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Editor's Choice

Differential Long-Term Outcomes of Zotarolimus-Eluting Stents Compared With Sirolimus-Eluting and Paclitaxel-Eluting Stents in Diabetic and Nondiabetic Patients: Two-Year Subgroup Analysis of the ZEST Randomized Trial

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Objectives: To evaluate the differential treatment effects of zotarolimus-eluting stents (ZES), sirolimus-eluting stents (SES), and paclitaxel-eluting stents (PES) according to diabetic status. Background: Diabetic patients have a higher risk of ischemic complications after stenting than nondiabetic patients. Methods: Using data from the ZEST randomized trial, comparing ZES with SES and PES, we evaluated relative outcomes among stents in diabetic and nondiabetic patients. The primary outcome was a major adverse cardiac event (MACE), defined as a composite of death, myocardial infarction, or ischemia-driven target-vessel revascularization. Results: Of the 2,645 patients enrolled in the ZEST trial, 760 (29%) had diabetes mellitus. Baseline clinical and angiographic characteristics were similar in the three stent groups, regardless of diabetic status. In diabetic patients, ZES showed similar rates of MACE as compared to PES (13.8% vs. 15.3%, $P = 0.58$), but higher rates of MACE than SES (13.8% vs. 7.7%, $P = 0.05$). In nondiabetic patients, ZES showed similar rates of MACE as compared to SES (10.3% vs. 10.8%, $P = 0.72$), whereas significantly lower rates of MACE compared to PES (10.3% vs. 15.3%, $P = 0.01$). In comparing the ZES and SES groups, there was a substantial interaction between diabetic status and stent types on MACE occurrence (Interaction $P = 0.07$). However, in comparison of ZES and PES, there were no significant interactions between diabetes and stent type on MACE (Interaction $P = 0.25$). Conclusions: In diabetic patients, SES showed the lowest rate of MACE compared with ZES and PES. But, in nondiabetic patients, SES and ZES showed significantly lower rates of MACE than PES. ZES shows a diabetes-related interaction on MACE compared with SES, but not with PES. © 2012 Wiley Periodicals, Inc.

Key words: percutaneous coronary intervention; coronary artery disease; diabetes

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INTRODUCTION

Patients with diabetes mellitus have less favorable clinical outcomes after percutaneous coronary intervention (PCI) than those without diabetes mellitus [1–3]. Although implantation of drug-eluting stents (DES) has reduced restenosis and repeat revascularization rates, the relative effects of different DES on clinical outcomes have not been completely determined.

The ZEST (Comparison of the Efficacy and Safety of **Z**otarolimus-**E**luting Stent with **S**irolimus-Eluting and Pacli**T**axel-Eluting Stent for Coronary Lesions) randomized trial showed that zotarolimus-eluting stents (ZES) had similar one-year rates of major adverse cardiovascular events (MACE) as compared to sirolimus-eluting stents (SES), but had significantly lower rates of events as compared to paclitaxel-eluting stents (PES) [4]. With long-term follow-up data of the ZEST trial, we determined that there are substantial interactions between diabetes status and different DES types on 2-year clinical outcomes.

METHODS

Study Population and Procedure

The ZEST trial was a prospective, randomized, single-blind, controlled study performed at 19 centers in Korea between October 2006 and January 2008. The details of this trial have been described elsewhere [4]. In brief, the ZEST trial had an "all-comers" design, with eligible patients being 18 years or older with either stable angina or an acute coronary syndrome with significant coronary artery disease suitable for stent implantation. Patients were considered to have diabetes mellitus if they had oral antidiabetic medications, insulin treatment, or had classic symptoms of hyperglycemia and random blood glucose level of 200 mg/dl or higher. There were no limitations on the number of lesions or vessels or on the length of the lesions, reflecting routine clinical practice. Eligible patients were randomized 1:1:1 to treatment with ZES (Endeavor; Medtronic Vascular), SES (Cypher select; Cordis, Johnson & Johnson), or PES (Taxus Liberte, Boston Scientific). Randomization was stratified by the presence or absence of diabetes mellitus. Patients with diabetes mellitus included those who were noninsulin-dependent and insulin-dependent, as defined by World Health Organization [5].

Stent implantation was performed according to standard techniques. The same randomly assigned stent had to be implanted in all lesions in patients requiring multilesion interventions, except when the assigned stent could not be inserted, in which case crossover to another device was allowed. All patients received at least 100 mg of aspirin and a 300- to 600-mg loading dose of clopidogrel before or during the procedure, as well as 100 mg/day of aspirin continuously and 75 mg/day clopidogrel for at least 12 months after the procedure.

Patient Follow-Up and Study Endpoints

Adverse events were assessed in the hospital, at 30 days and at 4, 9, 12, and 24 months. Clinical, angiographic, procedural, and outcome data were collected using a dedicated electronic case report form (e-CRF) by specialized personnel at the clinical data-management center who was unaware of treatment assignments. All outcomes of interest were confirmed by source documentation collected at each hospital and were centrally adjudicated by an independent clinical events committee, whose members were blinded as to the assigned stent.

