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CLINICAL RESEARCH
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Prospective randomized comparison of clinical and angiographic outcomes between everolimus-eluting vs. zotarolimus-eluting stents for treatment of coronary restenosis in drug-eluting stents: intravascular ultrasound volumetric analysis (RESTENT-ISR trial)

Soon Jun Hong[1], Chul Min Ahn[1,2], Byeong-Keuk Kim[2], Young-Guk Ko[2], Seung-Ho Hur[3], Cheol Woong Yu[1], Seung-Jin Lee[4], Cheol Ung Choi[5], Je Sang Kim[6], Jung-Han Yoon[7], Young Joon Hong[8], Jae-Woong Choi[9], Seung-Hyuk Choi[10], Yangsoo Jang[2]*, and Do-Sun Lim[1]*; RESTENT-ISR Investigator

[1]Department of Cardiology, Cardiovascular Center, Korea University Anam Hospital, 126-1, 5ka, Anam-dong, Sungbuk-ku, Seoul 136-705, Korea; [2]Severance Cardiovascular Hospital, Yonsei University, 50-1, Yonsei-ro, Seodaemun-gu, Seoul 120-752, Korea; [3]Keimyung University Dongsan Medical Center, 56 Dalseong-Ro, Jung-Gu, Daegu 700-712 Korea; [4]Soonchunhyang University Medical Center, 23-20, Byeongmyeong-dong, Dongnam-gu, Cheonan, Chungcheongnam-do 31151, Korea; [5]Korea University Guro Hospital, 148, Gurodong-ro, Guro-gu, Seoul 08308, Korea; [6]Sejong General Hospital, Sosabon-dong, Sosa-gu, Bucheon-si, Gyeonggi-do 14754, Korea; [7]Yonsei University Wonju College of Medicine, Wonju Christian Hospital, 20 Ilsan-ro, Wonju, Gangwon-do, Wonju 220-701, Korea; [8]Chonnam National University Hospital, 77 Yongbong-ro, Buk-gu, Gwangju 500-757, Korea; [9]Eulji General Hospital, 68 Hangeulbiseok-Ro, Nowon-Gu, Seoul 01830, Korea; and [10]Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea

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Aims At present no proven standard treatment for drug-eluting stent (DES) restenosis is available, and the efficacy and safety of everolimus-eluting stent (EES) and zotarolimus-eluting stent (ZES) for DES restenosis are limited. The purpose of this prospective, randomized 9-month intracoronary ultrasound (IVUS) and 3-year clinical follow-up study was to compare the effects of EESs and ZESs on neointima volume and major adverse cardiovascular events (MACEs) such as death, myocardial infarction (MI), target lesion revascularization (TLR) and stent thrombosis in DES restenosis patients.

Methods and results Patients were eligible for this study if they were between 40 and 75 years old with in-stent restenosis >50% by quantitative coronary angiographic analysis in DES or within 5 mm of the stent edges with signs of ischaemia. Eligible patients ($n = 304$, 146 women and 158 men) were randomly assigned to receive either EES (158 patients) or ZES (146 patients). The primary endpoint of the study was to compare neointima volume between the EES and ZES groups at the 9-month follow-up IVUS. MACEs, including death, non-fatal MI, stent thrombosis and the need for repeated TLR within 3 years, were noted. The 9-month angiographic and IVUS follow-up showed no significant differences in late lumen loss (0.40 ± 0.56 vs. 0.45 ± 0.61 mm, $P = 0.57$, respectively) and neointima volume (0.51 ± 0.48 vs. 0.56 ± 0.54 mm^3/1 mm, $P = 0.47$, respectively) in the EES and the ZES groups. Composite MACEs such as death, MI, stent thrombosis and TLR during 3-year follow-up were comparable between the two groups [15.8% ($n = 25$) in the EES group and 22.6% ($n = 33$) in the ZES group, $P = 0.276$], independent of *de novo* DES type, sex, age, body mass index, presence of diabetes, hypertension and dyslipidaemia.

Conclusions Patients with first- and second-generation DES restenosis, both EES and ZES implantation were effective and safe in reducing neointima volume and late loss with a comparable rate of MACEs independent of cardiovascular risk factors.

*Corresponding author: Tel: +82 2 920 5445, Fax: +82 2 927 1478, Email: dslmd@kumc.or.kr (for clinical follow-up); Tel: +82 2 2228 8460, Fax: +82 2 2227 7732, Email: jangys1212@yuhs.or.kr (for IVUS and QCA analysis)

Keywords Everolimus • Zotarolimus • Neointima • Restenosis

Introduction

After the introduction of first-generation drug-eluting stents (DESs) such as sirolimus-eluting stents (SESs) and paclitaxel-eluting stents (PESs) and second-generation DESs such as everolimus-eluting stents (EESs) (Xience V®; Abbott Vascular, Temecula, CA, USA) and zotarolimus-eluting stents (ZESs) (Endeavor Resolute®; Medtronic Cardiovascular, Santa Rosa, CA, USA), in-stent restenosis (ISR) rate dropped dramatically compared with bare-metal stents.[1,2] The EESs and the ZESs with thinner stent platform in addition to further modification in polymer have replaced the first-generation DESs. EESs and ZESs with better clinical outcomes compared with the earlier versions are the choice of DES in many coronary interventions.[3,4]

Many different factors such as poor percutaneous coronary intervention (PCI) technique, complex lesion type, patient comorbidity and genetic factors could influence DES restenosis.[5,6] Moreover, significant numbers of DES restenosis are found during the follow-up due to the high-volume of DES implantation in many different coronary lesions.[5–8] DES restenosis is perceived as a benign clinical entity due to its gradual process; however, it presents as myocardial infarction (MI) in 10% of cases.[9]

Various treatment options for DES restenosis are available in small scale studies with early studies using balloon angioplasty, vascular brachytherapy or rotablation.[10–12] Recent studies with drug-eluting balloons and DES implantation showed more favourable angiographic and clinical outcomes.[7,10,11,13,14] Bioresorbable vascular scaffolds and coronary artery bypass surgery could also be a treatment option after randomized clinical trials, although it would be challenging to include these two options in a randomized controlled trial with DES restenosis. However, data regarding ideal PCI strategy for patients with DES restenosis are still lacking and debated. Everolimus-eluting stents recently revealed superior long-term angiographic and clinical outcomes compared with drug-eluting balloons,[14] suggesting its promising role in the treatment of DES restenosis.

