

Original

Comparison of Mid-term Angiographic and Clinical Outcomes Following Zotarolimus-eluting Stent and Paclitaxel-eluting Stent Implantation Based on Lesion Complexity

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Abstract: First-generation drug-eluting stents (DESs) have reduced angiographic and clinical restenosis rates compared to bare-metal stents (BMSs). Zotarolimus-eluting stents (ZESs) are second-generation drug-eluting stents: however, the clinical efficacy of ZES implantation is unclear because late loss associated with ZESs is reportedly higher than that observed for other DESs. The aim of this study was to evaluate the clinical efficacy of ZESs compared to paclitaxel-eluting stents (PESs). We retrospectively evaluated the angiographic and clinical outcomes of 431 lesions in 342 patients treated with PESs and 153 lesions in 121 patients treated with ZESs in our hospital between May 2007 and December 2010. Follow-up angiographic examinations were performed eight months post-treatment and clinical outcomes were assessed one year after the procedure. Quantitative coronary angiographic analyses showed that late loss was significantly higher for ZESs than PESs (0.82 ± 0.73 mm vs 0.47 ± 0.68 mm; $P=0.003$). However, there was no significant difference in target lesion revascularization (TLR) between the two groups (ZES: 15 lesions, 9.8% vs PES: 25 lesions, 5.8%; $P=0.092$). When comparing stents according to the American College of Cardiology/American Heart Association (ACC/AHA) lesion type, the TLR rate in the ZES group was significantly lower than in the PES group (0% vs 70%; $P=0.038$) for Type A/B1 lesions, but the TLR rate for type B2/C lesions in the ZES group was significantly higher than in the PES group (15.8% vs 5.3%; $P=0.009$). Multivariate logistic regression analysis showed that dialysis (OR: 35.54; 95% CI: 3.15-400.67; $P=0.039$) and pre-minimal lumen diameter (OR: 0.036; 95% CI: 0.002-0.541; $P=0.016$) were independent predictors of TLR in ZES-treated lesions. However, no factors predicted TLR in PES-treated lesions. Our study demonstrated excellent outcomes with ZESs for simple lesions, but it is necessary to carefully implant ZESs in complex lesions, such as ACC/AHA type B2/C lesions..

Key words: Target lesion revascularization, drug-eluting stent, Zotarolimus-eluting stent, Paclitaxel-eluting stent, lesion complexity

Introduction

Previous studies have reported that patients treated with first-generation drug-eluting stents (DESs) had improved angiographic and clinical outcomes compared to those treated with bare-metal stents (BMSs)^{1,2)}. Zotarolimus-eluting stents (ZESs; Endeavor, Medtronic CardioVascular, Santa Rosa, CA, USA) are second-generation drug-eluting stents that deliver the potent anti-proliferative agent zotarolimus through a biocompatible phosphorylcholine polymer, that has a shorter drug-elution time (within two weeks), on a cobalt chromium-based thin-strut (0.0036") stent^{3,4)}. ZESs have been available in Japan since May 2009, and treatment with ZESs is associated with significant reductions in angiographic restenosis and target lesion revascularization (TLR) compared to treatment with BMSs^{5,6)}. However, the clinical efficacy after implantation of ZESs remains unclear because the late loss associated with ZESs is reportedly higher than that associated with other DESs⁷⁾. Limited information is available about the angiographic and clinical outcomes of first-generation DESs and ZESs, and few studies have focused on the impact of differential lesion complexity on the efficacy of these treatments^{3,8)}. The aim of this study was to evaluate and compare the clinical efficacies of the second generation DES, ZES, and the paclitaxel-eluting stent (PES; TAXUS, Boston Scientific Corporation, Natick, MA, USA), a first-generation DES. Furthermore, we performed a stratified analysis according to lesion complexity and compared the efficacies of ZESs and PESs in complex lesions, which were defined as type B2/C lesions, and in simple lesions, which were defined as type A/B1 lesions.

