

Comparison of short-term clinical outcomes between Resolute Onyx zotarolimus-eluting stents and everolimus-eluting stent in patients with acute myocardial infarction: Results from the Korea Acute Myocardial infarction Registry (KAMIR)

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Abstract

Background: *There are few studies which compare the efficacy and safety of the Resolute Onyx zotarolimus-eluting stent (O-ZES) and everolimus-eluting stent (EES) in patients with acute myocardial infarction (AMI). Therefore, the present study aimed to compare clinical outcomes of O-ZES and EES in patients with AMI undergoing successful percutaneous coronary intervention (PCI).*

Methods: *From January 2016 to December 2016, the Korea Acute Myocardial Infarction Registry (KAMIR) enrolled 3,364 consecutive patients. Among them, O-ZES was used in 402 patients and EES was used in 1,084 patients. The primary endpoint was target lesion failure (TLF), as defined by composite of cardiac death, target vessel myocardial infarction (TV-MI), and ischemic driven-target lesion revascularization (ID-TLR) at 6 month clinical follow-up.*

Results: *At 6 months, the incidence of TLF was not significantly different between O-ZES and EES group (4.0% vs. 3.9%, adjusted hazard ratio [HR] 1.17, 95% confidential interval [CI] 0.58–2.35, $p = 0.665$). O-ZES also showed similar results of cardiac death (3.7% vs. 3.4%, adjusted HR 1.25, 95% CI 0.59–2.63, $p = 0.560$), TV-MI (0.2% vs. 0.6%, adjusted HR 0.56, 95% CI 0.07–4.85, $p = 0.600$), ID-TLR (0.0% vs. 0.3%, $p = 0.524$), and definite or probable stent thrombosis (0.2% vs. 0.3%, adjusted HR 0.63, 95% CI 0.06–6.41, $p = 0.696$) when compared with EES.*

Conclusions: *The present study shows that implantation of O-ZES or EES provided similar clinical outcomes with similar risk at 6-month of TLF and definite/probable ST in patients with AMI undergoing successful PCI. (Cardiol J 2019; 26, 5: 469–476)*

Key words: drug-eluting stents, myocardial infarction, percutaneous coronary intervention

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Introduction

Compared with bare-metal stents (BMS), drug-eluting stents (DES) have shown better clinical outcomes for patients undergoing percutaneous coronary intervention (PCI) by potent prevention from neointimal hyperplasia [1]. However, early-generation DES produced late thrombotic events, more than 1-year, by delaying arterial healing of stented vessels [2–5]. New-generation DES have developed with thinner stent struts, more biocompatible polymer coatings for drug release, and a variety of antiproliferative agents [6]. This development has led to a significant improvement in the efficacy and safety of early-generation DES. In recent years, new-generation DES replaced early-generation DES because of improved stent design, similar or superior anti-restenotic efficacy, and consistently lower rates of late stent thrombosis (ST) [7, 8]. In fact, currently used DES is a standard treatment in modern clinical procedures and is used by most patients undergoing PCI.

Currently, thin strut and durable polymer-based zotarolimus-eluting stent (ZES) and everolimus-eluting stent (EES) are widely used. Resolute Onyx-ZES (O-ZES), the latest version of ZES, has thinner strut, 81 μm , than Resolute-ZES (R-ZES), prior version of ZES, which had 91 μm of strut thickness. R-ZES and EES have been directly compared in several randomized trials powered for non-inferiority with respect to composite clinical endpoints [9–11]. However, there are few studies to compare the safety and efficacy of O-ZES and EES in patients with acute myocardial infarction (AMI). Therefore, the present study aimed to compare clinical outcomes of O-ZES and EES in patients with AMI undergoing successful PCI.

Methods

Study design and patient population

The Korea Acute Myocardial Infarction Registry (KAMIR) is a prospective multicenter registry providing observational online data collected and designed to examine characteristics, treatment practices, and outcomes in patients presenting AMI with the support of the Korean Circulation Society [12].

Study protocols were approved by the ethics committee at each participating center, and followed principles of the Declaration of Helsinki. Written informed consent was given by each patient. If patients were unable to give consent

because of severity, informed consent was obtained from a relative or legal representative.