There has been no prospective randomized study comparing angiographic and clinical outcomes of EESs and ZESs for patients with DES restenosis. The purpose of this prospective, randomized, single-blinded, investigator-initiated 9-month intracoronary ultrasound (IVUS) and 3-year clinical follow-up study was to compare the effects of EESs and ZESs on neointima volume and major adverse cardiovascular events (MACEs) such as death, MI, target lesion revascularization (TLR) and stent thrombosis in DES restenosis patients.

Methods

Study patients

Patients were eligible for this study if they were between 40 and 75 years old with ISR >50% by quantitative coronary angiographic analysis in DES or within 5 mm of the stent edges with signs of significant ischaemia. A total of 4107 patients with suspected coronary restenosis in DES were screened for inclusion in the study at 22 tertiary hospitals in Korea from March 2010 through March 2012. Patients who did not fulfil the inclusion criteria ($n = 2802$) or who had any of the exclusion criteria ($n = 1001$) were excluded. Eligible patients ($n = 304$; 146 women and 158 men) were randomly assigned to receive either EES (158 patients) or ZES (146 patients) in addition to standard PCI management (*Figure 1*). We excluded patients with left main coronary lesions, distal coronary artery lesions unsuitable for IVUS evaluation, heart failure (ejection fraction < 30%), hepatic dysfunction (aspartate transaminase (AST) or alanine transaminase (ALT) > twice the upper limit), uncontrolled arrhythmia within the previous 3 months, serum creatinine >2.0 mg/dL or expected life expectancy of <1 year (*Figure 1*). Aspirin and clopidogrel were maintained in all patients during the 9-month follow-up. Dual oral antiplatelet agents were maintained for 36-month follow-up at the physician's discretion. Statins were administered to all patients unless contraindicated. The study was approved by the Hospital Institute Review Board at each participating centre, and written informed consent was obtained from all participants or their legal guardians.

A complete clinical workup was scheduled at 1, 4 and 9 months after the procedure, and all patients were asked to return after 9 months for angiographic and intravascular ultrasound (IVUS) follow-up. If clinically indicated, follow-up angiography was performed earlier. MACEs, including death, non-fatal MI, stent thrombosis and the need for repeated TLR within 36 months, were noted. The primary endpoint of the study was to compare neointima volume between the EES and ZES groups at the 9-month follow-up IVUS. The secondary endpoints were to compare late lumen loss at the 9-month follow-up angiography and MACEs, a composite of all-cause death, non-fatal MI, stent thrombosis and TLR during the 36-month follow-up.

Myocardial infarction was defined as an elevation in cardiac troponin above the 99th percentile of the upper reference limit or an elevation in creatine kinase-MB ≥2 times the upper normal value in addition to at least one of the following criteria: ischaemic symptoms, new electrocardiographic changes indicative of new ischaemia (ST-T changes or left bundle branch block), development of pathologic Q waves on electrocardiography or imaging evidence of new regional wall motion abnormality. TLR was defined as either PCI or coronary artery bypass grafting surgery because of restenosis or stent thrombosis of the target lesion that included the proximal and distal edge segments and the ostia of side branches. Stent thrombosis was classified as definite, probable or possible according to definitions proposed by the Academic Research Consortium.[15]

Angiographic analysis and intravascular ultrasound measurements

All participating patients received either EES or ZES for the treatment of coronary restenosis in DES according to the study protocol, and only neointima with at least >20% area stenosis was completely covered by EES or ZES; however, it was up to the discretion of cardiologists at each centre whether to cover the neointima of the previous stent with <20% area stenosis. Procedural success was defined as residual stenosis of <15% in the absence of closure during the first 48 h after the procedure. Coronary angiograms were obtained at baseline, immediately after stenting, and at the 9-month follow-up. Two identical orthogonal views were obtained after the intracoronary administration of nitrates and stored on digital CD-ROM. All the IVUS data from 22 participating

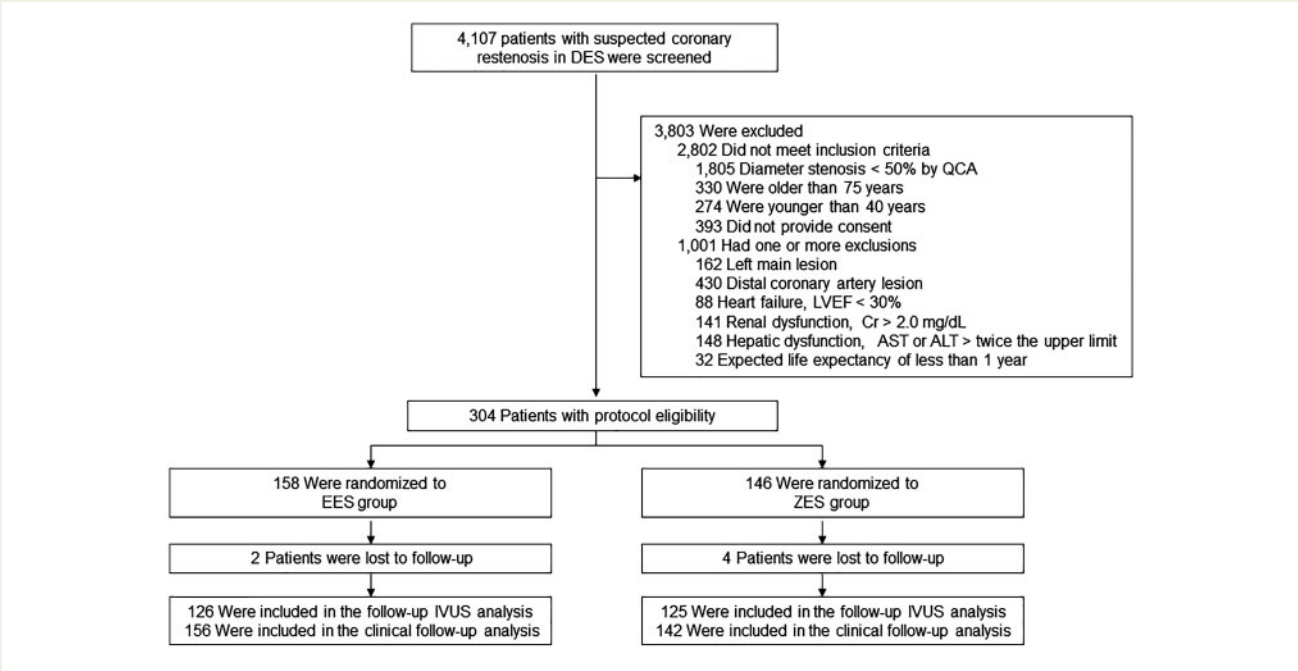

Figure 1 Study protocol. Patients who did not fulfil the inclusion criteria ($n = 2802$) or who had any of the exclusion criteria ($n = 1001$) were excluded. Eligible patients ($n = 304$) were randomly assigned to everolimus-eluting stent group (158 patients) or zotarolimus-eluting stent group (146 patients).

