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ORIGINAL STUDIES

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Clinical outcomes of contemporary drug-eluting stents in patients with and without diabetes mellitus: Multigroup propensity-score analysis using data from stent-specific, multicenter, prospective registries

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Abstract

Background: Whether the diabetic status differentially affects the clinical outcomes with different drug-eluting stents (DES) has been controversial.

Methods and Results: From stent-specific, prospective DES registries, we evaluated 17,184 patients (11,428 in non-diabetics and 5,756 in diabetics) who received several contemporary DES: 3570 sirolimus-eluting stents (SES), 5,023 cobalt-chromium everolimus-eluting stents (CoCr-EES), 2,985 platinum-chromium EES (PtCr-EES), 2,913 Resolute zotarolimus-eluting stents (Re-ZES), and 2,693 biodegradable-polymer biolimus-eluting stents (BP-BES). The primary outcome was patient-oriented composite endpoint (POCE, a composite of all-cause death, any myocardial infarction, and any revascularization) at 3-year follow-up and target-vessel failure (a composite of cardiac death, target-vessel myocardial infarction, and target-vessel revascularization) at 3 years was also evaluated. In non-diabetics, the rates of POCE were not significantly different (CoCr-EES 14.3%, PtCr-EES 13.0%, Re-ZES 14.3%, BP-BES 13.4%, and SES 14.6%; overall p = .39). In diabetics, similar results were revealed (CoCr-EES 18.4%, PtCr-EES 20.3%, Re-ZES 17.3%, BP-BES 17.7%, and SES 17.8%; overall p = .44). In multiple treatment propensity-score weighting analysis, regardless of the diabetic status, the hazard ratios for POCE between-individual comparison were similar. Target-vessel failure (a composite of cardiac death, target-vessel myocardial infarction, and target-vessel revascularization) was also comparable except the higher ratio of Re-ZES than PtCr-EES (hazard ratio 1.25, 1.26, 95% confidence interval 1.00–1.55, p = .048) in patients without diabetes.

Conclusions: In this clinical-practice registry study, regardless the diabetic status, the 3-year rates of the primary outcome were similar among different types of DES,

[†]The members of the IRIS-DES registry and the affiliations of the authors are listed in the Online Appendix

suggesting no differential clinical response between contemporary DES in patients with or without diabetes.

KEYWORDS
coronary artery disease, diabetes mellitus, drug-eluting stents, percutaneous coronary intervention

1 | INTRODUCTION

Diabetes mellitus is a highly prevalent disease that is frequently associated with significant coronary artery disease (CAD) requiring percutaneous coronary intervention (PCI).[1] Because diabetes mellitus is prone to have a greater atherosclerotic burden, diffuse, and long lesions in small-caliber vessels, and accelerated neointimal hyperplasia,[2] patients with diabetes undergoing PCI have higher rates of adverse outcomes than patients without diabetes.[3] Owing to a remarkable improvement of efficacy regarding angiographic and clinical restenosis, drug-eluting stents (DES) have become the standard devices used in PCI for patients with diabetes mellitus.[4] However, whether the diabetic status differentially influences the relative clinical outcomes of different types of DES has been a matter of considerable debate. Previous studies have reported contradictory results for the clinical outcomes of PCI with stents eluting rapamycin-analogs versus first-generation paclitaxel-eluting stents stratified by the presence of diabetes mellitus.[5,6]

Contemporary, newer-generation DES have been developed that use different antiproliferative drugs with improved drug release kinetics, novel stent materials, thinner strut platforms, easier delivery system, and more biocompatible or biodegradable polymers than their predecessors.[7] Additional studies are therefore required to examine individual efficacy and safety outcomes among different contemporary DES according to the diabetic status. We have conducted such an evaluation in our present study using stent-specific, prospective, clinical-practice registries that incorporate different types of contemporary DES.

2 | METHODS

2.1 | Study population

The study population comprised patients who underwent daily PCI procedures with DES implantation for significant CAD between July 15, 2007, and July 29, 2015 and was pooled from the Interventional Cardiology Research Incorporation Society–Drug-Eluting Stents (IRIS–DES) registry. The IRIS–DES registry has been described previously[8] and its members and author affiliations are listed in Online Appendix I. Briefly, the IRIS-DES involves a prospective, multicenter recruitment of unrestricted patients undergoing PCI with DES in Korea.

Our current analysis included patients treated with first-generation sirolimus-eluting stent (SES) and four different types of contemporary DES as follows: SES (Cipher Select, Cordis Corp), cobalt-chromium everolimus-eluting stents (CoCr-EES) (Xience V or Prime, Abbott Vascular), platinum-chromium EES (PtCr-EES) (Promus Element, Boston Scientific), Resolute zotarolimus-eluting stent (Re-ZES) (Resolute Integrity, Medtronic), and biodegradable-polymer biolimus-eluting stents (BP-BES) (BioMatrix, Biosensors, and Nobori, Terumo Clinical Supply). This registry was supported by the Cardio-Vascular Research Foundation, Seoul, Korea, and there was no industry involvement in the design, conduct, or analysis of the study. The key features of each stent stratum are summarized in Table S1. The study protocol was approved by the ethics committee at each participating center, and all patients provided written, informed consent.