The primary outcome of this analysis was the occurrence of MACE, defined as a composite of death from any cause, myocardial infarction (MI), or ischemia-driven target vessel revascularization (TVR) at 24 months. Secondary outcomes included the individual components of the primary outcome, the composite of death or MI, ischemia-driven target-lesion revascularization (TLR), and stent thrombosis.

All deaths were considered to be of cardiac causes unless a noncardiac cause could be identified. A diagnosis of MI was based on the presence of new Q waves in at least two contiguous leads on an electrocardiogram or an elevation of creatine kinase or its MB isoenzyme to at least three times the upper limit of the normal range. Revascularization was defined as ischemia-driven if there was stenosis of at least 50% of the diameter, as documented by a positive functional study, ischemic changes on an electrocardiogram, or ischemic symptoms, or in the absence of documented ischemia, if there was stenosis of at least 70% as assessed by quantitative coronary analysis. Stent thrombosis was assessed by Academic Research Consortium (ARC) definitions [6].

Statistical Analysis

All analyses were based on the intention-to-treat principle. Differences among treatment groups were evaluated by analysis of variance for continuous variables and by the χ^2 or Fisher's exact test for categorical variables. Cumulative event curves were generated by the Kaplan–Meier method and compared by the log-rank test. Cox proportional hazards model was used to determine hazard ratios for long-term outcomes between stent types. Interaction terms in the Cox model were used to test for the statistical significance of treatment effects among stents (ZES vs. SES or

TABLE I. Baseline Clinical Characteristics of the Patients[a]

Characteristics	Diabetic				Nondiabetic			
	Zotarolimus-eluting stent (268 Patients)	Sirolimus-eluting stent (247 Patients)	Paclitaxel-eluting stent (245 Patients)	*P*-value	Zotarolimus-eluting stent (615 Patients)	Sirolimus-eluting stent (631 Patients)	Paclitaxel-eluting stent (639 Patients)	*P*-value
Age — years	62.9 ± 9.2	63.2 ± 8.4	62.4 ± 9.6	0.65	61.2 ± 9.4	61.5 ± 9.9	61.8 ± 9.8	0.53
Male sex — no. (%)	157 (58.6)	148 (59.9)	157 (64.1)	0.42	429 (69.8)	443 (70.2)	425 (66.5)	0.30
Body-mass index — kg/m^2	25.4 ± 3.1	25.4 ± 3.3	25.3 ± 3.0	0.89	24.7 ± 2.8	24.8 ± 3.0	24.9 ± 2.9	0.56
Hypertension — no. (%)	199 (74.3)	176 (71.3)	174 (71.0)	0.66	353 (57.4)	341 (54.0)	366 (57.3)	0.40
Hyperlipidemia — no. (%)	133 (49.6)	119 (48.2)	117 (47.8)	0.91	333 (54.1)	332 (52.6)	329 (51.5)	0.64
Current smoker — no. (%)	59 (22.0)	59 (23.9)	70 (28.6)	0.21	177 (28.8)	197 (31.2)	173 (27.1)	0.26
Family history of CAD — no. (%)	12 (4.5)	9 (3.6)	13 (5.3)	0.67	36 (5.9)	35 (5.5)	39 (6.1)	0.91
Previous coronary angioplasty — no. (%)	26 (9.7)	25 (10.1)	15 (6.1)	0.22	49 (8.0)	57 (9.0)	68 (10.6)	0.26
Previous bypass surgery — no. (%)	2 (0.7)	1 (0.4)	0	0.40	4 (0.7)	5 (0.8)	5 (0.8)	0.95
Previous myocardial infarction — no. (%)	10 (3.7)	10 (4.0)	9 (3.7)	0.97	20 (3.3)	29 (4.6)	32 (5.0)	0.28
Previous congestive heart failure — no. (%)	2 (0.7)	3 (1.2)	4 (1.6)	0.65	7 (1.1)	1 (0.2)	3 (0.5)	0.07
Cerebrovascular disease — no. (%)	29 (10.8)	17 (6.9)	20 (8.2)	0.27	36 (5.9)	38 (6.0)	33 (5.2)	0.79
Peripheral vascular disease — no. (%)	6 (2.2)	9 (3.6)	11 (4.5)	0.37	9 (1.5)	12 (1.9)	6 (0.9)	0.35
Multivessel disease — no. (%)	143 (53.4)	137 (55.5)	137 (55.9)	0.82	271 (44.1)	293 (46.4)	273 (42.7)	0.40
Left ventricular ejection fraction — %	61.7 ± 8.3	61.7 ± 8.1	60.5 ± 8.4	0.24	60.7 ± 8.0	61.2 ± 8.2	61.1 ± 7.7	0.53
Clinical indication — no. (%)				0.12				0.38
Silent ischemia	20 (7.5)	13 (5.3)	22 (9.0)		28 (4.6)	31 (4.9)	34 (5.3)	
Chronic stable angina	122 (45.5)	89 (36.0)	93 (38.0)		226 (36.7)	254 (40.3)	250 (39.1)	
Unstable angina	109 (40.7)	119 (48.2)	107 (43.7)		301 (48.9)	305 (48.3)	296 (46.3)	
NSTEMI	17 (6.3)	26 (10.5)	23 (9.4)		60 (9.8)	41 (6.5)	59 (9.2)	

CAD, coronary artery disease; NSTEMI, non-ST-elevation myocardial infarction.
[a]Plus-minus values are means ± SDs. Data are given for the intention-to-treat population.

