCI, left circumflex coronary artery PCI, and right coronary artery PCI), ST-segment elevation myocardial infarction diagnosis, stent number, total stent length, mean stent diameter, and the duration of dual antiplatelet therapy ≥ 12 months.

good clinical outcomes (MACCE, NACE, cardiac death, non-fatal MI, any revascularization, and re-hospitalization), although many of them were not statistically insignificant. Additionally, the statistical process should be considered in interpreting these results. In total, 110 patients (patients with a follow-up of 0 days or patients with any missing value in 41 covariates) were excluded from the IPTW-adjusted analysis. Thus, selection bias may have occurred in this process, causing disparities in non-fatal MI outcomes before and after IPTW (p-value of 0.091 before IPTW, and 0.005 after IPTW).

Limitations of the study

There are several limitations to be considered when interpreting the results of this study. First, the contributing institutions in the KAMIR-NIH registry tended to be tertiary centers with a higher volume of patients than average medical institutes. Thus, the mortality rates and treatment practice patterns could not be generalized to all medical institutions treating STEMI patients. Second, the information concerning hemodialysis in the KAMIR-NIH registry was not considered, making it impossible to separate hemodialysis patients from non-hemodialysis patients. Third, detailed stent information such as stent material, stent linker type, strut thickness, and polymer coating, to account for the heterogeneity of each DES, were not included in the analysis. Moreover, the KAMIR--NIH registry does not include several important angiographic profiles and lesion characteristics such as the presence of bifurcation lesion, chronic total occlusion, overlapping stents, use of shock-wave intravascular lithotripsy and the use of rotational atherectomy. Fourth, considering the timing of data collection, older types of DESs, which are no longer used in routine clinical practice, could undoubtedly also be included in the analysis. Fifth, this study was based on an observational registry; however, it was a non-randomized study. Hence, although statistical adjustment using the propensity score weighting method was conducted to overcome this limitation, a large-scale multicenter randomized controlled trial is needed in the future.

Conclusions

In summary, there were no differences in the long-term clinical outcomes between the ZES, EES, and BES groups in AMI-RI patients undergoing PCI, except for non-fatal MI. Unlike EES, ZES may be a predictor of non-fatal MI.

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