2.2 | Procedures and follow-up

PCI was performed according to standard techniques for all patients in the IRIS–DES registry, at the discretion of each operator in the participating centers. This registry does not specify the stent types according to clinical or anatomic features; thus, each operator was responsible for the decision to select a specific DES.

Clinical follow-ups were conducted during hospitalization and at 30 days, 6 months, and 12 months post-discharge, and every 6 months thereafter, in accordance with protocol recommendations. For the accurate assessment of clinical endpoints, additional information was obtained from telephone interviews and from medical records obtained from other hospitals, as necessary. All baseline characteristics and outcome data were collected by specialized personnel at each participating center using a dedicated, electronic case report form. Monitoring and verification of registry data are periodically performed in the participating hospitals by members of the academic coordinating center (Clinical Research Center, Asan Medical Center, Seoul, Korea).[8]

2.3 | Study outcomes and definitions

The primary outcome for this study was patient-oriented composite endpoint (POCE, a composite of all-cause death, any myocardial infarction [MI], or any revascularization) in accordance with the Academic Research Consortium definition.[9] The secondary clinical outcomes included death (any cause, cardiac, or noncardiac cause), MI (periprocedural or spontaneous), repeat revascularization (any type, target-lesion revascularization [TLR] or target-vessel revascularization [TVR]), stent thrombosis, and target-vessel failure (a composite of cardiac death, target-vessel MI, or TVR) as a device-oriented outcome.

Death was considered to be from a cardiac cause unless an unequivocal noncardiac cause could be established. The diagnosis of

MI was based on the Society for Cardiovascular Angiography and Interventions definition of clinically relevant MI.[10] Definite or probable stent thrombosis was assessed in accordance with the Academic Research Consortium definition and categorized as early, late, or very late.[9] All outcomes of interest were confirmed using source documentation collected at each hospital and were centrally adjudicated by an independent clinical events committee, whose members were blind to the specific type of DES.

As predefined in the study protocol, medically treated diabetes mellitus was defined as treatment with oral hypoglycemic agents or insulin at the time of enrollment. Diet-controlled diabetic patients were included only if there was documentation of an abnormal blood glucose level after an overnight fast or an abnormal glucose tolerance test during hospitalization for PCI procedure.

2.4 | Statistical analysis

Cumulative clinical events were assessed using Kaplan–Meier estimates and compared with the log-rank test. All analyses were truncated at the 3-year follow-up stage owing to differences in the follow-up durations by DES type. To compensate for the nonrandomized design of this current study and minimize confounding and residual selection bias in the observational treatment comparisons, a propensity-score weighting method was applied to control for imbalances in various baseline characteristics across the treatment groups.[11] For the present analysis, multiple treatment propensity scores were applied using the Toolkit for Weighting and Analysis of Nonequivalent Groups (TWANG) method and corresponding inverse probabilities of treatment weight (the reciprocal of the propensity scores) were estimated via generalized boosted models through an iterative estimation procedure (n = 3,000), by using all the related baseline characteristics[12] (Online Appendix II). The balance of the pretreatment covariates was assessed, and significant improvement in baseline was achieved after weighting. (Table S2, Figures S1 and S2) For the evaluation of treatment effects, the PROC SURVEYPHREG procedure in the SAS software was used to correctly interpret weights as probability weights.

For the sake of missing data, albeit less than 5% once it was identified, we performed multiple imputations using Markov chain Monte Carlo in the SAS procedure. All reported p values were two-sided and were not adjusted for multiple testing. All analyses were performed with SAS software version 9.4 (SAS Institute, Cary, NC) and R software version 3.2.2 13 (R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org).

3 | RESULTS

3.1 | Study population and baseline characteristics

A flow diagram of the study is shown in Figure 1. Among the 17,196 patients between July 2007 and July 2015, 12 patients were excluded due to lack of information on diabetic status and thus 17,184 patients were finally included in the present analysis: 3,570 with SES, 5,023 patients with CoCr-EES, 2,985 with PtCr-EES, 2,913 with Re-ZES, and 2,693 with BP-BES. Among them, 5,756 (33.5%) had diabetes mellitus at the time of admission and a similar proportion (~30–35%) of diabetic patients was identified in each stent group.

As expected, patients with diabetes had an overall higher risk profile in terms of clinical, lesion, and procedural characteristics (Tables S3 and S4). The baseline demographics and clinical characteristics of the study population according to diabetic status and DES type are presented in Table S5. In both nondiabetic and diabetic patients, there were significant between-stent group differences. Table S6 lists the lesion and procedural characteristics according to diabetic status and DES type. Similar to the clinical characteristic profiles, there were significant differences between the nondiabetic and diabetic patients across the stent groups with regard to anatomic, lesion, and procedural characteristics.

3.2 | Clinical outcomes

The median clinical follow-up duration in the total population was 3.9 years (interquartile range 2.6–4.1). As shown in Table S7, the 3-year rates of clinical outcomes were significantly worse in the patients with diabetes mellitus, compared with those without diabetes mellitus.