hospitals were sent to the Severance hospital at Yonsei University which operated IVUS core laboratory, and either EES or ZES implanted at randomization was contoured and measured at 9-month follow-up IVUS, not the index stents at the *de novo* lesions. All angiographic, IVUS and clinical data were analysed by individuals who were unaware of the patients' treatment assignments. End-diastolic frames were chosen for quantitative analysis, which was performed using a computer-based TCS system, Version 2.02 (Medcon Inc., Tel-Aviv, Israel). The reference diameter, minimal luminal diameter, percentage of stenosis and lesion length were calculated as the average value of the two orthogonal views. The same views and calibrations were used at follow-up angiography. The average diameter of normal segments proximal and distal to the treated lesion was used as the reference diameter. Lesions were characterized according to the modified American College of Cardiology/American Heart Association classification.[16] Restenosis was defined as stenosis of >50% of the luminal diameter. Balloon angioplasty and stent implantation were performed according to standard clinical practice, as described previously.[17]

An IVUS examination (Galaxy II 3.6F, 40 MHz; Boston Scientific Scimed) was performed after EES or ZES implantation at baseline and at 9 months. An IVUS examination was performed at baseline to optimize stent expansion, and if underexpanded stent was found after IVUS examination, adjuvant ballooning was performed for optimal stent expansion. The ultrasound transducer was inserted and went along a guidewire into the target vessel with automated pullback at the rate of 0.5 mm/s. A coronary segment beginning 10 mm distal to and extending 10 mm proximal to the stented segment was analysed, and the IVUS examination was repeated at 9 months for the same stented segment. A computer-based contour-detection program was used for the IVUS measurements (INDEC Medical System Echoplaque 3.0, Santa Clara, CA, USA). An operator who was blinded to patient information performed measurements with digitized images with cross-sections spaced at 0.5 mm intervals. Vessel area, defined as the internal area of the external elastic membrane, and lumen area were measured at each cross-section. In the absence of neointima formation at the 9-month follow-up, stent area was used as the lumen area. All measured vessel areas at each cross-section were added and then divided by the number of total cross-sections in order to obtain the average vessel volume per unit area. Average lumen volume and neointima volume were calculated using the same method. Plaque volume was calculated by subtracting the lumen volume from the vessel volume, and neointima volume was calculated by subtracting the lumen volume from the stent volume. Because stent length differed in all participating patients, neointima volume was averaged per millimetre of stent length.

Baseline laboratory analysis

Venous blood samples were drawn from each patient after overnight fasting at the beginning of the study. Blood samples were centrifuged to obtain serum, and the serum was stored at −80 °C. Plasma glucose was measured using the glucose oxidase method. Total cholesterol, triglyceride, high-density lipoprotein cholesterol and low-density lipoprotein (LDL) cholesterol levels were determined using enzymatic methods with standard biochemical procedures on a B.M. Hitachi automated clinical chemistry analyser (Hitachi, Tokyo, Japan). High-sensitive C-reactive protein (hsCRP) levels were quantified using a latex nephelometer II (Dade Behring Inc., Newark, DE, USA).

Statistical analysis

Data are expressed as mean ± SD for continuous variables, and data for the categorical variables are expressed as the number and the percentage of patients. χ^2 Test was used for categoric variables. The change from baseline was calculated as the value obtained at the end of the treatment subtracted from the value obtained at the beginning of the intervention.

The results between two groups were compared by an unpaired Student's *t*-test. Angiographic analyses were performed according to the number of patients available for each analysis. This study design was for superiority, and the sample size of the study was determined based on estimation of the primary endpoint of IVUS neointimal volume from previous trials:[18,19] in the EES group, we assumed a neointimal volume index of $0.21 \pm 0.19\,mm^3/mm$ stented segment, and in the ZES group, we assumed a neointimal volume of $0.30 \pm 0.30\,mm^3/mm$ stented segment. Using a two-sided test for differences in independent binomial proportions with an alpha level of 0.05, we calculated that 248 patients (124 patients for each group) would have to undergo randomization for the study to have 80% power to detect a difference in the neointimal volume between 2 groups; therefore, we enrolled 146 patients in each group to account for 15% loss in follow-up IVUS. Variables that did not show a normal distribution were log-transformed for subsequent analyses. All analyses were performed according to the intention-to-treat principle, and the EES or ZES implantation for coronary restenosis in DES was used for analysis. Time-to-event curves were compared using the log-rank tests. Hazard ratios with 95% confidence intervals were estimated using the Cox proportional-hazards method. The consistency of treatment effects was assessed using Cox regression models with tests for interaction in prespecified subgroups (stent type, sex, age, body mass index, history of previous MI, smoking status and the presence of risk factors such as diabetes mellitus, hypertension, dyslipidaemia). A $P < 0.05$ was considered significant. IBM SPSS software (version 20.0) was used for analyses (IBM SPSS Corp., Armonk, NY, USA).

Results

Study patients

Baseline patients characteristics of the EES group ($n = 158$) and the ZES group ($n = 146$) were similar (*Table 1*). The mean ages of patients in the EES and ZES groups were similar, as were the rates of risk factors (*Table 1*). Rates of patients taking medications such as aspirin, clopidogrel and cilostazol before randomization were similar between the two groups, except for the beta-blockers with significantly higher number of patients in the ZES group (*Table 1*). Baseline lipid profiles such as total cholesterol and LDL-cholesterol levels and hsCRP levels did not show significant differences between the two groups (*Table 1*).

Baseline and 9-month angiographic and IVUS follow-up

In more than 60% of patients in each group, the left anterior descending coronary artery was the target vessel (*Table 2*). More than 70% of patients in both groups had complex lesions such as type B_2 or C lesions. Baseline and immediate postprocedure reference diameter, minimal luminal diameter, percentage of stenosis and mean lesion length for *de novo* lesions were not significantly different between the two groups (*Table 2*). More than 75% of patients had the first-generation DES such as SES (53.8% and 54.8%, respectively) and PES (27.8% and 22.6%, respectively) as *de novo* stents in the EES and ZES groups. The second-generation DES such as EES and ZES was also used as *de novo* stents in both groups (*Table 2*).