PES) by diabetic status on clinical outcomes. SAS software, version 9.1 (SAS Institute, Cary, NC) was used for all statistical analyses. No adjustments were made for multiple comparisons in secondary analyses. All *P*-values and confidence intervals were two-sided in subgroup analyses.

RESULTS

Baseline Characteristics and Procedural Results

Between October 2006 and January 2008, a total of 2,645 patients (3,613 lesions) were enrolled in the study and randomized to undergo implantation with ZES (883 patients; 1,190 lesions), SES (878 patients; 1,218 lesions) or PES (884 patients; 1,205 lesions). Of these patients, 760 patients were classified as diabetic and 1,885 patients, as nondiabetic. Among 760 diabetic patients, 268 patients received ZES, 247 patients received SES, and 245 patients received PES. Among 1,885 nondiabetic patients, 615 patients received ZES, 631 patients received SES, and 639 patients received PES. Baseline demographic and clinical characteristics were similar among the three groups of diabetic and three groups of nondiabetic patients (Table I), as were most of the lesion and procedural characteristics among stent groups (Table II).

Clinical Outcomes

Clinical follow-up at 24 months was completed for 98.6% of overall patients (98.7% of diabetic and 98.5% of nondiabetic patients). The 2-year rates of MACE was similar in diabetic and nondiabetic patients (12.3% vs. 12.2%, respectively; $P = 0.710$). The rate of death was 2.4% in diabetic patients and 0.8% in nondiabetic patients ($P = 0.001$). The TVR rate was 5.5% in diabetic patients and 6.1% in nondiabetic patients ($P = 0.717$). The rate of stent thrombosis was

TABLE II. Baseline Lesions and Procedural Characteristics[a]

Characteristics	Diabetic				Nondiabetic			
	Zotarolimus-eluting stent (354 Lesions)	Sirolimus-eluting stent (367 Lesions)	Paclitaxel-eluting stent (356 Lesions)	*P*-value	Zotarolimus-eluting stent (836 Lesions)	Sirolimus-eluting stent (851 Lesions)	Paclitaxel-eluting stent (849 Lesions)	*P*-value
Lesion characteristics								
Location — no. (%)				0.63				0.65
Left anterior descending	179 (50.6)	184 (50.1)	169 (47.5)		443 (53.0)	461 (54.2)	442 (52.1)	
Left circumflex	80 (22.6)	71 (19.3)	81 (22.8)		172 (20.6)	154 (18.1)	172 (20.3)	
Right coronary	95 (26.8)	112 (30.5)	106 (29.8)		221 (26.4)	236 (27.7)	234 (27.6)	
ACC-AHA B2 or C type — no. (%)	264 (74.6)	291 (79.3)	274 (77.0)	0.32	594 (71.1)	630 (74.0)	621 (73.1)	0.37
Total occlusion — no. (%)	19 (5.4)	18 (4.9)	25 (7.0)	0.44	49 (5.9)	58 (6.8)	71 (8.4)	0.13
Bifurcation lesions — no. (%)	54 (15.3)	35 (9.5)	46 (12.9)	0.07	127 (15.2)	116 (13.6)	120 (14.1)	0.65
Ostial lesion — no. (%)	27 (7.6)	16 (4.4)	26 (7.3)	0.14	58 (6.9)	56 (6.6)	56 (6.6)	0.95
Calcification — no. (%)				0.31				0.74
None or mild	337 (95.2)	345 (94.0)	325 (91.3)		792 (94.7)	800 (94.0)	807 (95.1)	
Moderate	11 (3.1)	14 (3.8)	19 (5.3)		29 (3.5)	29 (3.4)	27 (3.2)	
Severe	6 (1.7)	8 (2.2)	12 (3.4)		15 (1.8)	22 (2.6)	15 (1.8)	
Lesion length — mm				0.94				0.07
<10	21 (5.9)	19 (5.2)	18 (5.1)		52 (6.2)	52 (6.1)	43 (5.1)	
10–20	128 (36.2)	125 (34.1)	128 (36.0)		338 (40.4)	319 (37.5)	376 (44.3)	
>20	205 (57.9)	223 (60.8)	210 (59.0)		446 (53.3)	480 (56.4)	430 (50.6)	
Procedural characteristics								
No. of stents per lesion	1.2 ± 0.5	1.2 ± 0.4	1.2 ± 0.5	0.56	1.2 ± 0.5	1.2 ± 0.4	1.2 ± 0.4	0.44
No. of stents per patient	1.6 ± 0.9	1.7 ± 0.9	1.8 ± 1.1	0.27	1.6 ± 0.9	1.6 ± 0.9	1.6 ± 0.9	0.85
Length of stents per lesion — mm	28.1 ± 13.4	29.9 ± 14.2	30.3 ± 15.8	0.09	27.8 ± 13.0	28.5 ± 13.2	28.3 ± 13.6	0.59
Length of stents per patient — mm	38.7 ± 24.5	36.2 ± 23.8	38.9 ± 25.1	0.42	40.2 ± 27.7	39.0 ± 24.4	38.9 ± 25.2	0.65
Maximal stent diameter — mm	3.4 ± 0.5	3.5 ± 0.5	3.4 ± 0.5	0.44	3.5 ± 0.5	3.5 ± 0.4	3.6 ± 0.5	<0.001
Maximal pressure — atm	15.3 ± 3.4	16.9 ± 3.2	15.6 ± 3.5	<0.001	15.4 ± 3.6	16.8 ± 3.3	15.3 ± 3.6	<0.001
Intravascular ultrasound guidance — no. (%)	135 (38.1)	124 (33.8)	141 (39.6)	0.24	353 (42.2)	390 (45.8)	350 (41.2)	0.13
Use of glycoprotein IIb-IIIa inhibitors per patient — no. (%)	8 (3.0)	4 (1.6)	5 (2.0)	0.56	11 (1.8)	11 (1.7)	9 (1.4)	0.85