Kaplan–Meier estimates of primary and secondary outcomes at the 3-year follow-up according to diabetic status and DES type are presented in Figure 2 and Table S8. In patients without diabetes mellitus, there were no significant between-stent group differences in the 3-year rates of POCE. There were also no significant between-group differences with respect to mortality, repeat revascularization, and target-vessel failure. However, there was a significant difference in the rate of MI, mainly driven by periprocedural MI. Late or very late stent thrombosis occurred more frequently in SES (0.3%), compared to other contemporary DES. Among the diabetic patients, there were no significant differences in the primary and secondary clinical outcomes at the 3-year follow-up other than a higher incidence of TLR in the SES group.

The adjusted hazard ratios for multiple DES comparisons from the multiple treatment propensity-score weighting method are indicated in Table 1 and Figure 3 (SES as the reference group). In nondiabetic patients, the hazard ratios between-individual stent comparisons were similar with respect to the risk of POCE and target-vessel failure except the higher risk of target-vessel failure in Re-ZES compared with PtCr-EES. Statistically significance differences were also observed in the nondiabetic patients with regard to MI in PtCr-EES versus CoCr-EES, Re-ZES versus PtCr-EES, and SES versus PtCr-EES comparisons and with regard to death in the comparison of SES versus Re-ZES. Among the patients with diabetes mellitus, no significant between-stent group differences were observed in any of the measured primary or secondary outcomes parameters except the higher risk of MI in CoCr-EES compared with BP-BES.

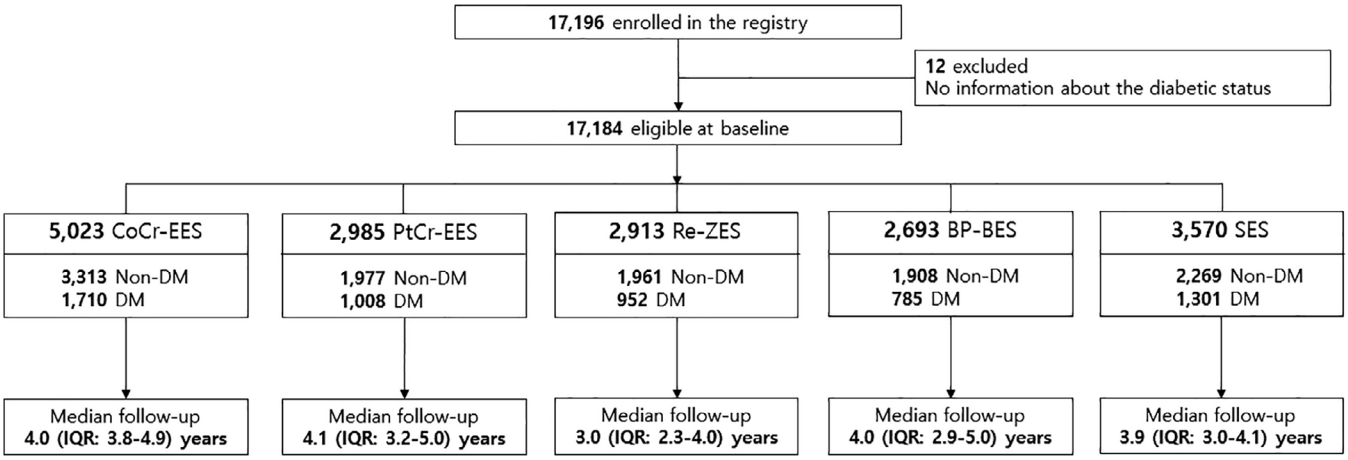

FIGURE 1 Study flow diagram. BP-BES, biodegradable-polymer biolimus-eluting stents; CoCr-EES, cobalt-chromium everolimus-eluting stents; DM, diabetes mellitus: IQR, interquartile range; PtCr-EES, platinum-chromium everolimus-eluting stents; Re-ZES, resolute zotarolimus-eluting stents; SES, sirolimus-eluting stents