About 80% of patients in each group demonstrated focal type of ISR, IC type as the most common form of coronary restenosis in both groups. Baseline and immediate postprocedure reference diameter, minimal luminal diameter, percentage of stenosis and mean ISR

Table 1 Baseline characteristics of study subjects

Variable	Everolimus stent (*N* = 158)	Zotarolimus stent (*N* = 146)	*P*-value
Age (years)	64.1 ± 8.9	62.2 ± 10.2	0.09
Male (%)	106 (67.1%)	52 (32.9%)	0.71
Height (cm)	161.9 ± 9.2	162.0 ± 9.6	0.90
Weight (kg)	65.9 ± 11.5	65.1 ± 11.2	0.52
Body mass index (kg/m^2)	25.1 ± 3.4	24.7 ± 2.9	0.27
Systolic blood pressure (mmHg)	134 ± 11	132 ± 10	0.18
Diastolic blood pressure (mmHg)	73 ± 9	71 ± 8	0.28
Risk factors			
Hypertension (%)	92 (58.2%)	77 (52.7%)	0.34
Diabetes (%)	58 (36.7%)	53 (36.3%)	0.94
Current smoker (%)	24 (15.2%)	34 (23.3%)	0.07
Dyslipidaemia (%)	106 (67.1%)	103 (70.5%)	0.52
Peripheral vascular disease (%)	4 (2.5%)	7 (4.8%)	0.36
Previous MI (%)	39 (24.7%)	46 (31.5%)	0.19
Previous CVA (%)	9 (5.7%)	6 (4.1%)	0.52
Unstable angina pectoris (%)	76 (48.1%)	74 (50.7%)	0.88
Stable angina (%)	69 (43.7%)	62 (42.5%)	0.83
NSTEMI (%)	4 (2.5%)	3 (2.1%)	1.00
Silent myocardial ischaemia (%)	9 (5.7%)	7 (4.8%)	0.73
Ejection fraction (%)	61.3 ± 9.2	58.9 ± 10.1	0.16
Medications before randomization			
Aspirin (%)	139 (88.0%)	128 (87.7%)	0.94
Clopidogrel (%)	121 (76.6%)	110 (75.3%)	0.80
Cilostazol (%)	19 (12.0%)	18 (12.3%)	0.94
ACE inhibitor (%)	27 (17.1%)	30 (20.5%)	0.44
ARB (%)	65 (41.1%)	58 (39.7%)	0.80
Beta-blocker (%)	77 (48.7%)	90 (61.6%)	0.02
Statin (%)	129 (81.6%)	116 (79.5%)	0.63
Biguanides[a]	53 (91.4%)	48 (90.6%)	0.88
α-Glucosidase inhibitors[a]	8 (13.8%)	4 (7.5%)	0.37
Sulfonylureas[a]	30 (51.7%)	32 (60.4%)	0.36
Insulin[a]	12 (20.7%)	9 (17.0%)	0.62
Total cholesterol, mg/dL	140.8 ± 36.4	140.7 ± 35.9	0.99
LDL cholesterol, mg/dL	79.0 ± 31.2	77.8 ± 26.7	0.75
HDL cholesterol, mg/dL	41.8 ± 10.6	44.2 ± 13.6	0.10
Triglyceride, mg/dL	120.2 ± 73.3	120.4 ± 95.7	0.98
Fasting glucose, mg/dl	129.4 ± 52.9	128.1 ± 46.1	0.86
HbA1c, %[a]	7.3 ± 0.6	7.2 ± 0.6	0.74
Creatinine, mg/dL	1.0 ± 0.4	0.9 ± 0.3	0.30
hsCRP, mg/dL	1.34 ± 4.3	2.99 ± 9.5	0.11

The body mass index is the weight in kilograms divided by the square of the height in meters.
ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CVA, cerebral vascular accident; HbA1c, haemoglobin A1c; HDL, high-density lipoprotein; hsCRP, high-sensitive C-reactive protein; LDL, low-density lipoprotein; MI, myocardial infarction; NSTEMI, non-ST elevation myocardial infarction.
[a]Analysis was done only for diabetic patients.

Table 2 Angiographic characteristics of *de novo* lesions that led to DES restenosis

Variable	Everolimus stent (*N* = 158)	Zotarolimus stent (*N* = 146)	*P*-value
De novo lesion location (%)			0.54
Left anterior descending artery	97 (61.4%)	98 (67.1%)	
Left circumflex artery	17 (10.8%)	16 (11.0%)	
Right	43 (27.2%)	32 (21.9%)	
Ramus intermedius	1 (0.6%)	0 (0.0%)	
Presentations for the *de novo* angiogram			
STEMI (%)	4 (2.5%)	6 (4.1%)	0.44
NSTEMI (%)	32 (20.3%)	35 (24.0%)	0.43
Unstable angina pectoris (%)	52 (32.9%)	39 (26.7%)	0.24
Stable angina (%)	59 (37.3%)	54 (37.0%)	0.95
Silent myocardial ischaemia (%)	11 (7.0%)	12 (8.2%)	0.68
Time interval between the *de novo* PCI and restenosis (months)	52.7 ± 39.9	53.2 ± 35.7	0.43
Type of *de novo* lesion (%)			0.07
A	10 (6.3%)	4 (2.7%)	
B_1	34 (21.5%)	19 (13.0%)	
B_2	59 (37.3%)	59 (40.4%)	
C	55 (34.8%)	64 (43.8%)	
De novo stent type (%)			0.39
Sirolimus-eluting stent	85 (53.8%)	80 (54.8%)	
Paclitaxel-eluting stent	44 (27.8%)	33 (22.6%)	
Zotarolimus-eluting stent	14 (8.9%)	21 (14.4%)	
Everolimus-eluting stent	15 (9.5%)	12 (8.2%)	
Baseline (*de novo* lesion)			
Reference diameter (mm)	3.06 ± 0.52	3.12 ± 0.50	0.44
Minimal lumen diameter (mm)	0.69 ± 0.45	0.81 ± 0.47	0.10
Percentage of stenosis	77.1 ± 15.2	73.0 ± 16.1	0.11
Mean lesion length (mm)	22.5 ± 13.1	24.7 ± 14.2	0.29
Postprocedure (*de novo* lesion)			
Reference diameter (mm)	3.19 ± 0.53	3.29 ± 0.57	0.34
Minimal lumen diameter (mm)	2.87 ± 0.65	2.92 ± 0.45	0.51
Percentage of stenosis	10.1 ± 9.9	10.9 ± 10.4	0.68
Acute gain (mm)	2.19 ± 0.68	2.15 ± 0.64	0.15
Mean stent length (mm)	25.3 ± 7.1	27.0 ± 6.4	0.10
Mean stent diameter (mm)	3.07 ± 0.46	3.13 ± 0.48	0.25
Overlapping stents at *de novo* lesion	24 (15.2%)	23 (15.8%)	0.89