ACC, American College of Cardiology; AHA, American Heart Association.

[a]Plus–minus values are means ± SDs. Data are given for the intention-to-treat population.

1.1% in diabetic patients and 0.4% in nondiabetic patients ($P = 0.058$). When we compared clinical outcomes between diabetic and nondiabetic patients for each stent group, no stent group showed any significant difference of clinical outcomes between diabetic and nondiabetic patients.

Among diabetic patients, in comparison with PES, ZES showed similar 2-year rates of MACE (13.8% vs. 15.3%; $P = 0.584$), but ZES showed higher rates of MACE compared with SES (13.8% vs. 7.7%; $P = 0.052$) (Table III). The rate of death or MI was similar among the groups, but the TLR rate was significantly lower in the SES (1.3%) than in the ZES (6.8%) or PES (6.6%) group ($P = 0.018$). The TVR rate was also significantly lower in the SES (1.7%) than in the ZES (7.2%) or PES (7.4%) group ($P = 0.018$). The rates of definite or probable stent thrombosis in the ZES, SES, and PES groups were 1.5%, 0%, and 1.9%, respectively. The cumulative 2-year incidence rates of clinical outcomes in diabetic patients are shown in Fig. 1.

By contrast, among nondiabetic patients, the 2-year rates of MACE was similar in the ZES and SES groups (10.3% vs. 10.8%; $P = 0.724$), but was significantly lower in the ZES than in the PES group (10.3% vs. 15.3%; $P = 0.007$) (Table III). The rate of death or MI was similar in the three groups, but TLR rate was significantly higher in the PES (8.8%) than in the ZES (5.1%) or SES group (3.7%) group ($P < 0.001$). The TVR rate was also significantly higher in the PES (9.1%) than in the ZES (5.6%) or SES (3.7%) group ($P = 0.001$). The rates of definite or probable stent thrombosis in the ZES, SES, and PES groups were 0.3%, 0.3%, and 0.6%, respectively. The cumulative 2-year rates of clinical outcomes in nondiabetic patients are shown in Fig. 2.

TABLE III. Clinical Events at Two-Year Follow-Up[a]

Characteristics	Diabetic				Non-diabetic			
	Zotarolimus-eluting stent (268 Patients)	Sirolimus-eluting stent (247 Patients)	Paclitaxel-eluting stent (245 Patients)	*P*-value	Zotarolimus-eluting stent (615 Patients)	Sirolimus-eluting stent (631 Patients)	Paclitaxel-eluting stent (639 Patients)	*P*-value
Follow-up at 2 years								
Death	7 (2.6)	3 (1.2)	8 (3.3)	0.178	4 (0.7)	8 (1.3)	4 (0.6)	0.507
Cardiac	6 (2.4)	2 (0.9)	5 (2.3)	0.442	4 (0.7)	5 (0.9)	2 (0.3)	0.744
Noncardiac	1 (0.4)	1 (0.5)	3 (1.4)	0.321	0	3 (0.5)	2 (0.3)	0.496
Myocardial infarction	17 (6.3)	14 (5.7)	19 (7.8)	0.608	30 (4.9)	43 (6.8)	44 (6.9)	0.260
Q-wave	3 (1.2)	0	2 (0.8)	0.273	3 (0.5)	3 (0.5)	3 (0.5)	0.999
Non-Q-wave	14 (5.2)	14 (5.7)	17 (7.0)	0.606	27 (4.4)	40 (6.4)	41 (6.4)	0.228
Death or myocardial infarction	22 (8.2)	17 (6.9)	23 (9.6)	0.573	33 (5.4)	49 (7.8)	47 (7.4)	0.220
Ischemia-driven TLR[b]	18 (6.8)	3 (1.3)	16 (6.6)	0.018	31 (5.1)	17 (2.7)	56 (8.8)	<0.001
Ischemia-driven TVR[b]	19 (7.2)	4 (1.7)	18 (7.4)	0.018	34 (5.6)	23 (3.7)	58 (9.1)	0.001
Stent thrombosis								
Definite	3 (1.1)	0	3 (1.5)	0.224	1 (0.2)	2 (0.3)	4 (0.6)	0.387
Definite or probable	4 (1.5)	0	4 (1.9)	0.138	2 (0.3)	2 (0.3)	4 (0.6)	0.627
Acute	1 (0.4)	0	1 (0.4)	0.616	1 (0.2)	0	2 (0.3)	0.376
Subacute	2 (0.7)	0	2 (0.8)	0.377	1 (0.2)	0	0	0.356
Late	1 (0.4)	0	1 (0.4)	0.616	0	2 (0.3)	2 (0.3)	0.379
Any	4 (1.5)	0	4 (1.9)	0.138	3 (0.5)	3 (0.5)	6 (0.9)	0.500
MACE[c]	37 (13.8)	19 (7.7)	37 (15.3)	0.047	63 (10.3)	68 (10.8)	98 (15.3)	0.011