Methods

Study population

We retrospectively evaluated the angiographic and clinical outcomes of 431 lesions in 342 patients treated with PESs and 153 lesions in 121 patients treated with ZESs in daily practice between May 2007 and Dec 2010 at our hospital. Follow-up angiographic examinations were performed eight months post-treatment and clinical outcomes were assessed one year after the procedure.

Angioplasty procedures

All procedures were performed with a 7- or 8-French-gauge guiding catheter and a femoral approach. Stents were deployed with or without predilatation according to standard techniques. In all cases, the stent was placed so that its entire length covered the lesion, and dilation pressure was applied to the stent until the lesion was sufficiently dilated under transillumination. Intravascular ultrasound (IVUS) was used in all cases during predilatation to determine stent diameter, and following stent deployment and post-dilatation to check stent apposition. After stent implantation, aspirin (at least 100 mg/day) was prescribed for an indefinite duration, and clopidogrel (75 mg/day) or ticlopidine (200 mg/day) was

administered for at least 12 months.

Definitions

Anginal symptoms were defined according to the Canadian Cardiovascular Society classification. Major adverse cardiac events (MACE) were defined as death from any cause, myocardial infarction (MI), or TLR. TLR was defined as any repeat revascularization procedure (percutaneous or surgical) of the original target lesion site. Target vessel revascularization was defined as clinically driven percutaneous revascularization or bypass of the target lesion or any segment of the epicardial coronary artery containing the target lesion. Acute coronary syndrome (ACS) was defined as acute myocardial infarction or unstable angina pectoris. A calcified lesion was defined as an identifiable radiopaque image in the case of still images obtained before injecting contrast agent or an identifiable dark image on moving images. Lesions longer than 20 mm were defined as long lesions. Target restenosis was defined as stenosis of 50% or more based on follow-up remote-phase coronary angiography results. In addition, we defined type A/B1 lesions as “simple” lesions and type B2/C lesions as “complex” lesions.

Quantitative coronary angiography (QCA) was performed with the QCA-CMS cardiovascular analysis system manufactured by Medis. Lesion length, minimum vascular diameter, and control vascular diameter were measured from the dilated phase frames, and all measurements were taken from an angle showing minimal lesion contraction. The same angles were used in pre-treatment, post-treatment, and follow-up remote-phase coronary angiography. The rate of stenosis, acquired inner diameter in the acute phase, and loss of inner diameter in the remote phase were then calculated.

Statistical analysis

Quantitative data are presented as the mean \pm SD, and categorical data are presented as percentages. Statistical analysis was performed using the chi-square test or Fisher's exact test (two-tailed) for categorical variables. Student's *t*-tests were used for the comparison of continuous variables, and *P* values of 0.05 or less were considered significant. Univariate and multivariate analyses of continuous ratios, including 95% confidence intervals (CI), were calculated using the Cox proportional hazards model. Factors with *P* values less than 0.05 in the univariate analysis were entered into the multivariate model. Statistical analysis was performed using commercially available software.

Results

Baseline patient characteristics were similar among all ZES and PES patients except for the higher percentages of dialysis and smoking in the PES group ($P = 0.028$ and $P = 0.002$, respectively) and the higher percentage of ACS in the ZES group ($P < 0.0001$; Table 1).

Lesion characteristics and quantitative angiographic analysis data are listed in Table 2.

Table 1. Baseline characteristics of all patients

	ZES	PES	<i>P</i> value
Patients, n	121	342	
Age, years	66.35 ± 12.71	67.35 ± 10.26	0.386
Male gender, n (%)	95 (78.5)	273 (79.8)	0.759
Risk factor			
Hypertension, n (%)	90 (74.4)	223 (65.2)	0.064
Diabetes mellitus, n (%)	63 (52.1)	182 (53.2)	0.828
Dyslipidemia, n (%)	81 (66.9)	205 (59.9)	0.173
Current or past smoking, n (%)	75 (62.0)	157 (45.9)	0.002
Dialysis, n (%)	5 (4.1)	37 (10.8)	0.028
Family history, n (%)	20 (16.5)	65 (19.0)	0.545
Left ventricular ejection fraction, %	52.57 ± 10.93	51.61 ± 13.08	0.531
Clinical presentation			
Stable angina or silent ischemia, n (%)	53 (43.8)	226 (66.1)	–
Unstable angina or acute myocardial infarction, n (%)	68 (56.2)	116 (33.9)	<i>P</i> < 0.0001