Among 3,364 patients enrolled in KAMIR between January 2016 and December 2016, a total of 1,486 patients with AMI were selected who had undergone successful PCI with O-ZES (Resolute Onyx™, Medtronic Cardiovascular, Santa Rosa, CA) or EES (XIENCE™, Abbot Vascular Santa Clara, CA / SYNERGY™, Boston Scientific, Natick, MA). 402 patients with AMI were treated with O-ZES and 1,084 patients were treated with EES, 620 of XIENCE™ and 464 of SYNERGY™ (Fig. 1).

Study endpoints, definitions, and interventional procedures

The primary endpoint was target lesion failure (TLF), being defined as a composite of cardiac death, target vessel myocardial infarction (TV-MI), and ischemic driven-target lesion revascularization (ID-TLR) at 6 months clinical follow-up. The secondary endpoints were individual components of the TLF and definite/probable ST as defined by the Academic Research Consortium [13].

Death was regarded as cardiac in origin unless obvious non-cardiac causes could be identified. Myocardial infarction (MI) was defined as either the development of new pathological Q waves ≥ 0.04 s in duration in ≥ 2 contiguous leads or an elevation of creatine phosphokinase levels to > 2 times normal with positive creatine phosphokinase-MB or troponin I or T levels. TV-MI was defined as MI attributable to target vessel. TLR was considered ischemic-driven if associated with a positive functional study, a target lesion stenosis $\geq 50\%$ by core laboratory quantitative analysis with ischemic symptoms or a target lesion stenosis $\geq 70\%$ with or without documented ischemia.

Hypertension was defined as a history of hypertension diagnosed and treated with medication, diet and/or exercise, or blood pressure > 140 mmHg systolic or 90 mmHg diastolic on at least two occasions, or currently on antihypertensive pharmacologic therapy. Diabetes mellitus (DM) was defined as a history of DM, regardless of duration of disease, need for antidiabetic agents, or a fasting blood glucose > 126 mg/dL. Family history of ischemic heart disease was indicated if the patient had any direct blood relatives (parents, siblings, children) who had any of the preceding, which were diagnosed at age < 55 years.

All patients who underwent PCI received 300 mg acetylsalicylic acid (ASA) and 300 or 600 mg clopidogrel, or prasugrel 60 mg, or ticagrelor 180 mg as a loading dose prior to PCI. After PCI,

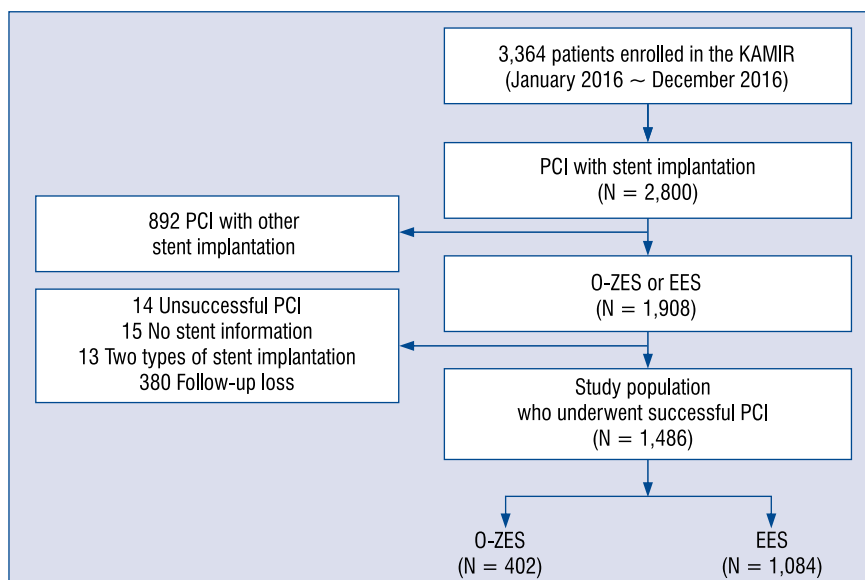


Figure 1. Patients flow chart, EES — everolimus-eluting stent; KAMIR — Korea Acute Myocardial Infarction Registry; O-ZES — Resolute Onyx zotarolimus-eluting stent; PCI — percutaneous coronary intervention.