TLR, target lesion revascularization; TVR, target vessel revascularization

[a]Percentages and *P*-values were from the intention-to-treat analysis and were calculated with the use of Kaplan–Meier estimates with log-rank test.

[b]*P*-values of *post hoc* multiple comparisons for secondary clinical outcomes. No adjustments were made for multiple comparisons in secondary analyses; for target-lesion revascularization of diabetic patients (zotarolimus- vs. sirolimus-stent, $P = 0.009$; zotarolimus- vs. paclitaxel-stent, $P = 0.912$; sirolimus- vs. paclitaxel-stent, $P = 0.006$), for target-lesion revascularization of nondiabetic patients (zotarolimus- vs. sirolimus-stent, $P = 0.067$; zotarolimus- vs. paclitaxel-stent, $P = 0.010$; sirolimus- vs. paclitaxel-stent, $P < 0.001$), for target-vessel revascularization of diabetic patients (zotarolimus- vs. sirolimus-stent, $P = 0.012$; zotarolimus- vs. paclitaxel-stent, $P = 0.759$; sirolimus- vs. paclitaxel-stent, $P = 0.005$), for target-vessel revascularization of nondiabetic patients (zotarolimus- vs. sirolimus-stent, $P = 0.190$; zotarolimus- vs. paclitaxel-stent, $P = 0.017$; sirolimus- vs. paclitaxel-stent, $P < 0.001$).

[c]For major adverse cardiac events (defined as a composite of death, myocardial infarction, or ischemia-driven target-vessel revascularization) at 24 months. In diabetic patients, $P = 0.052$ for comparison of zotarolimus- and sirolimus-stents, $P = 0.584$ for comparison of zotarolimus- and paclitaxel-stents, $P = 0.016$ for comparison of sirolimus- and paclitaxel-stents. In nondiabetic patients, $P = 0.724$ for comparison of zotarolimus- and sirolimus-stents, $P=0.007$ for comparison of zotarolimus- and paclitaxel-stents, and $P = 0.019$ for comparison of sirolimus- and paclitaxel-stents.

When we assessed whether the clinical outcomes for the three different stents varied significantly according to diabetes status, in comparison of ZES with SES groups, we observed a substantial interaction between diabetic status and stent types on MACE occurrence (interaction $P = 0.07$). However, in comparing the ZES and PES groups, we observed no significant interaction between diabetes and stent type on MACE (interaction $P = 0.25$). As secondary outcomes, in comparison of ZES with SES groups, there were no significant interactions between the presence or absence of diabetes and stent groups for death ($P_{\text{interaction}} = 0.12$), the composite of death and MI ($P_{\text{interaction}} = 0.18$), TVR ($P_{\text{interaction}} = 0.15$) or stent thrombosis ($P_{\text{interaction}} = 0.94$). In comparison of ZES with PES groups, there were no significant interactions between the occurrence of diabetes and ZES and PES for death ($P_{\text{interaction}} = 0.73$), the composite of death or MI ($P_{\text{interaction}} = 0.63$), TVR ($P_{\text{interaction}} = 0.29$), or stent thrombosis ($P_{\text{interaction}} = 0.61$) (Table IV).

DISCUSSION

The major findings of this analysis were that (1) in diabetic patients, ZES showed similar 2-year rates of MACE as compared to PES, but higher rates of MACE compared to SES; (2) in nondiabetic patients, the 2-year rates of MACE were similar in patients with ZES and SES, but were significantly lower with ZES than with PES, and (3) there was a substantial diabetes-related interaction on MACE outcomes between ZES and SES, but not between ZES and PES.