ZES, zotarolimus-eluting stents ; PES, paclitaxel-eluting stents

There were no significant differences in target vessel location, chronic total occlusion lesions, bifurcation lesions, long lesions, or small vessels between the two groups. The number of calcified lesions in the PES group was significantly higher than in the ZES group ($P = 0.0006$). With respect to lesion complexity determined according to the modified American College of Cardiology / American Heart Association (ACC / AHA) classification, 62.1% of ZES lesions and 70.3% of PES lesions were characterized as complex lesions. Although the percentage of complex lesions in the PES group was higher than that in the ZES group, the difference was not significant ($P = 0.061$). However, the percentage of type A lesions in the ZES group was significantly higher than in the PES group ($P = 0.002$), and the percentage of type C lesions in the PES group was significantly higher than in the ZES group ($P = 0.001$).

The eight-month angiographic follow-up rate was 51%. At eight months, there were significant differences in the minimal lumen diameter (MLD), percent diameter stenosis (% DS), and late loss between the two groups. Late loss was significantly higher in the ZES group than in the PES group (0.82 ± 0.73 mm vs 0.47 ± 0.68 mm ; $P = 0.003$), although the difference in the restenosis rate between the two groups was not significant ($P = 0.191$). At the one-year clinical follow-up, MI occurred in three patients in the PES group but not in the ZES group, and there were three deaths in the ZES group and six deaths in the PES group, but the differences were not significant ($P = 0.328$ and $P = 0.512$, respectively ; Table 3). Despite the significant difference in late loss, the difference in the TLR rate was not significant between both stent types (ZES : 15 lesions, 9.8% vs PES : 25 lesions, 5.8% ; $P = 0.092$). In addition, the percentage of total MACE was not significantly different between the two groups (ZES : 11.8% vs PES : 7.2% ; $P = 0.080$).

Table 2. Lesion characteristics and quantitative coronary analysis in all patients

	ZES	PES	P value
Lesion, n	153	431	
Lesion characteristics			
Target vessel			
Left main trunk, n (%)	16 (10.5)	48 (11.1)	0.817
Left anterior descending, n (%)	65 (42.5)	181 (42.0)	0.916
Left circumflex, n (%)	37 (24.2)	97 (22.5)	0.672
Right coronary, n (%)	50 (35.0)	152 (35.3)	0.563
Bifurcation, n (%)	64 (41.8)	204 (47.3)	0.241
Long lesion, n (%)	74 (48.4)	209 (48.5)	0.979
Calcified lesion, n (%)	16 (10.5)	101 (23.4)	0.0006
Small vessel lesion, n (%)	61 (39.9)	140 (32.5)	0.099
CTO, n (%)	12 (7.8)	47 (10.7)	0.28
AHA lesion type			
A, n (%)	24 (15.7)	31 (7.2)	0.002
B1, n (%)	34 (22.2)	97 (22.5)	0.942
B2, n (%)	61 (39.9)	144 (33.4)	0.151
C, n (%)	34 (22.2)	159 (36.9)	0.001
type B2 / C, n (%)	95 (62.1)	303 (70.3)	0.061
QCA			
Pre-PCI			
MLD, mm	0.58 ± 0.50	0.51 ± 0.43	0.152
RD, mm	2.97 ± 1.24	2.67 ± 0.71	0.863
%DS, %	85.1 ± 13.8	80.3 ± 17.6	0.408
Post-PCI			
MLD, mm	2.65 ± 0.68	2.62 ± 0.54	0.708
RD, mm	2.99 ± 0.57	3.05 ± 0.59	0.402
%DS, %	12.0 ± 6.6	14.6 ± 10.7	0.011
Follow-up			
MLD, mm	1.89 ± 0.84	2.11 ± 0.73	0.041
RD, mm	2.78 ± 0.50	4.31 ± 0.50	0.467
%DS, %	32.4 ± 26.2	25.6 ± 22.6	0.037
Acute gain, mm	2.08 ± 0.59	2.08 ± 0.59	0.903
Late loss, mm	0.82 ± 0.73	0.47 ± 0.68	0.003