100–300 mg ASA and 75 mg clopidogrel, or 5 or 10 mg prasugrel one daily or 90 mg ticagrelor twice daily were prescribed for maintenance dose. Medication such as beta-blocker, angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB), and statin were prescribed during hospitalization and after discharge. Coronary artery angiography and stent implantation were performed by standard methods. The selection of PCI timing, medication, vascular access, use of glycoprotein IIb/IIIa inhibitor, use of coronary stents were at physician discretion. Clinical follow-up was done at 6 months after enrollment.

Statistical analysis

All continuous variables were expressed as the mean with standard deviation (SD) or median with interquartile ranges (IQR), when appropriate. All categorical variables were reported as numbers with percentages. The continuous variables were compared using the unpaired t-test or Mann-Whitney U test, as appropriate. The categorical variables were analyzed by using a χ^2 test or Fisher's exact test. The Cox proportional hazard regression modeling (with adjustment for covariates) was used to assess clinical outcomes. A Kaplan-Meier analysis was performed on data from the O-ZES and EES patient groups to compare 6-month TLF and cardiac death, and the difference was determined using a log-rank test. Variables had significance in univariate analysis ($p < 0.100$) for endpoints

which were included in multivariate analysis. The following variables were included in multivariate Cox regression analysis: age ≥ 65 , body mass index ≥ 25 kg/m², hypertension, DM, dyslipidemia, family history of ischemic heart disease, history of MI, history of angina, history of heart failure, history of cerebrovascular accident, Killip classification III/IV, left ventricular ejection fraction $\leq 50\%$, left main or multivessel disease, image-guided PCI, ACC/AHA B2/C lesion, pre Thrombolysis In Myocardial Infarction (TIMI) flow grade 0/1.

All analyses were two-tailed, and p value < 0.05 was considered to reflect significance. All statistical analyses were performed using SPSS for Windows software (ver. 21.0; SPSS Inc., Chicago, IL, USA).

Results

A total of 1,486 patients with AMI underwent successful PCI were included in the present study. The average age of the total population was 64.1 ± 12.3 years and 75.4% were men. The mean stent diameter was 3.14 ± 0.44 mm and the mean stent length was 30.6 ± 15.1 mm. The average number of stents used per vessel was 1.22 ± 0.45 .

Baseline characteristics and coronary angiographic findings

Mean age was similar for the O-ZES and EES group (64.2 ± 12.2 vs. 64.0 ± 12.4 , $p = 0.802$). The O-ZES group had higher prevalence of past his-

Table 1. Baseline clinical and laboratory characteristics of patients in both groups.

Variables	O-ZES (n = 402)	EES (n = 1,084)	P
Demographic:			
Age [years]	64.0 ± 12.4	64.2 ± 12.2	0.802
Male sex	305 (75.9%)	816 (75.3%)	0.813
BMI [kg/m ²]	24.2 ± 3.5	24.1 ± 3.4	0.832
Cardiovascular risk factors:			
Hypertension	206 (51.2%)	541 (49.9%)	0.647
Diabetes mellitus	122 (30.3%)	294 (27.1%)	0.218
Dyslipidemia	52 (12.9%)	128 (11.8%)	0.554
Current smoking	158 (39.3%)	446 (41.1%)	0.521
Family history of IHD	35 (8.7%)	106 (9.8%)	0.531
Medical history:			
Angina	36 (9.0%)	70 (6.5%)	0.097
Myocardial infarction	30 (7.5%)	45 (4.2%)	0.010
Heart failure	5 (1.2%)	11 (1.0%)	0.704
Cerebrovascular accident	24 (9.0%)	73 (6.7%)	0.596
Vital sign on admission:			
SBP [mmHg]	131 ± 29	129 ± 29	0.191
DBP [mmHg]	78 ± 18	78 ± 18	0.641
Heart rate [bpm]	79 ± 19	78 ± 20	0.474
STEMI	207 (51.5%)	566 (52.2%)	0.805
Killip classification III/IV	58 (14.5%)	151 (14.5%)	0.997
LVEF [%]	52.3 (11.5%)	52.8 (11.2%)	0.388
Laboratory findings:			
Total cholesterol [mg/dL]	174 (146–203)	177 (145–206)	0.965
Triglyceride [mg/dL]	110 (81–151)	110 (78–162)	0.360
HDL-cholesterol [mg/dL]	41 (35–52)	42 (35–49)	0.466
LDL-cholesterol [mg/dL]	109 (86–133)	111 (85–138)	0.461
Creatinine [g/dL]	0.9 (0.8–1.1)	0.9 (0.8–1.1)	0.292
hsCRP [mg/dL]	0.30 (0.14–1.07)	0.30 (0.14–1.20)	0.689
Peak CK-MB [ng/mL]	41 (10–170)	51.3 (10–189)	0.160
Peak troponin-I [ng/mL]	18.9 (4.1–40.0)	22.8 (4.8–40)	0.990

