Comparison of Contemporary Drug-Eluting Stents in Patients Undergoing Complex High-Risk Indicated Procedures

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ABSTRACT

BACKGROUND Limited data are available on the relative performances of diverse contemporary drug-eluting stents (DES) in patients undergoing complex high-risk indicated procedures (CHIP).

OBJECTIVES The purpose of this study was to evaluate the comparative effectiveness of contemporary second-generation DES for CHIP patients in "real-world" settings.

METHODS Of 28,843 patients enrolled in the IRIS-DES registry, a total of 6,645 patients with CHIP characteristics who received 5 different types of contemporary DES were finally included: 3,752 with cobalt-chromium everolimus-eluting stents (CoCr-EES), 1,258 with Resolute zotarolimus-eluting stents (Re-ZES), 864 with platinum-chromium EES (PtCr-EES), 437 with ultrathin strut biodegradable-polymer sirolimus-eluting stents (UT-SES), and 334 with bioresorbable polymer SES (BP-SES). The primary outcome was target-vessel failure (a composite of cardiac death, target-vessel myocardial infarction, and target-vessel revascularization) at 12 months.

RESULTS At 12 months, the rate of target-vessel failure was highest in the CoCr-EES (7.1%) group; intermediate in the Re-ZES (5.0%), PtCr-EES (4.6%), and BP-SES (4.2%) groups; and lowest in the UT-SES (3.8%) group (overall long-rank P = 0.001). In multiple-treatment propensity-score analysis, the adjusted hazard ratios (HRs) for target-vessel failure were significantly lower in the Re-ZES (HR: 0.71; 95% confidence interval [CI]: 0.52-0.97), the UT-SES (HR: 0.52; 95% CI: 0.29-0.95), and BP-SES (HR: 0.33; 95% CI: 0.16-0.70) groups than in the CoCr-EES group (referent).

CONCLUSIONS In this contemporary PCI registry, we observed the differential risks of target-vessel failure according to various types of contemporary DES in patients with CHIP characteristics. However, owing to inherent selection bias, the results should be considered hypothesis-generating, highlighting the need for further randomized trials. (Evaluation of the First, Second, and New Drug-Eluting Stents in Routine Clinical Practice [IRIS-DES]; NCT01186133) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
 Percutaneous coronary intervention (PCI) for the treatment of obstructive coronary artery disease (CAD) is one of the most commonly performed cardiovascular procedures. Over the past 2 decades, PCI with stenting has made many advances. In particular, drug-eluting stents (DES) have shown greater efficacy than bare-metal stents (1,2) and DES are now widely used in a broader range of patients, including higher-risk clinical comorbidity and greater anatomic complexity. In addition, the technology and engineering of DES have substantially improved and newer-generation DES have included various types of antiproliferative drugs with improved drug release kinetics, novel stent materials, thin strut platforms, and biocompatible or biodegradable polymers (3,4).

In the contemporary PCI practice, the number of patients with severe CAD requiring revascularization but who are at high procedural risk owing to patient comorbidities, complexity of coronary anatomy, and/or poor hemodynamics, has been substantially increased. Therefore, the proportions of patients requiring complex high-risk indicated procedures (CHIP) are rapidly growing (5,6). Until recently, the optimal management for these high-risk patients was still lacking and also limited data were available on the relative performances of newer-generation, contemporary DES for CHIP interventions. The present study therefore compared the effectiveness and safety profiles of several contemporary DES for patients with CHIP characteristics using data from a real-world clinical-practice PCI registry.

METHODS

STUDY POPULATION. The study population was derived from the IRIS-DES (Interventional Cardiology Research In-Cooperation Society-Drug-Eluting Stents) registry. The design of the IRIS-DES registry and the associated ongoing analyses have been described (7-11). In brief, the IRIS-DES study involved prospective, multicenter recruitment of unrestricted patients undergoing PCI with DES in Korea and consisted of several arms of first- and second-generation DES in a real-world setting. In this registry, the exclusion criteria were minimal: patients were excluded if they had cardiogenic shock, had been diagnosed with a malignancy or other comorbid condition and had a life expectancy <12 months, were treated with a combination of different DES types, had active bleeding contraindicating treatment with dual-antiplatelet therapy, or had undergone or were scheduled to undergo planned surgery necessitating the interruption of antiplatelet drugs within 6 months after PCI.

The target population of the present study included consecutive patients with CHIP characteristics who underwent PCI with contemporary DES. Based on prior literature (5,12,13), patients with CHIP characteristics were selected in whom both clinical and angiographic criteria had been met (Supplemental Figure 1): 1) clinical criteria of CHIP were 1 of the following characteristics: multiple comorbidities (ie, age >75 years, diabetes mellitus, chronic renal disease, previous bypass surgery, history of cerebrovascular disease, peripheral artery disease, or chronic lung disease, ST-segment elevation myocardial infarction (MI) requiring primary PCI, poor ventricular function/hemodynamic instability (ie, severe left ventricular dysfunction, defined as ejection fraction <30% or clinical presentation with cardiogenic shock); and 2) angiographic criteria of CHIP were any of the following characteristics: complex coronary lesions (ie, unprotected left main disease, multivessel disease, severely calcified lesions, very diffuse long lesions [total stent length >40 mm], bifurcation lesions, or chronic total occlusion). In our study, CHIP patients should have at least 1 clinical criterion as well as at least 1 angiographic criterion.