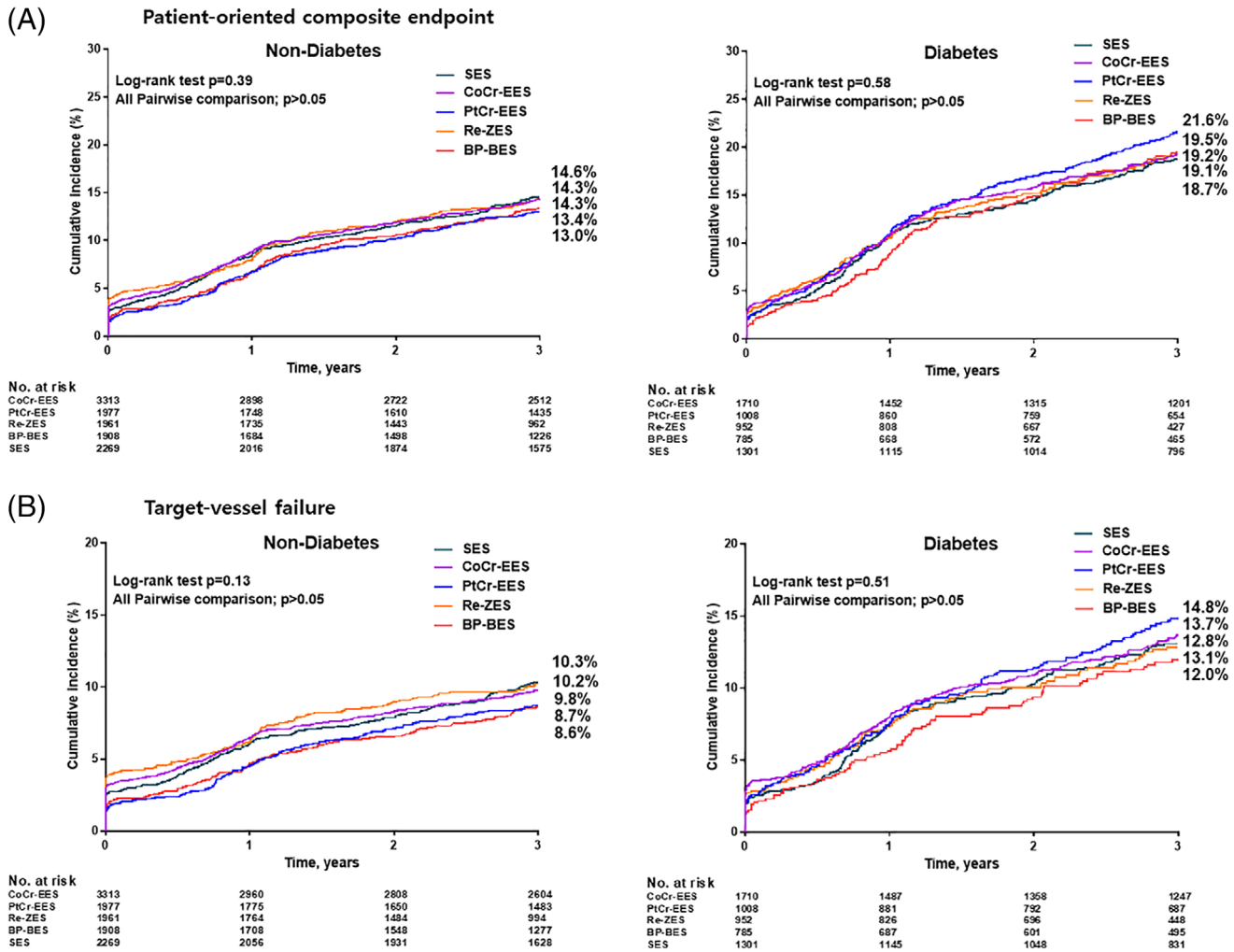

FIGURE 2 Cumulative 3-year incidence of patient-oriented composite endpoint and target-vessel failure according to the presence or absence of diabetes mellitus and types of drug-eluting stents. Kaplan–Meier curves are shown for patient-oriented composite endpoint (A) and target-vessel failure (B). *p* Values were calculated using the log-rank test. Patient-oriented composite endpoint was defined as the composite of all-cause death, any myocardial infarction, or any revascularization. Target-vessel failure was defined as death from cardiac causes, target-vessel myocardial infarction, or target-vessel revascularization. Abbreviations are as defined in Figure 1 [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Adjusted Hazard Ratios for Primary and Key Secondary Clinical Outcomes Between Different DESs Among Non-Diabetic and Diabetic Patients in Propensity-Score Analysis*