Data are expressed as median (interquartile range), mean ± standard deviation or number (percentage) unless otherwise indicated; O-ZES — Resolute Onyx zotarolimus-eluting stent; EES — everolimus-eluting stent; BMI — body mass index; IHD — ischemic heart disease; SBP — systolic blood pressure; DBP — diastolic blood pressure; STEMI — ST-elevation myocardial infarction; LVEF — left ventricular ejection fraction; HDL — high-density lipoprotein; LDL — low-density lipoprotein; hsCRP — high-sensitivity C-reactive protein; CK — creatine kinase

tory of MI when compared with EES group (7.5% vs. 4.2%, $p = 0.010$). In laboratory findings, there were no significant differences in either group. In terms of procedural characteristics, pre-PCI TIMI flow grade 0/1 was higher in O-ZES group than in EES group (59.5% vs. 53.2%, $p = 0.028$). In angiographic findings, O-ZES group more frequently had left main or multivessel disease than in EES group (56.7% vs. 49.0%, $p = 0.008$). ACEI/ARB was less prescribed in the O-ZES group than in the EES group (73.6% vs. 78.9%, $p = 0.032$) (Tables 1, 2).

Six-month clinical outcomes

The 6-month clinical outcomes did not differ between the two groups as shown in Table 3. In Cox proportional hazard analysis, O-ZES also showed no statistical differences in the incidence of TLF (4.0% vs. 3.9%, adjusted hazard ratio [HR] 1.17, 95% confidential interval [CI] 0.58–2.35, $p = 0.665$) (Fig. 2A), cardiac death (3.7% vs. 3.4%, adjusted HR 1.25, 95% CI 0.59–2.63, $p = 0.560$) (Fig. 2B), TV-MI (0.2% vs. 0.6%, adjusted HR 0.56, 95% CI 0.07–4.85, $p = 0.600$), ID-TLR (0.0% vs. 0.3%,

Table 2. Characteristics of coronary angiography, procedures and discharge medication between the two groups.

Variables	O-ZES (n = 402)	EES (n = 1,084)	P
Trans-radial access	189 (47.0%)	498 (46.3%)	0.802
Image-guided PCI	123 (30.6%)	359 (33.1%)	0.351
Glycoprotein IIb/IIIa inhibitor	45 (11.5%)	163 (15.2%)	0.070
Pre-PCI TIMI flow grade 0/1	237 (59.5%)	573 (53.2%)	0.028
Infarct-related artery:			0.532
Left anterior descending	186 (46.3%)	528 (48.8%)	
Left circumflex	65 (16.2%)	180 (16.6%)	
Right coronary	140 (34.8%)	337 (31.1%)	
Left main	11 (2.7%)	38 (3.5%)	
Involved vessel type:			0.008
Single vessel	174 (43.3%)	551 (51.0%)	
Left main or multivessel	228 (56.7%)	530 (49.0%)	
ACC/AHA B2/C lesion	354 (90.1%)	952 (89.3%)	0.670
Implanted stent:			
Stent number	1.25 ± 0.46	1.20 ± 0.45	0.077
Stent diameter [mm]	3.12 ± 0.46	3.15 ± 0.43	0.222
Stent length [mm]	31.0 ± 14.8	30.4 ± 15.2	0.498
Medical treatment at discharge:			
Acetylsalicylic acid	393 (97.8%)	1,064 (98.2%)	0.626
P2Y12 receptor inhibitor:	393 (97.8%)	1,060 (97.8%)	0.931
Clopidogrel	200 (50.6%)	532 (50.1%)	
Ticagrelor	170 (43.0%)	457 (43.0%)	
Prasugrel	25 (6.3%)	73 (6.9%)	
Statin	371 (92.3%)	1,021 (94.2%)	
ACEI/ARB	296 (73.6%)	855 (78.9%)	0.032
Beta-blocker	314 (78.1%)	863 (79.6%)	0.526
Calcium channel blocker	34 (8.5%)	69 (6.4%)	0.158

Data are expressed as mean ± standard deviation or number (percentage) unless otherwise indicated; O-ZES — Resolute Onyx zotarolimus-eluting stent; EES — everolimus-eluting stent; PCI — percutaneous coronary intervention; TIMI — Thrombolysis In Myocardial Infarction; ACC — American College of Cardiology; AHA — American Heart Association; ACEI — angiotensin-converting enzyme inhibitor; ARB — angiotensin II receptor blocker.