Diabetic patients are at higher risk of adverse cardiac events and restenosis than nondiabetic patients after PCI. These adverse outcomes have been dramatically reduced with the introduction of DES. The TAXUS-IV trial showed that PES was highly effective in reducing restenosis in diabetic patients [7]. The Diabetes and Sirolimus-Eluting Stent (DIABETES) trial and the subgroup analysis of SIRolImUS-coated Bx Velocity balloon-expandable stent in the treatment of patients

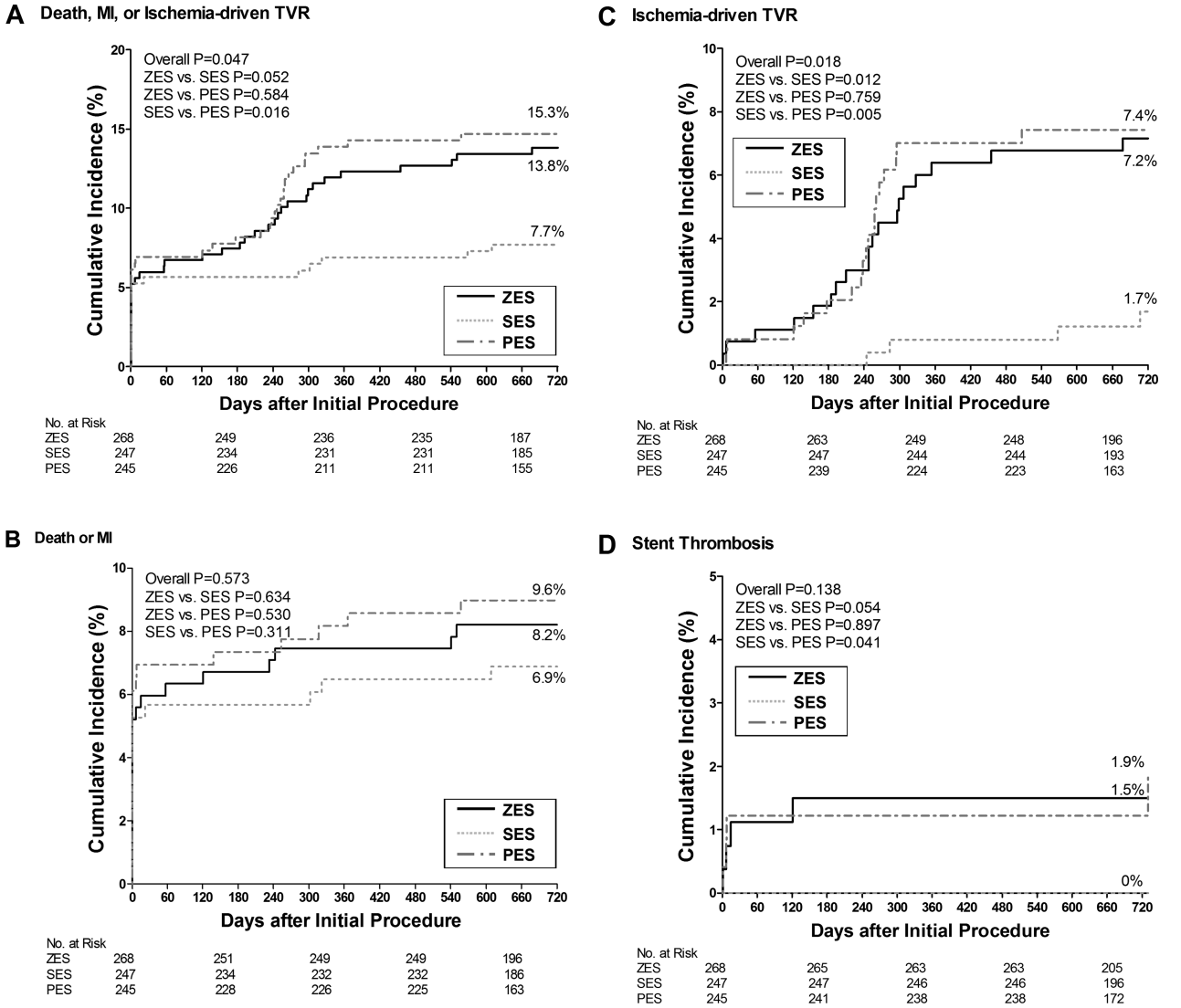

Fig. 1. Cumulative incidence of 2-year clinical outcomes in diabetic patients. Kaplan–Meier cumulative incidence curves of clinical outcomes for up to 2 years in diabetic patients who received ZES, SES, or PES. *P*-values for comparisons of ZES with SES and PES are two-sided comparisons using the log-rank test. (A) Composite of death, myocardial infarction (MI), or ischemia-driven target-vessel revascularization (TVR). (B) Composite of death or MI. (C) TVR. (D) Stent thrombosis.

with *de novo* coronary artery lesions (SIRIUS) trial demonstrated that implantation of SES in diabetic patients was safe and effective in reducing restenosis when compared with BMS [8,9]. Regarding overall performance of ZES, several trials have evaluated the safety and efficacy of ZES in diabetic patients. For example, the ENDEAVOR II trial showed that ZES was safe and reduced restenosis rates at 9, 12, and 24 months as compared with BMS. Subgroup analysis showed that TLR rates were higher in diabetic than nondiabetic patients receiving both ZES and BMS [10].