	Patients Without Diabetes Mellitus						Patients With Diabetes Mellitus					
Individual Comparison	**POCE†**	**Death**	**MI**	**RR**	**ST**	**TVF‡**	**POCE †**	**Death**	**MI**	**RR**	**ST**	**TVF‡**
CoCr-EES vs. SES	0.99 (0.85-1.15) P=0.91	0.79 (0.59-1.04) P=0.09	0.99 (0.74-1.32) P=0.94	1.00 (0.85-1.28) P=0.67	0.36 (0.07-1.91) P=0.23	1.00 (0.83-1.19) P=0.98	1.09 (0.91-1.30) P=0.36	1.19 (0.89-1.58) P=0.24	1.40 (0.96-2.05) P=0.08	0.92 (0.72-1.17) P=0.48		1.10 (0.89-1.36) P=0.39
PtCr-EES vs. SES	0.87 (0.73-1.03) P=0.11	0.87 (0.63-1.19) P=0.39	**0.65 (0.46-0.93) P=0.02**	0.94 (0.74-1.18) P=0.58	1.47 (0.40-5.35) P=0.56	0.86 (0.69-1.06) P=0.15	1.22 (1.00-1.49) P=0.05	1.31 (0.96-1.79) P=0.09	1.30 (0.83-2.02) P=0.25	1.08 (0.83-1.40) P=0.58		1.20 (0.94-1.52) P=0.14
Re-ZES vs. SES	1.01 (0.85-1.20) P=0.95	**0.70 (0.05-0.99) P=0.04**	1.18 (0.86-1.61) P=0.30	1.00 (0.79-1.27) P=0.99	0.94 (0.21-4.18) P=0.93	1.07 (0.87-1.31) P=0.54	1.03 (0.84-1.27) P=0.76	1.04 (0.74-1.48) P=0.80	1.18 (0.76-1.85) P=0.46	0.95 (0.72-1.26) P=0.73		1.00 (0.77-1.29) P=0.98
BP-BES vs. SES	1.03 (0.86-1.24) P=0.73	1.23 (0.87-1.73) P=0.24	1.12 (0.77-1.63) P=0.56	0.95 (0.75-1.21) P=0.70	4.54 (0.51-40.13) P=0.17	1.07 (0.85-1.33) P=0.58	0.97 (0.77-1.21) P=0.77	0.84 (0.59-1.19) P=0.32	1.27 (0.72-2.23) P=0.41	1.06 (0.78-1.43) P=0.72		1.10 (0.83-1.46) P=0.49
PtCr-EES vs. CoCr-EES	0.87 (0.75-1.02) P=0.10	1.10 (0.82-1.49) P=0.51	**0.66 (0.47-0.92) P=0.01**	0.90 (0.73-1.11) P=0.31	4.13 (0.80-21.3) P=0.09	0.86 (0.71-1.04) P=0.12	1.13 (0.94-1.35) P=0.20	1.10 (0.83-1.47) P=0.49	0.92 (0.62-1.37) P=0.70	1.17 (0.91-1.51) P=0.21		1.09 (0.88-1.36) P=0.44
Re-ZES vs. CoCr-EES	1.02 (0.87-1.19) P=0.85	0.89 (0.64-1.23) P=0.48	1.19 (0.90-1.58) P=0.23	0.96 (0.77-1.19) P=0.69	2.63 (0.43-16.02) P=0.29	1.07 (0.89-1.29) P=0.48	0.95 (0.78-1.16) P=0.62	0.88 (0.64-1.22) P=0.44	0.85 (0.57-1.25) P=0.40	1.04 (0.79-1.35) P=0.79		0.91 (0.71-1.15) P=0.42
BP-BES vs. CoCr-EES	0.98 (0.83-1.16) P=0.79	1.04 (0.75-1.43) P=0.83	0.90 (0.63-1.28) P=0.57	1.00 (0.81-1.25) P=0.97	0.62 (0.06-6.86) P=0.70	0.94 (0.76-1.16) P=0.57	0.95 (0.77-1.10) P=0.36	1.01 (0.73-1.39) P=0.96	**0.56 (0.33-0.95) P=0.03**	1.03 (0.77-1.38) P=0.84		0.82 (0.63-1.08) P=0.16
Re-ZES vs. PtCr-EES	1.16 (0.97-1.39) P=0.11	0.81 (0.56-1.15) 0.24	**1.80 (1.27-2.57) P=0.001**	1.07 (0.84-1.37) P=0.59	0.64 (0.15-2.76) P=0.55	**1.25 (1.00-1.55) P=0.048**	0.84 (0.68-1.05) P=0.12	0.80 (0.56-1.13) P=0.20	0.91 (0.58-1.44) P=0.70	0.88 (0.66-1.18) P=0.40		0.83 (0.64-1.08) P=0.17
BP-BES vs. PtCr-EES	1.12 (0.92-1.35) P=0.25	0.94 (0.66-1.34) P=0.73	1.37 (0.91-2.06) P=0.14	1.12 (0.87-1.44) P=0.37	0.15 (0.02-1.29) P=0.08	1.10 (0.86-1.39) P=0.45	0.85 (0.67-1.06) P=0.15	0.91 (0.64-1.29) P=0.61	0.61 (0.34-1.08) P=0.09	0.88 (0.64-1.20) P=0.42		0.76 (0.57-1.01) P=0.06
BP-BES vs. Re-ZES	0.96 (0.80-1.16) P=0.70	1.16 (0.80-1.70) P=0.43	0.76 (0.52-1.10) P=0.15	1.05 (0.82-1.35) P=0.71	0.24 (0.02-2.30) P=0.21	0.88 (0.70-1.11) P=0.28	1.00 (0.79-1.27) P=0.99	1.14 (0.78-1.68) P=0.49	0.67 (0.38-1.18) P=0.17	0.99 (0.72-1.38) P=0.96		0.91 (0.67-1.23) P=0.54

* Values are the hazard ratio (95% confidence interval). Statistically significant values are highlighted in bold.

† POCE was defined as a composite of all-cause death, any MI, or any revascularization.

‡ Target-vessel failure was defined as a composite of death from cardiac causes, target-vessel MI, or TVR.

§ Hazard ratios for ST were not available because of low event rates.

Abbreviations: BP-BES, biodegradable-polymer biolimus-eluting stent(s); CoCr-EES, cobalt-chromium everolimus-eluting stent(s); MI, myocardial infarction; PtCr-EES, platinum-chromium everolimus-eluting stent(s); Re-ZES, Resolute zotarolimus-eluting stent(s); RR, repeat revascularization (any revascularization); SES, sirolimus-eluting stent(s); ST stent thrombosis.