$p = 0.524$), and definite/probable ST (0.2% vs. 0.3%, adjusted HR 0.63, 95% CI 0.06–6.41, $p = 0.696$) when compared with EES (Table 3).

Discussion

There have been no studies to directly compare clinical outcomes between O-ZES and EES in specific high-risk groups, such as patients with AMI. This is the first multicenter and currently the largest observational study investigating clinical outcomes of AMI patients undergoing successful PCI with O-ZES or EES. The present study demonstrates that implantation of O-ZES or EES provided similar short-term clinical outcomes in patients with AMI undergoing successful PCI.

There are several studies regarding a comparison of clinical outcomes after PCI with R-ZES. In the RESOLUTE All Comers trial (A Randomized Comparison of a Zotarolimus-Eluting Stent with an Everolimus-Eluting Stent for Percutaneous Coronary Intervention), compared with the EES, the TLF did not significantly differ between R-ZES and EES in complex patients, such as AMI (8.9% in R-ZES group vs. 9.7% in EES group, $p = 0.66$) at 1-year follow-up [14]. In another randomized TWENTE trial, complex patients treated with R-ZES and EES showed similar TLF during 2-year follow-up (11.7% in R-ZES group vs. 10.9% in EES group, $p = 0.68$) [15]. In these two randomized trials, however, patients with AMI were only 43.6% and 37.1%, respectively, when compared with the

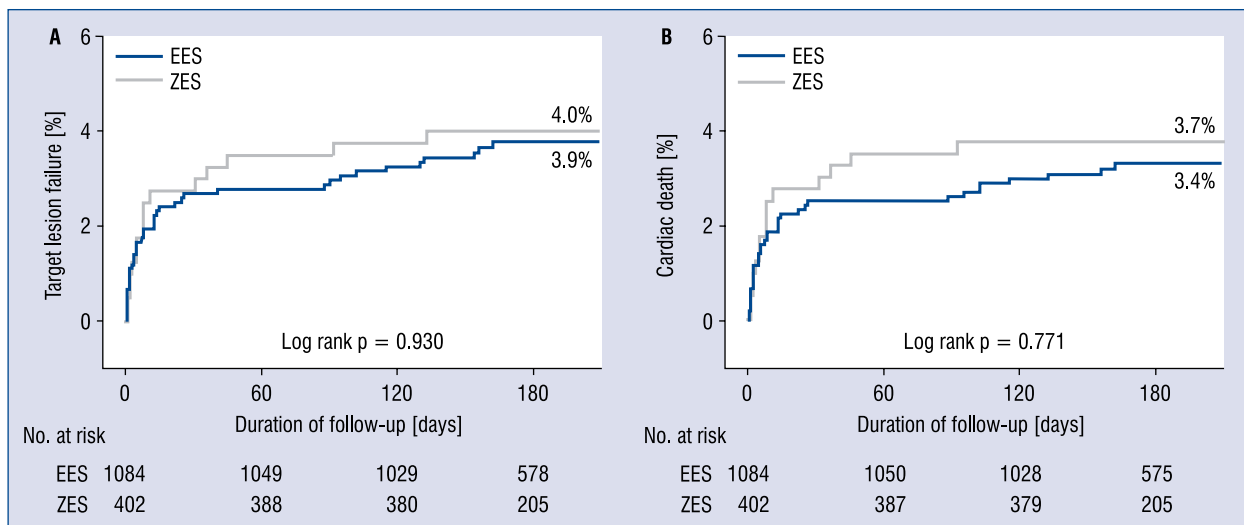


Figure 2. Kaplan-Meier curves for 6-month target lesion failure (A) and cardiac death (B) in patients with acute myocardial infarction; EES — everolimus-eluting stent; ZES — zotarolimus-eluting stent.