However, there have been limited data evaluating relative treatment effects of different DES types. We therefore compared the relative outcomes of ZES with those of SES and PES over 2-years in both diabetic and nondiabetic patients. The ZES group showed higher rates of MACE than the SES group in diabetic patients, whereas they showed similar rates in nondiabetic patients. ZES shows a diabetes-related treatment interaction on MACE as compared with SES. We cannot exactly explain the mechanism of this phenomenon. It would be partly explained by differences of stent platforms, drug-delivery systems, active drugs, or elution kinetics [11–13]. The complex lesion characteristics, which are generally found in diabetic patients, might exacerbate this difference between stent types.

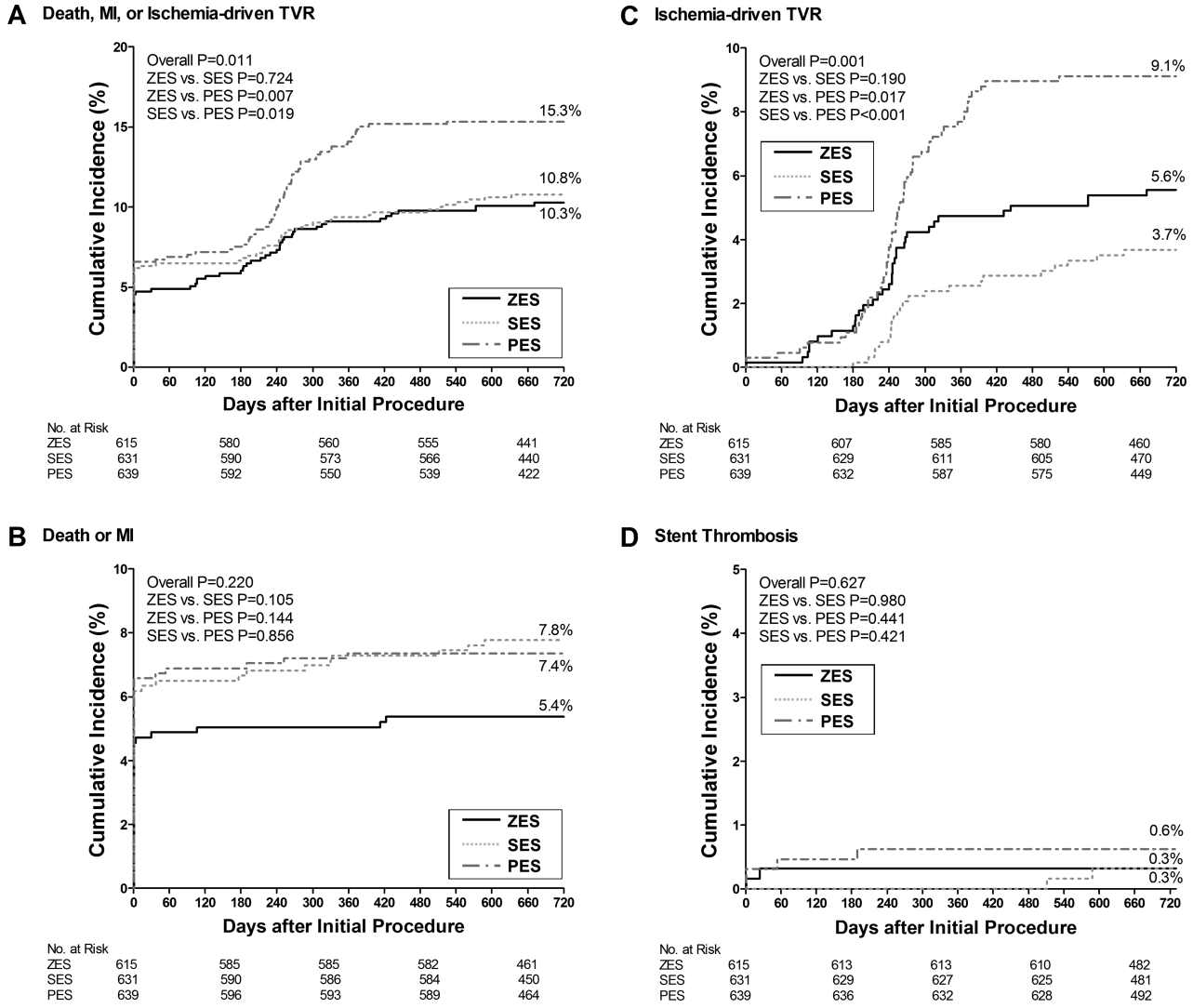

Fig. 2. Cumulative incidence of 2-year clinical outcomes in nondiabetic patients. Kaplan–Meier cumulative incidence curves of clinical outcomes for up to 2 years in nondiabetic patients who received ZES, SES, or PES. *P*-values for comparisons of ZES with SES and PES are two-sided comparisons using the log-rank test. (A) Composite of death, myocardial infarction (MI), or ischemia-driven target-vessel revascularization (TVR). (B) Composite of death or MI. (C) TVR. (D) Stent thrombosis.