CTO, chronic total occlusion ; QCA, quantitative coronary analysis

PCI, percutaneous coronary intervention ; MLD, minimal lumen diameter ;

RD, reference diameter ; %DS, % diameter stenosis

ZES, zotarolimus-eluting stents ; PES, paclitaxel-eluting stents

Subgroup analysis stratified by lesion complexity

When comparing the two groups based on lesion complexity, the baseline patient characteristics stratified by complexity were well balanced between the ZES and PES groups for both simple and complex lesions. However, there was a higher percentage of dialysis patients in the PES group with simple lesions ($P = 0.012$) and a higher percentage of smoking patients

Table 3. Restenosis and clinical outcomes in all patients

Variable	ZES (n = 153)	PES (n = 431)	P value
Restenosis, n (%)	20 (13.1)	76 (17.6)	0.191
MACE, n (%)	18 (11.8)	31 (7.2)	0.080
Target lesion revascularization, n (%)	15 (9.8)	25 (5.8)	0.092
Death, n (%)	3 (2.0)	6 (1.4)	0.512
Myocardial infarction, (%)	0 (0)	3 (0.7)	0.328
Target vessel revascularization, n (%)	19 (12.4)	38 (8.8)	0.197
CABG, n (%)	0 (0)	3 (0.7)	0.328

MACE, major adverse cardiac event : all-cause death, myocardial infarction, target lesion revascularization
 CABG, coronary artery bypass graft ; ZES, zotarolimus-eluting stents ; PES, paclitaxel-eluting stents

Table 4. Patient characteristics, stratified by complexity

Variable	Simple (A / B1) lesion (n = 151)			Complex (B2 / C) lesion (n = 312)		
	ZES	PES	P value	ZES	PES	P value
Patients, n	44	107		77	235	
Age, years	67.96 ± 11.86	67.57 ± 9.75	0.837	65.43 ± 13.15	67.25 ± 10.51	0.217
Male, n (%)	34 (77.3)	87 (81.3)	0.572	61 (79.2)	186 (79.1)	0.989
Risk factor						
Hypertension, n (%)	33 (75.0)	73 (68.2)	0.408	57 (74.0)	150 (63.8)	0.100
Diabetes mellitus, n (%)	25 (56.8)	58 (54.2)	0.769	38 (49.4)	124 (52.8)	0.603
Dyslipidemia, n (%)	34 (77.3)	68 (63.6)	0.102	47 (61.0)	137 (58.3)	0.671
Current or past smoking, n (%)	31 (70.5)	55 (51.4)	0.032	44 (57.1)	102 (43.4)	0.036
Dialysis, n (%)	0 (0)	14 (13.1)	0.012	5 (6.5)	23 (9.8)	0.380
Family history, n (%)	10 (22.7)	24 (22.4)	0.968	10 (13.0)	41 (17.4)	0.358
Left ventricular ejection fraction, %	53.79 ± 12.06	54.44 ± 11.96	0.801	51.86 ± 10.24	50.22 ± 13.44	0.391
Clinical presentation						
Stable angina or silent ischemia, n (%)	21 (47.7)	77 (72.0)	–	32 (41.6)	150 (63.8)	–
Unstable angina or acute myocardial infarction, n (%)	23 (52.3)	30 (28.0)	0.005	45 (58.4)	85 (36.2)	0.001

ZES, zotarolimus-eluting stents ; PES, paclitaxel-eluting stents

in the ZES group with both simple and complex lesions ($P = 0.032$ and $P = 0.036$, respectively ; Table 4). There were also significant differences in diagnoses among patients with both simple and complex lesions ($P = 0.005$ and $P = 0.001$, respectively).