Table 3 Angiographic and IVUS characteristics of in-stent restenosis at randomization

Variable	Everolimus stent (*N* = 158)	Zotarolimus stent (*N* = 146)	*P*-value
In-stent restenosis pattern (%)			0.82
IB	54 (34.2%)	50 (34.2%)	
IC	70 (44.3%)	57 (39.0%)	
ID	6 (3.8%)	8 (5.5%)	
II	19 (12.0%)	21 (14.4%)	
III	4 (2.5%)	4 (2.7%)	
IV	5 (3.2%)	6 (4.1%)	
Baseline QCA (ISR lesion)			
Reference diameter (mm)	3.07 ± 0.50	3.15 ± 0.53	0.32
Minimal lumen diameter (mm)	0.78 ± 0.45	0.89 ± 0.62	0.22
Percentage of stenosis	74.1 ± 14.7	72.2 ± 17.1	0.46
Late lumen loss (mm)	2.07 ± 0.69	2.02 ± 0.85	0.75
Mean ISR lesion length (mm)	17.2 ± 8.4	17.8 ± 9.4	0.60
Postprocedure QCA (ISR lesion)			
Reference diameter (mm)	3.20 ± 0.50	3.25 ± 0.53	0.55
Minimal lumen diameter (mm)	2.82 ± 0.50	2.86 ± 0.47	0.57
Percentage of stenosis	11.9 ± 11.4	11.8 ± 11.2	0.90
Acute gain (mm)	2.05 ± 0.62	2.01 ± 0.67	0.68
Mean stent length (mm)	21.7 ± 5.8	21.6 ± 6.5	0.96
Mean stent diameter (mm)	3.15 ± 0.42	3.08 ± 0.40	0.07
Overlapping stents at ISR lesion	5 (3.2%)	3 (2.1%)	0.73
Baseline IVUS (mm^3/1 mm)			
Total vessel volume	13.8 ± 6.4	13.1 ± 6.5	0.45
Stent volume	7.1 ± 3.5	7.3 ± 4.5	0.81
Lumen volume	0.5 ± 0.8	0.6 ± 0.7	0.78
Neointima volume	6.6 ± 3.0	6.6 ± 4.1	0.93
Postprocedure IVUS (mm^3/1 mm)			
Total vessel volume	15.0 ± 6.7	14.4 ± 6.8	0.25
Stent volume	7.7 ± 2.9	8.1 ± 2.6	0.12
Lumen volume	7.7 ± 2.9	8.1 ± 2.6	0.12

All IVUS volumes are given in mm^3/1 mm stented segment.
ISR, in-stent restenosis; IVUS, intravascular ultrasound; QCA, quantitative coronary angiography.

lesion length for ISR lesions were not significantly different between the two groups (*Table 3*). Baseline and postprocedure IVUS showed no significant differences in total vessel volume, total plaque volume and lumen volume between the two groups (*Table 3*).

The angiographic and IVUS follow-up was performed in more than 80% of patients in both groups [80% of patients ($n = 126$) in the EES

Table 4 Angiographic and IVUS follow-up

Variable	Everolimus stent (*N* = 158)	Zotarolimus stent (*N* = 146)	*P*-value
Number of patients with angiographic f/u	126 (80%)	125 (86%)	0.18
Nine-month follow-up			
Reference diameter (mm)	3.05 ± 0.35	3.06 ± 0.34	0.77
Minimal lumen diameter (mm)	2.54 ± 0.44	2.53 ± 0.43	0.82
Percentage of stenosis	16.7 ± 9.4	17.4 ± 12.0	0.22
Late lumen loss (mm)	0.40 ± 0.56	0.45 ± 0.61	0.57
Nine-month follow-up IVUS (mm^3/1 mm)			
Total vessel volume	16.0 ± 7.8	15.2 ± 7.6	0.13
Stent volume	6.9 ± 3.5	6.7 ± 3.0	0.83
Lumen volume	6.4 ± 3.4	6.1 ± 2.9	0.09
Neointima volume	0.51 ± 0.48	0.56 ± 0.54	0.47

f/u, follow-up; IVUS, intravascular ultrasound.

group and 86% of patients ($n = 125$) in the ZES group]. The 9-month angiographic and IVUS follow-up showed no significant differences in late lumen loss (0.40 ± 0.56 vs. 0.45 ± 0.61 mm, $P = 0.57$, respectively) and neointima volume (0.51 ± 0.48 vs. 0.56 ± 0.54 mm^3/1 mm, $P = 0.47$, respectively) in the EES and the ZES groups (*Table 4*, *Figure 2*).

Major adverse cardiovascular events during the 3-year follow-up

Three-year cumulative rates of death [0.6% ($n = 1$) in the EES group and 2.1% ($n = 3$) in the ZES group, $P = 0.276$], MI [1.9% ($n = 3$) in the EES group and 2.7% ($n = 4$) in the ZES group, $P = 0.685$], definite/probable stent thrombosis [2.5% ($n = 4$) in the EES group and 1.4% ($n = 2$) in the ZES group, $P = 0.470$] and TLR [14.5% ($n = 23$) in the EES group and 21.2% ($n = 31$) in the ZES group, $P = 0.230$] were similar in both groups during the 36-month follow-up period. Ischaemic-driven TLR occurred in 16 patients (10.1%) in the EES group and 14 patients (9.6%) in the ZES group ($P = 0.88$). Composite MACEs such as death, MI, stent thrombosis and TLR [15.8% ($n = 25$) in the EES group and 22.6% ($n = 33$) in the ZES group, $P = 0.276$] revealed no significant differences between the two groups within the first 3-year follow-up, with most of TLR accumulating around 9-month angiographic and IVUS follow-up period (*Figure 3*). The landmark analysis for MACEs at 9 months showed no significant differences in cardiovascular events before (HR 1.03, CI 0.42–2.54) and after 9 months (HR 0.63, CI 0.33–1.22) (Supplementary material online, *Figure S1*).