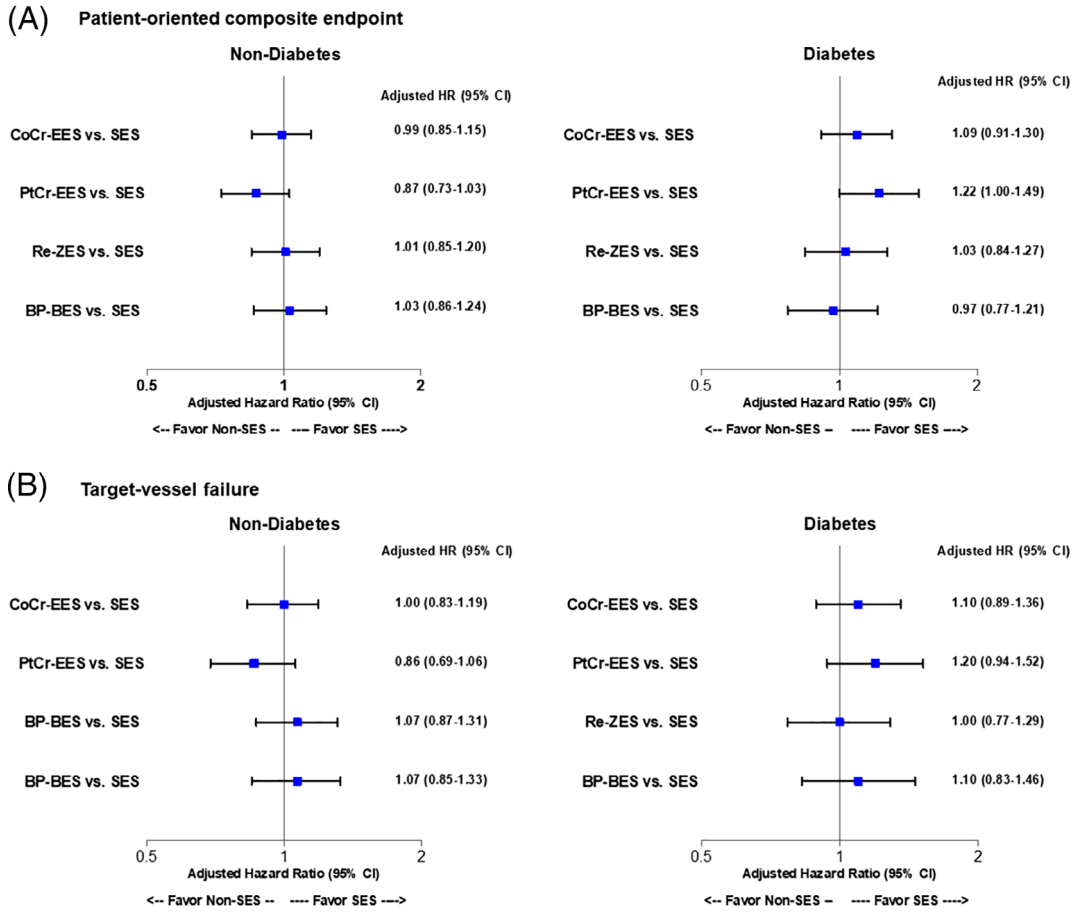

FIGURE 3 Propensity score-adjusted hazard ratio for patient-oriented composite endpoint and target-vessel failure in nondiabetic and in diabetic patients according to different types of drug-eluting stents. Adjusted hazard ratios are shown for comparison of different types of DES with CoCr-EES as the reference device (A, patient-oriented composite endpoint; B, target-vessel failure). Patient-oriented composite endpoint was defined as a composite of all-cause death, any myocardial infarction, or any revascularization. Target-vessel failure was defined as death from cardiac causes, target-vessel myocardial infarction, or target-vessel revascularization. CI, confidence interval; HR, hazard ratio; other abbreviations are as defined in Figure 1 [Color figure can be viewed at wileyonlinelibrary.com]

3.3 | Influence of insulin treatment

Of the 5,756 patients in our current study series with diabetes mellitus at baseline, 809 (14.1%) were treated with insulin. Regardless of any types of first-generation SES or contemporary DES, a significant gradient was consistently present as for the 3-year primary and secondary clinical outcomes, that is, the 3-year rates of most adverse events were highest in the insulin-treated diabetic patients, intermediate in the non–insulin-treated diabetic patients, and lowest in the nondiabetic patients (Figure 4).

3.4 | Time-trend analysis

We divided the study patients into two different time periods (Period 1, 2007–2010; Period 2, 2011–2015). The incidence of diabetic mellitus was slightly higher in the Period 1 (34.4% vs. 32.7%). Considerable differences in both the clinical and lesion or procedural characteristics were noted between two groups (Tables S9 and S10). The rates of POCE and target-vessel failure did not statistically differ between two time periods (16.0 vs. 15.6%; p = .59, 10.9 vs. 10.8%; p = .92, respectively) (Figure S3).

4 | DISCUSSION

The major findings of the present study providing a pairwise comparison of the long-term effectiveness and safety of contemporary DES stratified by the presence or absence of diabetes mellitus, are that the 3-year rates of POCE were similar among different types of contemporary DES regardless the diabetic status. We did not therefore identify any differential impact of diabetes mellitus on the relative clinical outcomes of several types of contemporary DES. However, PCI with contemporary DES was consistently found to be associated with a linear gradient of higher risk of adverse events in accordance with diabetic status (i.e., nondiabetic vs. non–insulin-treated diabetic vs. insulin-treated diabetic).