Lesion characteristics and quantitative angiographic analysis data stratified by complexity are listed in Table 5. Lesion locations between the two groups were well matched except for the higher percentage of left anterior descending locations of simple lesions in the ZES group ($P = 0.002$) and right coronary artery locations of simple lesions in the PES group

Table 5. Lesion characteristics and quantitative coronary analysis, stratified for complexity

	Simple (A / B1) lesion (n = 186)			Complex (B2 / C) lesion (n = 312)		
	ZES	PES	<i>P</i> value	ZES	PES	<i>P</i> value
Lesion, n	58	128		95	303	
Lesion characteristics						
Target vessel						
Left main trunk, n (%)	2 (3.4)	2 (1.6)	0.412	14 (14.7)	46 (15.2)	0.916
Left anterior descending, n (%)	31 (53.4)	38 (29.7)	0.002	34 (35.8)	143 (47.2)	0.051
Left circumflex, n (%)	11 (19.0)	29 (22.7)	0.570	26 (27.4)	68 (22.4)	0.324
Right coronary, n (%)	15 (25.9)	60 (46.9)	0.007	35 (36.8)	92 (30.4)	0.237
Bifurcation, n (%)	11 (19.0)	34 (26.6)	0.262	53 (55.7)	170 (56.1)	0.957
Long lesion, n (%)	—	—	—	55 (23.9)	55 (23.9)	0.140
Calcified lesion, n (%)	0 (0)	19 (14.8)	0.002	16 (16.8)	82 (27.1)	0.044
Small vessel lesion, n (%)	19 (32.8)	32 (25.0)	0.272	42 (44.2)	108 (35.6)	0.133
CTO, n (%)	—	—	—	12 (12.6)	47 (15.5)	0.491
QCA						
Pre-PCI						
MLD, mm	0.81 ± 0.51	0.70 ± 0.43	0.246	0.44 ± 0.44	0.55 ± 0.43	0.136
RD, mm	2.78 ± 0.60	2.64 ± 0.64	0.273	2.62 ± 0.66	2.69 ± 0.77	0.605
%DS, %	72.1 ± 15.2	75.6 ± 13.4	0.209	82.8 ± 16.7	78.5 ± 19.5	0.154
Post-PCI						
MLD, mm	2.77 ± 0.62	2.76 ± 0.41	0.897	2.57 ± 0.45	2.55 ± 0.61	0.856
RD, mm	3.09 ± 0.64	3.10 ± 0.48	0.875	2.93 ± 0.51	3.01 ± 0.55	0.405
%DS, %	10.3 ± 5.7	11.4 ± 7.5	0.392	13.1 ± 7.0	14.3 ± 13.7	0.466
Follow-up						
MLD, mm	2.19 ± 0.63	2.28 ± 0.66	0.551	1.71 ± 0.91	2.08 ± 0.78	0.029
RD, mm	2.81 ± 0.66	2.89 ± 0.45	0.544	2.75 ± 0.48	2.77 ± 0.67	0.890
%DS, %	22.1 ± 13.3	21.5 ± 18.5	0.857	38.8 ± 30.0	25.7 ± 24.3	0.017
Acute gain, mm	1.95 ± 0.59	2.04 ± 0.56	0.443	2.15 ± 0.58	2.04 ± 0.60	0.272
Late loss, mm	0.59 ± 0.45	0.49 ± 0.57	0.431	0.97 ± 0.83	0.48 ± 0.72	0.002

CTO, chronic total occlusion ; QCA, quantitative coronary analysis

PCI, percutaneous coronary intervention ; MLD, minimal lumen diameter ; RD, reference diameter

%DS, % diameter stenosis ; ZES, zotarolimus-eluting stents ; PES, paclitaxel-eluting stents

($P = 0.007$). As to complex lesions, the percentage of left circumflex lesions in the PES group was higher, but the difference was not significant ($P = 0.051$). The number of calcified simple and complex lesions in the PES group was significantly higher than in the ZES group ($P = 0.002$ and $P = 0.044$, respectively).