Considering patients with PES in diabetic and nondiabetic subsets, the rate of MACE was 7.7% in diabetic patients and 10.3% in nondiabetic patients. The rate of ischemia-driven TVR was 1.7% and 3.7%, respectively. These results are consistent with the results from TAXUS-IV trial [7]. However, previous TAXUS trials showed better early and late outcomes in diabetic patients [14,15]. In addition, another registry data showed that PES showed better outcomes as compared with SES [16,17]. In a subgroup analysis of the ENDEAVOR IV trial, there was no significant interaction between stent type (PES and ZES) and diabetes status on clinical outcomes (individual MACE components, TVR, or stent thrombosis) [18]. It might be known that paclitaxel simultaneously blocks two cellular pathways that promote restenosis of the vessel, while sirolimus can only shut down one such pathway [19]. By contrast, our results showed that SES had lower rate of MACE and lower rate of TLR than PES. This discrepancy might be explained in part by differences in clinical or lesion characteristics, interventional practice, or race or ethnic group between our population of patients and those enrolled in other studies.

Although diabetes was shown to be an independent predictor of stent thrombosis in patients with drug eluting stents [20,21], the rates of stent thrombosis

TABLE IV. Interaction of Diabetes with Stent Types on Clinical Outcomes Over Two-Years

Outcomes	ZES vs. SES			Interaction *P* for diabetes status[a]	ZES vs. PES			Interaction *P* for diabetes status
	Hazard ratio	(95% CI)	*P*-value		Hazard ratio	(95% CI)	p Value	
Overall								
Death	1.11	(0.49–2.48)	0.81	0.12	0.87	(0.41–1.86)	0.73	0.73
Death and MI	0.83	(0.58–1.19)	0.31	0.18	0.78	(0.55–1.10)	0.16	0.63
TVR	1.85	(1.21–2.82)	0.01	0.15	0.68	(0.48–0.97)	0.03	0.29
Stent thrombosis	2.99	(0.60–14.82)	0.18	0.94	0.75	(0.26–2.16)	0.59	0.61
MACE	1.12	(0.84–1.49)	0.43	0.07	0.73	(0.56–0.94)	0.02	0.25
Diabetic patients								
Death	2.36	(0.63–8.94)	0.21		0.70	(0.26–1.87)	0.48	
Death and MI	1.16	(0.63–2.15)	0.64		0.83	(0.47–1.49)	0.53	
TVR	3.04	(1.21–7.61)	0.02		0.91	(0.48–1.71)	0.76	
Stent thrombosis	60.65	(0.02–)	0.32		0.90	(0.23–3.65)	0.90	
MACE	1.68	(0.99–2.87)	0.06		0.88	(0.56–1.39)	0.59	
Nondiabetic patients								
Death	0.58	(0.19–1.80)	0.35		0.96	(0.28–3.32)	0.95	
Death and MI	0.70	(0.45–1.09)	0.11		0.73	(0.47–1.13)	0.15	
TVR	1.41	(0.84–2.36)	0.19		0.60	(0.39–0.92)	0.02	
Stent thrombosis	1.03	(0.14–7.28)	0.98		0.52	(0.10–2.84)	0.45	
MACE	0.94	(0.67–1.32)	0.73		0.65	(0.48–0.90)	0.01	

MI, myocardial infarction; TVR, target vessel revascularization; MACE, major adverse cardiac events.
[a]Interaction *P* for diabetes status represents the likelihood for interaction between diabetic status and stents for the clinical outcomes.

following implantation of all three stent types were extremely low in both diabetic and nondiabetic patients. Because we analyzed a limited population of patient, the low rate of stent thrombosis we observed should be interpreted with caution and not generalized to larger patient populations.

Study Limitations

Although the ZEST trial was a well-powered, randomized trial comparing the relative safety and efficacy of ZES with both SES and PES, this subgroup analysis was not powered to assess the superiority or inferiority of hard clinical outcomes or low frequency events (death, MI, or stent thrombosis). To overcome this limitation, substantially larger populations and longer follow-up durations are required. The ongoing randomized PROTECT (Patient Related OuTcomes with Endeavor versus Cypher stenting Trial), comparing late stent thrombosis, death, and MI over 3 years in 8,800 patients receiving ZES or SES will provide a critical evaluation of the relative safety of these two stent types [22]. In addition, the ZEST trial excluded patients with ST-segment elevation MI and left main disease, which may have larger sized vessels. Therefore, larger vessel size may attenuate the differences among stents in patients with diabetes.

CONCLUSIONS

In diabetic patients, SES showed the lowest rate of MACE compared with ZES and PES. But, in non-diabetic patients, SES and ZES showed significantly lower rates of MACE than PES. ZES shows a diabetes-related treatment interaction on MACE compared with SES, but not compared with PES.

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