Table 3. Six-month cumulative clinical outcomes in both groups.

	O-ZES (n = 402)	EES (n = 1,084)	Unadjusted			Adjusted		
			HR	95% CI	P	HR	95% CI	P
Target lesion failure	16 (4.0%)	42 (3.9%)	1.03	0.58–1.83	0.930	1.17	0.58–2.35	0.665
Cardiac death	15 (3.7%)	37 (3.4%)	1.09	0.60–1.99	0.771	1.25	0.59–2.63	0.560
TV-MI	1 (0.2%)	6 (0.6%)	0.45	0.05–3.71	0.456	0.56	0.07–4.85	0.600
ID-TLR	0 (0.0%)	3 (0.3%)			0.524			
Definite/probable ST	1 (0.2%)	3 (0.3%)	0.92	0.10–8.79	0.938	0.63	0.06–6.41	0.696

Data are expressed as number (percentage). O-ZES — new developed Resolute Onyx zotarolimus-eluting stent; EES — everolimus-eluting stent; HR — hazard ratio; CI — confidence interval; TV-MI — target vessel myocardial infarction; ischemic driven-target lesion revascularization; ST — stent thrombosis

present study which enrolled all patients with AMI. ST-elevation myocardial infarction (STEMI) patients receiving R-ZES had similar 5-year clinical outcomes as compared with those receiving EES in the RESOLUTE All Comers trial (TLF, 7.6% in R-ZES group vs. 10.4% in EES group, adjusted $p = 0.123$; definite/probable ST, 0.8% in R-ZES group vs. 1.3% in EES group, adjusted $p = 0.868$) [16]. In the RESOLUTE Global Clinical Trial Program comprising 10 prospective trials, R-ZES showed good long-term clinical outcomes. In 7618 patients treated with R-ZES, the 5-year cumulative incidence of TLF was 13.4%, cardiac death 5.0%, TV-MI 4.4%, and ID-TLR 6.3% [17]. In the RESOLUTE Global Clinical Trial Program, STEMI patients treated with R-ZES also had good 3-year clinical outcomes, including TLF 9.8%, cardiac death 2.9%, TV-MI 1.6%, ID-TLR 7.0%, and definite/probable ST 2.8% [16].

Regarding the safety and efficacy of O-ZES, O-ZES showed 1-year TLF rate of 4.4% and similar efficacy and safety compared with most contemporary DES [18]. O-ZES demonstrated superiority for 8-month in-stent late lumen loss compared with the historical control R-ZES in the RESOLUTE ONYX core trial (0.24 ± 0.39 mm with O-ZES vs. 0.36 ± 0.52 mm with R-ZES, $p = 0.029$) [19]. Moreover, 2.0 mm O-ZES was associated with a low rate of TLF and late lumen loss without definite/probable ST at 12 month follow-up for treatment of coronary lesions with a very small reference vessel diameter, less than 2.25 mm in the recent study [20]. These favorable clinical outcomes including angiographic benefit of O-ZES could be explained by characteristics of O-ZES. O-ZES has a swaged shape and a larger strut width-to-thickness ratio (strut width 91 μ m and thickness 81 μ m) to maintain radial strength despite thinner strut

when compared with R-ZES. O-ZES also has a dense inner core composed of the platinum-iridium alloy for increased radiopacity. The enhanced radiopacity of O-ZES might have contributed to less geographic miss which was associated with increased target vessel revascularization [21].

Limitations of the study

There were several limitations in the present study. First, it was a retrospective study and there were possibilities for selection bias. Therefore multivariate analysis was undertaken to overcome these limitations. Secondly, the number of patients included in O-ZES group was relatively small, and thus, this study is less robust because of the small sample size. Thirdly, EES group included durable polymer everolimus-eluting stent (XIENCE™) and bioresorbable polymer everolimus-eluting stent (SYNERGY™). Differing stent features can be a possible confounding factor. Finally, interval of follow-up was too short to analyze long-term clinical outcomes. Thus, more extensive and long-term data are needed.

Conclusions

This study shows that implantation of O-ZES or EES provided similar clinical outcomes with similar risk of 6-month TLF and definite/probable ST in patients with AMI undergoing successful PCI.

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Conflict of interest: None declared

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