When comparing QCA data among the patients with simple lesions, no differences were found between the ZES and PES groups, including late loss. Conversely, in patients with complex lesions, there were significant differences in follow-up MLD (ZES: 1.71 ± 0.91 mm vs PES: 2.08 ± 0.78 mm ; $P = 0.029$), %DS (ZES: $38.79\% \pm 29.99\%$ vs PES: $25.71\% \pm 24.28\%$; $P = 0.017$), and late loss (ZES: 0.97 ± 0.83 mm vs PES: 0.48 ± 0.72 mm ; $P = 0.002$).

Table 6. Restenosis and clinical outcomes stratified by complexity

Variable	Simple (A / B1) lesion (n = 186)			Complex (B2 / C) lesion (n = 398)		
	ZES (n = 58)	PES (n = 128)	P value	ZES (n = 95)	PES (n = 303)	P value
Restenosis, n (%)	2 (3.4)	23 (18.0)	0.007	19 (20)	53 (17.5)	0.580
MACE, n (%)	1 (1.7)	12 (9.4)	0.058	18 (17.9)	20 (6.6)	0.0004
Target lesion revascularization, n (%)	0 (0)	9 (7.0)	0.038	15 (15.8)	16 (5.3)	0.009
Death, n (%)	1 (1.7)	1 (0.8)	0.513	3 (3.2)	6 (2.0)	0.501
Myocardial infarction, (%)	0 (0)	2 (1.6)	0.361	0 (0)	2 (0.7)	0.427
Target vessel revascularization, n (%)	1 (1.7)	11 (8.6)	0.077	18 (18.9)	27 (8.9)	0.007
CABG, n (%)	0 (0)	0 (0)	–	0 (0)	3 (1.0)	0.319

MACE, major adverse cardiac event : all-cause death, myocardial infarction, target lesion revascularization
 CABG, coronary artery bypass graft ; ZES, zotarolimus-eluting stents ; PES, paclitaxel-eluting stents

Restenosis rates and clinical outcomes stratified by complexity are summarized in Table 6. Among the patients with simple lesions, the TLR rate in the ZES group was significantly lower than that in the PES group (ZES: 0% vs PES: 7.0% ; $P = 0.038$). Although there was a higher percentage of MACE in the PES group (ZES: 1.7% vs PES: 9.4%), the difference was not significant ($P = 0.058$). In the complex lesion subgroup, the TLR rate in the ZES group was significantly higher than in the PES group (ZES: 15.8% vs PES: 5.3% ; $P = 0.009$). In addition, the percentage of total MACE in the ZES group with complex lesions was significantly higher than in the PES group (ZES: 17.9% vs PES: 6.6% ; $P = 0.0004$).

Multivariate analysis

Multivariate logistic regression analysis showed that dialysis [odds ratio (OR) : 35.54 ; 95% CI : 3.15-400.67 ; $P = 0.039$] and pre-MLD (OR : 0.036 ; 95% CI : 0.002-0.541 ; $P = 0.016$) were independent predictors of TLR in lesions treated with ZESs. In contrast, no factors predicted TLR in patients with lesions treated with PESs.

Discussion

Although DESs are now widely used, the clinical efficacy of ZES implantation still remains unclear, as it has been reported that the late loss in patients treated with ZESs is higher than that observed in patients treated with other DESs⁷⁾. There is limited information about the angiographic and clinical outcomes of patients treated with first-generation DESs and ZESs, and to the best of our knowledge, few studies have focused on examining these variables based on differential lesion complexity. We therefore retrospectively compared the angiographic and clinical outcomes of patients treated with the second-generation

DES, ZES, and the first-generation DES, PES, based on lesion complexity.