Subgroup analysis for MACEs during the 3 years of follow-up revealed no significant interaction between stent type and other variables except for current smoking (*Figure 4*). The EES group showed lower rate of MACE in non-smokers, and all other analysed subgroups showed comparable rates of MACEs (*Figure 4*).

Discussion

The long-term clinical efficacy and safety of EES and ZES implantation in patients with DES restenosis have not been evaluated. This is the first prospective, randomized, single-blind, investigator-initiated study to compare the effects of EES and ZES in reducing neointima volume and MACEs in patients with coronary restenosis in DES during 36-month follow-up. We report for the first time that EES and ZES showed comparable neointima volume during the 9-month follow-up IVUS in patients with DES restenosis; moreover, EES and ZES revealed overall similar efficacy and safety during the 3-year clinical follow-up. EES and ZES showed comparable cardiovascular events in DES restenosis, independent of types of DES used for the *de novo* lesions, sex, age, presence of diabetes, hypertension and dyslipidaemia.

With widespread use of DES in coronary intervention, DES restenosis is frequently found in clinical practices. Few clinical trials addressing this clinically relevant issue have been published so far,[2,7,20–22] and in patients with DES restenosis, no randomized trials comparing newer generation DESs have been studied to the best of our knowledge. A randomized trial comparing the efficacy and safety of SES and PES in SES restenosis demonstrated that either repeat SES or switch to PES was associated with a comparable clinical outcomes.[2] Target lesion revascularization rate was 16.6% for SES and 14.6% for PES during 12-month clinical follow-up,[2] and the TLR rate in our study [14.5% ($n = 23$) in the EES group and 21.2% ($n = 31$) in the ZES group, $P = 0.230$] could not be directly compared with the previous studies as the 36-month follow-up was relatively longer than those of previous studies.[2,20,21] In ISAR-DESIRE II trial, late losses were 0.40 ± 0.65 mm in the SES group and 0.38 ± 0.59 mm in the PES group which were comparable to the results of this study.[2] In the j-Cypher registry, 966 patients with SES restenosis were treated with either repeat SES implantation or balloon dilatation, and repeat SES implantation showed significantly lower rate of TLR (23.8% vs. 37.7%) during 24-month follow-up.[20] Paclitaxel-eluting balloon was compared with PESs and balloon angioplasty in patients with DES restenosis in ISAR-DESIRE III trial, and paclitaxel-eluting balloon was non-inferior to PES in terms of diameter stenosis at 6–8 months and TLR at 3 years;[7,13] however, first-generation PES, which is not frequently used in real world clinical practice, was compared with paclitaxel-eluting balloon in ISAR-DESIRE III trial. Although there have been no efficacy and safety data for using EES and ZES for DES restenosis, many coronary interventionists have used such stents for the treatment of DES failure. In a recent study, EES showed superior long-term clinical and angiographic outcomes compared with drug-eluting balloon in patients with DES restenosis.[14] Although drug-eluting balloon was recommended as class IA in the ESC guideline,[23] beneficial role of drug-eluting balloon in comparison to DES could not be concluded from our study. Our trial supports evidence that EES and ZES performed equally in DES restenosis, filling in the insufficient data of current interventional practices.

Coronary restenosis rate after DES implantation dropped dramatically compared with those of bare-metal stents or balloon angioplasty alone; however, with the extensive use of DES in the treatment of coronary artery stenosis together with the increased number of PCI procedures worldwide, the absolute numbers of DES restenosis have increased in recent years. Coronary restenosis

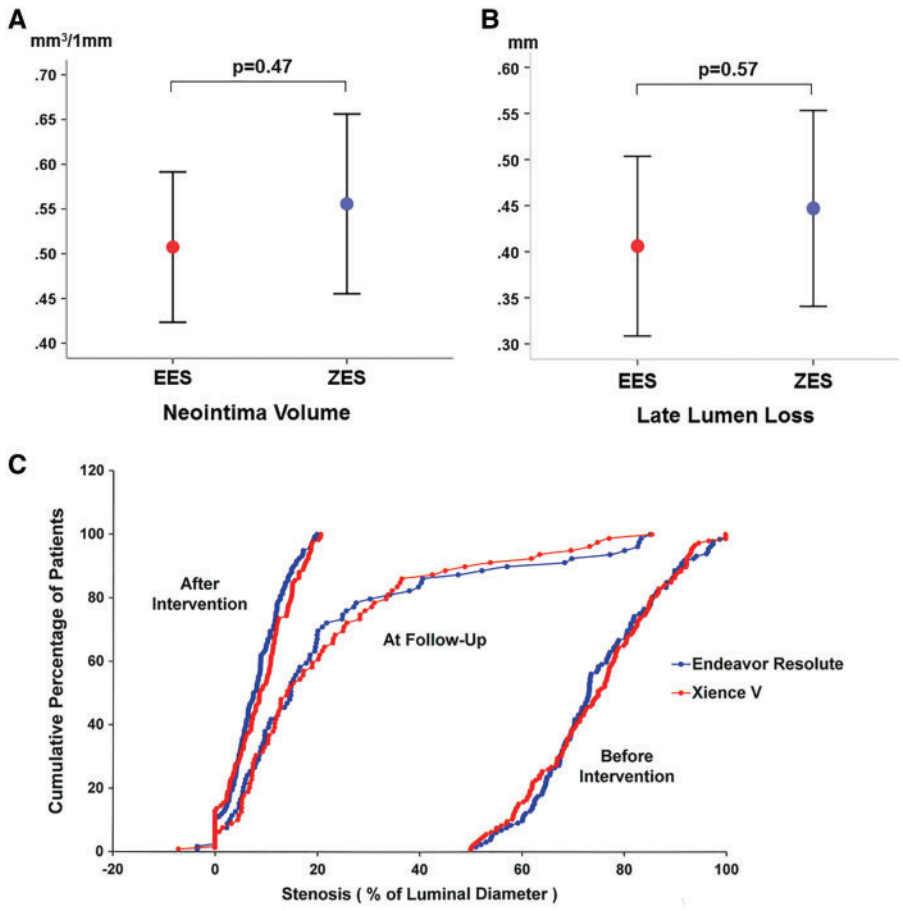

Figure 2 Neointima volume, late lumen loss and diameter stenosis at 9-month follow-up. Neointima volume (*A*) (0.51 ± 0.48 vs. 0.56 ± 0.54 mm^3/1 mm, $P = 0.47$, respectively), late lumen loss (*B*) (0.40 ± 0.56 vs. 0.45 ± 0.61 mm, $P = 0.57$, respectively) and per cent diameter stenosis (*C*) at 9-month follow-up showed no significant differences between the everolimus-eluting stent and the zotarolimus-eluting stent groups.