Among the first generation DESs, SES showed an advantage over PES for stent thrombosis and longer event-free follow-up. When these results were followed to 5 years, the early advantage

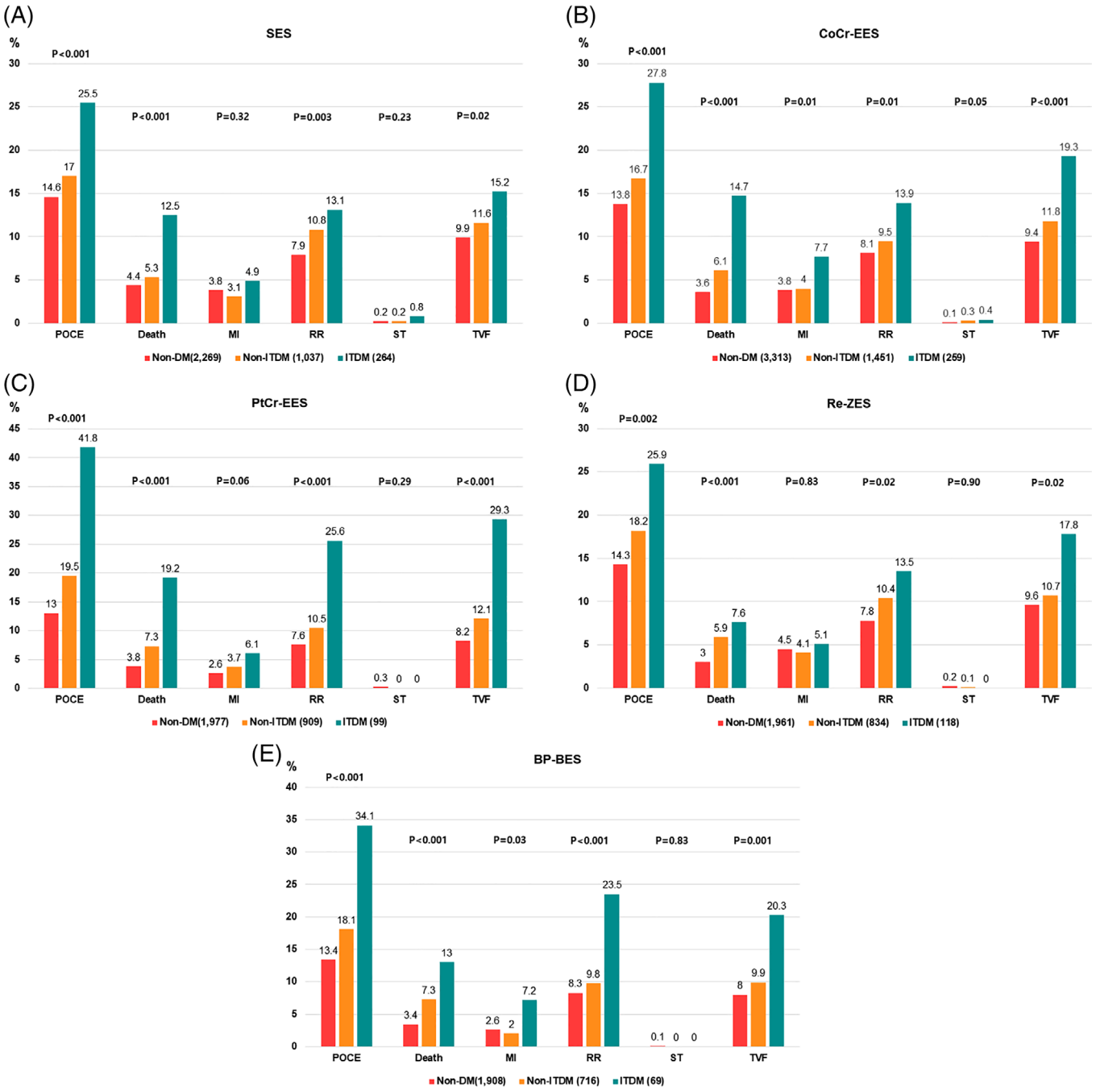

FIGURE 4 Three-year rates of adverse events according to diabetic status (nondiabetic vs. non–insulin-treated diabetic vs. insulin-treated diabetic) in each stent group [Color figure can be viewed at wileyonlinelibrary.com]

of SES was lost in the general population, but SES remained advantageous for diabetic patients.[13] Of note, a previous pooled analysis of four clinical trials suggested differential clinical response to EES versus PES in patients with and without diabetes, in which the use of EES resulted in significant reductions of adverse events in nondiabetic patients, but no different treatment effects in diabetic patients.[5] By contrast, a study from Swedish Coronary Angiography and Angioplasty Registry reported that EES was consistently associated with improved outcomes compared with first-generation SES and PES in diabetic patients.[14] Subsequently, the Taxus Element versus Xience Prime in a Diabetic Population (TUXEDO) trial demonstrated that EES was superior to PES with regard to several end points, including target-vessel failure, MI, and stent thrombosis.[6] On the other hand, a recent meta-analysis demonstrated that ZES was associated with significantly higher rates of TLR with numerically higher rates of stent thrombosis compared to first-generation DESs in diabetics.[15] Thus, the selection of a specific type of DES in patients with diabetes remains a controversial issue for the contemporary PCI practice with several second-generation DES.