In our study, approximately 73.8% of the study population had high-risk ACC/AHA type B2/C coronary lesions. With respect to clinical diagnosis and regardless of lesion complexity, the percentage of ACS patients was higher in the ZES group than in the PES group. In addition, there were significant differences between the ZES and PES groups with respect to lesion characteristics: the percentage of type A lesions was significantly higher in the ZES group than in the PES group. However, the percentages of type C lesions and calcified lesions in the PES group were significantly higher than in the ZES group. Additionally, there were significant differences between the ZES and PES groups with respect to the percentage of dialysis patients. Several explanations exist for these differences. Firstly, patients in this study were not randomly assigned to a given DES type. In our hospital, the use of ZESs was preferred for ACS cases over other DESs. Similarly, the use of PESs was preferred for dialysis cases over other DESs, as PESs are reportedly more effective in dialysis cases⁹⁾. It is possible that there could be a relationship between the higher percentage of dialysis and lesion calcification in the PES group. Secondly, several randomized studies have demonstrated the superiority of DESs over BMSs for the treatment of ACS¹⁰⁾. However, during the era of first-generation DESs, the use of DESs for ACS cases was debated due to the risk of late and very late stent thrombosis (VLST)¹¹⁻¹³⁾. Therefore, the use of BMSs for ACS cases instead of first-generation DESs, such as sirolimus-eluting stents (SESs) and PESs, is preferred in our hospital. Thirdly, everolimus-eluting stents (EESs; Abbott Vascular, Santa Clara, CA, USA) have been available in Japan since February 2010, and they are used more commonly than ZESs in complex cases in our hospital.

Upon analyzing the angiographic data after ZES implantation, the late loss was found to be greater (0.82 ± 0.73 mm) in the current study than previously reported (0.61 ± 0.49 mm)⁷⁾. In addition, the late loss in the ZES group was significantly greater than that in the PES group. There are three reasons for the greater late loss observed in the ZES group compared to the PES group⁴⁾. Firstly, the increased neointimal hyperplasia associated with ZESs is due to differences in the pharmacological activity of zotarolimus compared to other DESs. Secondly, the more rapid elution kinetics of zotarolimus from the phosphorylcholine polymer, which results in 95% elution over approximately 15 days¹⁴⁾, influences the biological efficacy of ZESs compared to the slower release of other DESs. Thirdly, there are differences in the biological responses to either the stent or the phosphorylcholine polymer itself. Whereas the late loss seen in the ZES group was overall significantly greater than in the PES group in our study, the difference in the TLR rate was not significant (ZES: 9.8% vs PES: 5.8%; $P = 0.092$). However, the TLR rate in the ZES group was relatively higher than previously reported (4.5%¹⁵⁾ and 4.9%¹⁶⁾).

In the lesion complexity subgroups divided according to ACC/AHA lesion type, ZESs resulted in excellent outcomes for A/B1 lesions, which were classified as “simple” lesions. However, for B2/C lesions, which were classified as “complex” lesions, the incidence of

TLR was significantly higher in the ZES group than in the PES group. The complexity of lesions increased the incidence of TLR in the ZES group. Lotan *et al* investigated and compared real-world outcomes of ZESs based on data from the E-Five Registry. Patients ranged from those requiring standard use ZES treatment for simple lesions to those needing extended use for lesions with complex characteristics¹⁵. They reported that the TLR rate was significantly higher in the extended-use group compared to the standard-use group (standard : 2.8% vs extended : 5.0% ; $P < 0.001$).

A number of factors associated with a higher risk of TLR in ZES-treated patients have been reported in many studies. For example, Mehta *et al* compared patients treated with ENDEAVOR I, II, or III who required TLR to patients who did not require TLR¹⁶. Multivariate analysis suggested that older age (OR : 1.03 ; 95% CI : 1.00-1.06), male sex (OR : 1.79 ; 95% CI : 0.88-3.65), and longer lesion length (OR : 1.03 ; 95% CI : 0.99-1.07) were independent risk factors for TLR after ZES implantation¹⁶. In our study, multivariate analysis identified pre-MLD and dialysis as predictors of TLR in the ZES group. It is well known that patients on dialysis have lesions with more complex characteristics, such as increased media thickness, massive calcification of coronary lesions, and multi-vessel disease, compared to patients not on dialysis. To the best of our knowledge, no study has focused on dialysis in ZES-treated patients. The reasons for this remain unclear. Further studies will be necessary to confirm these results.