usually presents as recurrent angina in most cases; however, not all ISR are benign in nature with about 5–11% of coronary restenosis presenting as acute MI.[2,22,24] The rate of coronary restenosis ranges from 3% to 20% depending on the type of DES, the duration of follow-up and the complexity of native coronary vessel.[5] Implantation of DES for the treatment of DES restenosis has been known for worse outcomes than implanting DES for the treatment of bare-metal stent restenosis.[2,12,21,24,25] Although DES implantation has been widely accepted for the effective treatment of bare-metal stent restenosis, the most appropriate treatment for DES restenosis remains to be determined. With the advent of second-generation DESs such as EES and ZES, we sought to find better treatment options for the management of DES restenosis in this study. DES such as EES and ZES in this study demonstrated comparable outcomes to other treatment modalities, if not better, for the treatment of DES restenosis; however, late lumen loss of EES and ZES after treatment for DES restenosis showed higher late losses than when used for *de novo* lesions. The mechanism of relatively poor performance of EES and ZES when used for DES restenosis is multifactorial, and the precise mechanisms are still under study. Biological, mechanical and technical factors may contribute to restenosis after EES or ZES implantation for DES restenosis. Potential genetic factors such as drug resistance or hypersensitive could be possible; moreover, complex lesion type and patient comorbidity which are frequently encountered in patients with DES restenosis could influence on the performance of EES or ZES.

Furthermore, the ideal angiographic follow-up interval for assessing DES efficacy for the treatment of DES restenosis remains unknown, and previous studies including our trial arbitrarily evaluated angiographic follow-up between 6 and 12 months after DES implantation.[2,7] With long-term 36-month clinical follow-up in this study, ischaemia-driven TLRs, which reflect clinically significant coronary restenosis, could be evaluated beyond the limit of predefined angiographic follow-up time point. About 80% of DES restenosis were focal type in this study, comparable rates to previous trials.[26,27] EES or ZES implantations on top of previous DES were effective in reducing stent thrombosis, with 2.5% ($n = 4$) in the EES group and 1.4% ($n = 2$) in the ZES group ($P = 0.470$) during the 36-month follow-up.

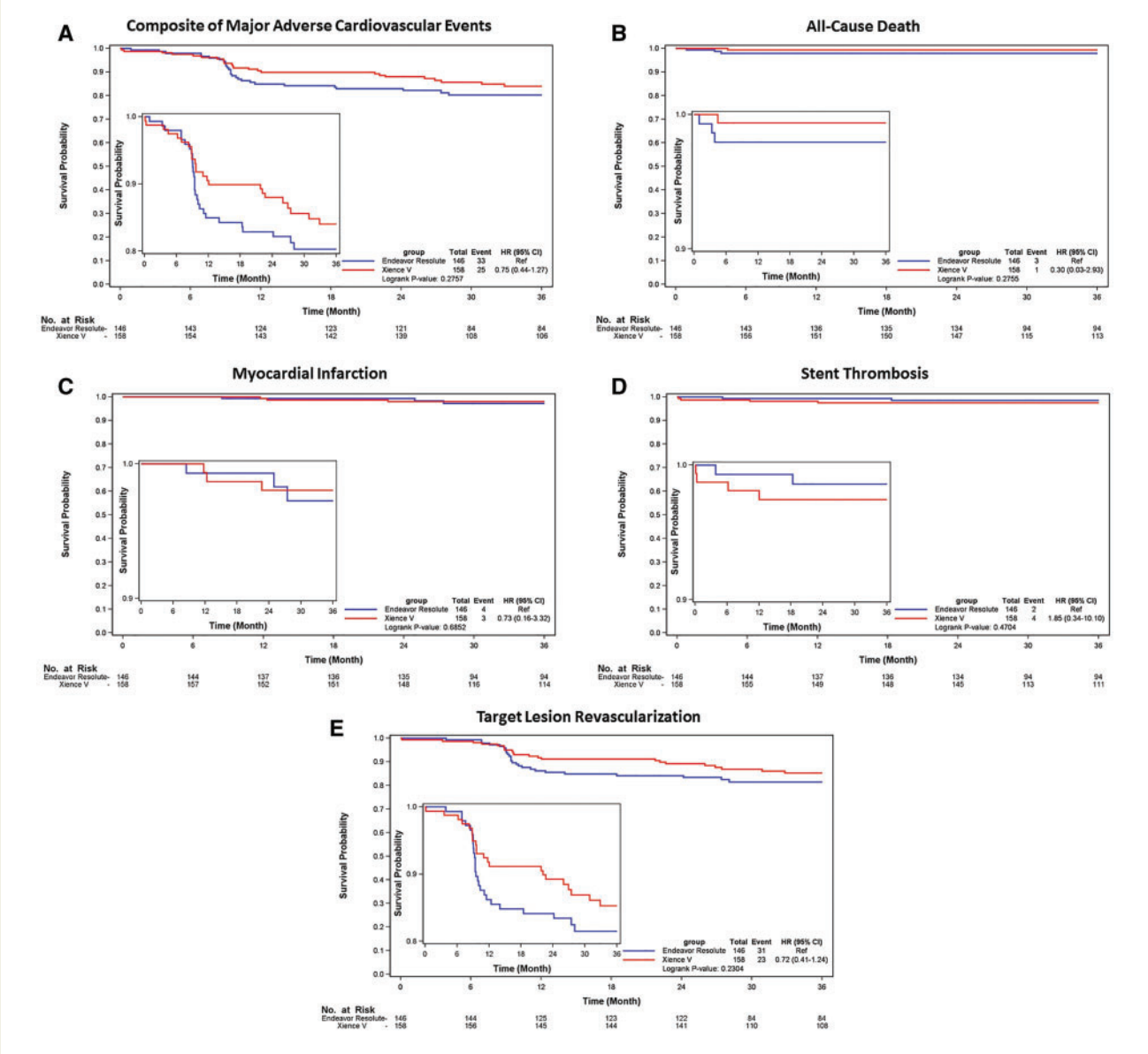

Figure 3 Major adverse cardiovascular events during the 3-year follow-up. (*A*) Composite of major adverse cardiovascular event, (*B*) rates of death, (*C*) myocardial infarction, (*D*) stent thrombosis and (*E*) target lesion revascularization were comparable between the two groups during the follow-up.