Our large-scale study using stent-specific, clinical registries to determine the long-term relative effectiveness and safety of diverse types of current-generation DES in patients with or without diabetes can provide considerable evidence as for whether differential clinical response of different DES according to the diabetic status exists. Our present analysis indicated no significant between-stent group differences with respect to POCE and target-vessel failure as a device-related outcome. These findings are similar to those of previous analyses of clinical trials or observation studies[16–18] or different in some extent.[19] Beyond these previous findings, the various treatment comparisons made in our present study might contribute substantially to the understanding of real-life clinical situations and may help for the choice of DES in diabetics in the contemporary practice setting. Especially, due to the inherent nature of prospective observational registry, we used propensity score methods to reduce the impact of treatment selection bias or potential confounding variable.

In the present study, no significant differences in composite primary or secondary outcomes were observed between SES and contemporary DES, which was in line with the previous investigations.[20] Of note, even though extremely low stent thrombosis in our population was demonstrated, on pairwise comparison with Kaplan–Meier estimates, the use of SES was associated with a higher incidence of stent thrombosis than contemporary DES in non-diabetics. This finding might support the improved safety of second-generation DES compared with first-generation SES.[21] On the other hand, the relatively low incidence of stent thrombosis in this series, compared with the previous studies, might be partly explained by differences in clinical or lesions characterizes, the particulars of PCI procedure (i.e., more frequent use of intravascular ultrasound), and the use of second-generation DES.[21,22] Furthermore, ethnic disparity might contribute to the relatively low incidence of stent thrombosis. Data exist suggesting interethnic differences in thrombogenicity and accordingly, East Asians appear to have the lower level of thrombogenicity and integrated hypercoagulability compared with Western population.[23] In addition, there are marked interethnic differences in the pharmacokinetics and pharmacodynamics of P2Y12 receptor blockers revealing more potent inhibition of platelet function in East Asians.[24]

In our study, a risk-gradient was found to consistently associate with diabetes severity so that the 3-year rates of adverse events were greatest among insulin-treated diabetic patients, intermediate in non–insulin-treated diabetic patients, and lowest in nondiabetic patients. These findings are in line with data reported in previous studies indicating that insulin treatment was associated with an increased risk of cardiovascular events, compared with the non-insulin treatment in diabetic patients.[5,25] In addition, it has been suggested that the overall results in studies of diabetic patients strongly are influenced by the percentage of insulin-dependent patients examined.[26] By contrast, subgroup analysis from the TUXEDO Trial has suggested that patients with insulin-treated diabetes had a significantly increased unadjusted risk of cardiovascular events, but that this association was largely attenuated after a propensity-score adjustment.[27] The authors of that analysis suggested that the increased possibility of adverse cardiovascular events in patients with insulin-treated diabetes could be accounted for by differences in comorbidities, diabetes duration, and diabetes control rather than by direct atherogenic or thrombogenic effects of insulin.[27]

For diabetic patients, the Cre8 stent, a polymer-free amphilimus-eluting stent (AES), has demonstrated promising preliminary results. The Cre8 stent is characterized by a permanent biocompatible i-Carbofilm strut coating and abluminal reservoirs, loaded with a polymer-free sirolimus formulation (amphilimus), in order to obtain a more efficient targeted elution toward the vessel wall.[28] In a study comparing AES with CoCr-EES, in patients with diabetes, 1-year TLR was 2.5% in the Cre8 group versus 14.6% in the EES group (p = .056), showing trends of superior efficacy of the Cre8 stent.[29] In addition, a study with AES compared with BP-BES in diabetics, target-lesion failure (5 vs. 13%, p = .002) and TLR (4 vs. 9%, p = .019) were significantly lower in AES.[30] These findings suggest that the Cre8 stent can be a useful option in PCI in this challenging population. Further researches are ongoing to confirm these encouraging results.[28]

Several limitations deserve to comment. First, as this study is observational in nature, the overall findings should be considered hypothetical and hypothesis-generating only. Second, the choice of the specific stent in our registries was not randomized and thus subject to selection bias. Although we used propensity analysis to enable an even more rigorous adjustment for differences in baseline characteristics, the estimates of relative treatment effects can still be biased due to unknown measured confounders. Third, PES (TAXUS stent) has been at the center of controversy regarding the clinical response in patients with or without diabetes but is not included in the IRIS–DES registry. In, addition, we could not evaluate other newer DES such as AES or second-generation SES in this series. Fourth, the study enrollment period was relatively long and different between stent groups, which might be a source of bias. However, when dividing the population into two time period groups, the rates of POCE and target-vessel failure did not differ, hence, the different enrollment period between stent groups did not likely affect the overall study results. Finally, owing to the limited number of hard clinical endpoints, our study was underpowered to detect significant differences in serious safety outcomes such as stent thrombosis or mortality.

5 | CONCLUSIONS

In this contemporary clinical-practice registry study involving PCI with current-generation DES, the 3-year rates of POCE were similar for different types of contemporary DES, regardless of the presence or absence of diabetes mellitus. This suggests that there is no differential clinical response between different contemporary high-performance metallic DES in diabetic and nondiabetic patients. These observational findings warrant further investigation and should be confirmed or refuted through large-scale, clinical trials with a longer-term follow-up.

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CONFLICT OF INTEREST

None.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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