Many studies have compared ZESs with other DESs^{3,4,8}), but few studies have focused on differential lesion complexity. Leon *et al* concluded that ZESs have similar levels of clinical safety and efficacy as PESs in simple and medium complexity single de novo lesions³). Similarly, Stefanini *et al* compared ZESs with EESs on the basis of lesion complexity and reported that the newer-generation ZESs and EESs proved to be safe and effective, regardless of complexity, with similar clinical and angiographic outcomes obtained for both stent types over one year⁸). However, the definitions of complexity used in these articles were slightly different from the definitions used in this report. For example, in the latter article, the definition of “complex” included characteristics such as acute MI within 72 h, left ventricular ejection fractions less than 30%, renal insufficiency or failure, treatment of bifurcations, saphenous vein grafts, arterial grafts, in-stent restenosis, unprotected left main lesions, treatment of more than two vessels, lesion lengths over 27 mm, more than one lesion / vessel, lesion with thrombus, or lesion with total occlusion⁸). As described in the Methods section, we defined A / B1 lesions as “simple” lesions and B2 / C lesions as “complex” lesions. By isolating complex lesions from lesions with the clinical characteristics described by Stefanini *et al*⁸), we were able to design this study such that the clinical outcomes attributable to specific types of lesion complexity could be assessed. Therefore, it is difficult to simply compare the results from other studies to our results.

Although the decision to use ZESs should not be negatively influenced by lesion complexity, a greater late loss was found to be associated with a greater risk for TLR. In addi-

tion, both the mid-term outcomes and the long-term outcomes, such as late stent thrombosis and VLST, should be considered. Recent studies using IVUS¹⁷⁾, optical coherence tomography¹⁸⁾, and angioscopy¹⁹⁾ reported that DESs demonstrated reduced late loss and had an inhibitory effect on neointimal hyperplasia but might be associated with a risk of late stent thrombosis or VLST due to incomplete neointimal coverage¹⁹⁾. According to these articles, neointimal coverage after ZES implantation was nearly complete, which was similar to the pattern observed with BMSs when compared to the first-generation DESs. A pooled analysis with a long-term follow-up of ZES-treated patients indicated that the frequency of VLST was less than 1%, which was similar to results observed after BMS treatment²⁰⁾. Kang *et al* compared ZESs with SESs, and PESs with IVUS and reported that ZESs had no late stent malpositions²¹⁾. Although a larger amount of neointimal hyperplasia leads to the need for TLR, the coverage of ZES struts with neointimal hyperplasia may offer a protective advantage for early vessel healing. Thus, the greater late loss of ZESs may not translate into worse clinical outcomes, and is therefore not necessarily a disadvantage of ZESs. In addition, it is unknown whether there are differences in late safety outcomes specific to the different types of DESs relative to the duration of dual antiplatelet therapy (DAPT). It is believed that the duration of DAPT after ZES implantation may be shorter compared to other DESs due to the more rapid elution kinetics of zotarolimus from the phosphorylcholine polymer²²⁾. The overall attributes of ZESs versus other stents must be considered when making decisions in clinical practice.

Study limitations

This study has several limitations that should be noted. Firstly, this study was conducted at a single center, was retrospective, was relatively small, and patients were not randomly assigned to given DES types. The unblinded evaluation of stent type was at the discretion of the operators. Secondly, we only analyzed the patients up to one year post-implantation and did not investigate long-term follow-ups. A one-year follow-up may be too short to capture late events, such as VLST, after implantation of these DESs. A longer follow-up is necessary to assess the safety and efficacy of ZES implantations. Thirdly, the eight-month angiographic follow-up rate was relatively low (51%) compared to previous reports.

Conclusion

Our study suggested that patients treated with ZESs demonstrated excellent mid-term angiographic and clinical outcomes for simple lesions compared to those treated with PESs, but it is necessary to implant ZESs carefully in complex lesions. However, the decision to use ZESs should not be negatively influenced by lesion complexity alone. Both mid-term and long-term outcomes should be considered. Therefore, the overall attributes of ZESs versus other DESs must be considered when making decisions in clinical practice.

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