Most of the TLR, with comparable outcomes in both groups, occurred around the 9-month follow-up due to the planned invasive surveillance at that time; moreover, the rate of ischaemia-driven TLR was also comparable between the two groups [8.9% ($n = 14$) in the EES group and 11.0% ($n = 16$) in the ZES group ($P = 0.540$)] during the 36-month follow-up. The degrees of blood pressure, glucose and lipid control were similar between the two groups during the 36-month follow-up period, thereby offsetting the blood pressure, glucose and lipid lowering effects on neointima volume and cardiovascular events. Moreover, all patients underwent IVUS examination after stent implantation for the management of DES restenosis in our trial, thereby eliminating chances for underexpanded stents and major edge dissections.

Study limitations

Our findings should not be extrapolated to all DES restenosis because we excluded patients with coronary restenosis with heart failure, renal dysfunction, left main restenosis and distal coronary lesions. Also, the difference in the primary endpoint could be potentially clinically relevant due to the limited data regarding competing risk events. The sample size and binary outcomes were underpowered to compare clinical events in this study. In addition to paclitaxel-eluting balloon with its well-known efficacy in the treatment of DES restenosis, DES with biodegradable polymer and bioresorbable vascular scaffold could be a potential treatment option for patients with DES restenosis.[2,7,13,28,29] About 80% of patients in this study showed

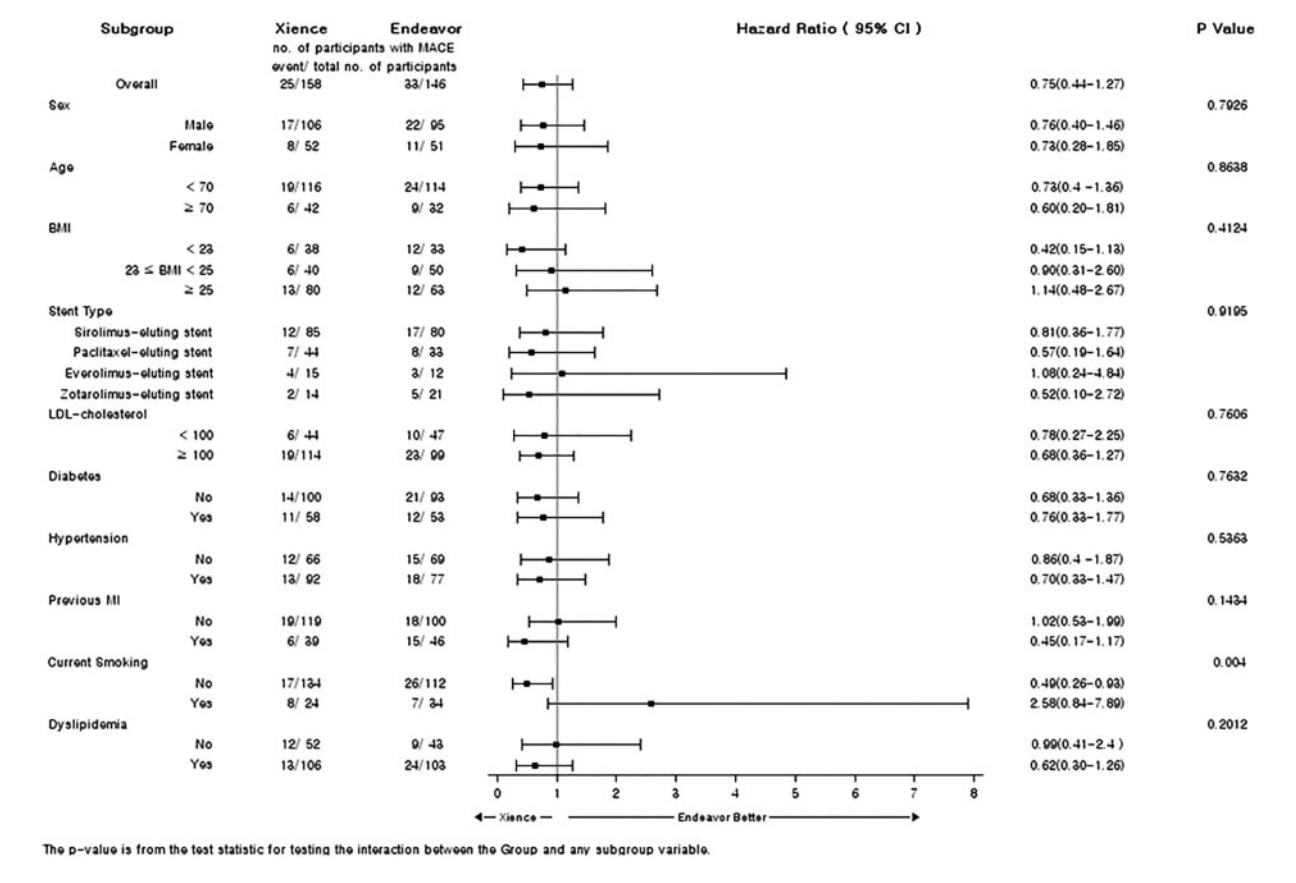

Figure 4 Subgroup analysis for major adverse cardiovascular event during the 3-year follow-up. All analysed subgroups showed comparable rates of major adverse cardiovascular events with no significant interaction between stent type and other variables except for current smoking. The everolimus-eluting stent group showed lower rate of major adverse cardiovascular event in non-smokers.

focal type I DES restenosis, representing the reality of DES restenosis in Korea. A randomized multicentre study comparing drug-eluting balloon, DES with biodegradable polymer and bioresorbable vascular scaffold in addition to EES and ZES for treatment of DES restenosis is warranted with a large cohort of participants.

Conclusions

Drug-eluting stent restenosis treated with either EES or ZES benefits not only from its anti-restenotic effects but also its safety during the 36-month clinical follow-up. This study demonstrated that patients with first- and second-generation DES restenosis, both EES and ZES implantation reduced neointima volume and late loss with a similar rate of MACEs independent of age, sex, body mass index, presence of diabetes, hypertension and dyslipidaemia. Anti-restenotic effects by both EES and ZES may provide additional therapeutic options in the management of DES restenosis with significant ischaemia.

Supplementary material

Supplementary material is available at *European Heart Journal* online,

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