The current analysis included patients implanted with 5 different types of newer-generation, contemporary DES: cobalt-chromium durable polymer everolimus-eluting stents (CoCr-EES) (Xience Prime, Xpedition or Alpine, Abbott Vascular), durable polymer Resolute-zotarolimus-eluting stents (Re-ZES) (Resolute Onyx, Medtronic Inc.), ultrathin strut biodegradable-polymer platinum-chromium EES (PtCr-EES) (Synergy, Boston Scientific), ultrathin strut biodegradable-polymer cobalt-chromium sirolimus-eluting stents (UT-SES) (Orsiro, Biotronik), and biodegradable polymer sirolimus-eluting stents (BP-SES) (Ultimaster, Terumo Corporation).

The study registry was supported by the Cardiovascular Research Foundation, Seoul, Korea, and there was no industry involvement in the design or conduct of this study, the analysis of results, or the decision to publish the study. The ethics committee of each participating center approved the study protocol (institutional review board no. 2014-0154), and all patients provided written informed consent.

PCI PROCEDURES AND CLINICAL FOLLOW-UP. All PCI procedures involved the use of standard interventional techniques according to local practice.
The registry did not specify stent types according to clinical or anatomic characteristics and thus the choice of specific DES type was at the discretion of each operator. The study protocol specified, however, that the type of stent implanted into the target lesion also be implanted into other nontarget lesions. Periprocedural anticoagulants were administered according to standard regimens. Administration of glycoprotein IIb/IIIa inhibitors was at the discretion of the treating physicians. All patients undergoing PCI received a loading dose of aspirin (200-300 mg) and P2Y12 receptor inhibitor (clopidogrel [300-600 mg], prasugrel [180 mg], or ticagrelor [60 mg]) before or during the procedure if they did not receive chronic therapy. Aspirin was continued indefinitely, and P2Y12 receptor inhibitors were administered for at least 12 months, regardless of DES type. Drugs for secondary prevention were prescribed according to current guidelines. Patients were clinically followed-up during hospitalization and at 30 days, 6 and 12 months, and every 6 months thereafter. At these visits, data pertaining to patients’ clinical status, interventions, and outcome events were recorded. All baseline and subsequent clinical and angiographic characteristics were collected using dedicated, electronic case report forms by specialized personnel at each participating center. This Internet-based system provided each center with immediate and continuous feedback on the processes and quality-of-care measurements. Registry data at the participating hospitals were periodically monitored and verified by members of the academic coordinating center (Clinical Research Center, Asan Medical Center, Seoul, Korea) (7,10).

**STUDY OUTCOMES AND DEFINITIONS.** The primary outcome of the study was target-vessel failure, defined as a composite of cardiac death, target-vessel MI, or clinically driven target-vessel revascularization (TVR). Secondary outcomes included individual components of the primary outcome; death from any cause; any revascularization; stent thrombosis; and major adverse cardiac events (MACE), a composite of all-cause death, any MI, or any revascularization. Death was considered cardiac unless an unequivocal noncardiac cause could be established. In our registry, routine measurements of cardiac enzyme were performed in all patients. The diagnosis of MI was based on the Society for Cardiovascular Angiography and Interventions definition of clinically relevant MI (14). In brief, MI was defined as follows: 1) within 72 hours after PCI, an increase of creatine kinase-myocardial band (CK-MB) >10× upper reference limit (URL) or CK-MB >5× URL with new pathological Q waves or new bundle-branch block, or documented new graft or new coronary occlusion on angiography, or a new or worsening regional wall motion abnormality or loss of viable myocardium on imaging studies; 2) if occurring after 48 hours following the index revascularization, any increase in the CK-MB above the upper limit of normal with symptoms or signs suggestive of ischemia. Repeat revascularization included any type of percutaneous or surgical revascularization procedures regardless of TVR or non-TVR. Stent thrombosis (definite or probable) was defined according to the Academic Research Consortium criteria (15). 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 to the study devices.

**STATISTICAL ANALYSIS.** Baseline characteristics, including patient demographics, risk factors and comorbidities, clinical presentation, cardiac status, and anatomic and procedural features, were described according to each specific type of DES. Categorical variables are presented as numbers (percentages), with differences among treatment groups analyzed by chi-square or Fisher’s exact tests, as appropriate. Continuous variables are presented as mean ± SD, with differences among treatment groups evaluated by analysis of variance. Cumulative outcomes were assessed by the Kaplan-Meier method and compared by log-rank tests. To minimize confounding and residual selection bias in comparing observational treatments, a propensity-score weighting method was used to control for imbalances in baseline characteristics among patients treated with 5 different DES types. Multiple-treatment propensity scores were determined using the Toolkit for Weighting and Analysis of Nonequivalent Groups (TWANG) method, and the corresponding inverse probabilities of treatment weight (the reciprocals of the propensity scores) were estimated using generalized boosted models through an iterative estimation procedure (n = 3,000) based on clinically relevant baseline characteristics (11,16). Evaluation of the balance of the pretreatment covariates showed significant improvements at baseline after weighting, with a standardized effect size <0.10 for any covariate indicating a relatively small imbalance (17,18). In the multiple-treatment propensity-score weighted cohort, we compared outcomes using the weighted log-rank test and plotted weighted survival functions. We estimated the hazard ratio for each outcome with weighted Cox proportional hazards models.
Two-sided $P$ values of < 0.05 were considered to indicate statistical significance, and all reported $P$ values were provided without multiplicity adjustment. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc.) and R software version 3.6.0 with TWANG package.

RESULTS

STUDY POPULATION AND BASELINE CHARACTERISTICS. A flow diagram of the study is shown in Figure 1. Of the 28,843 patients enrolled in the IRIS-DES registry, a total of 6,645 (23.0%) patients who had both clinical and angiographical CHIP criteria and were treated with newer-generation contemporary DES between February 2014 and December 2018 were finally included in the current analysis. Among them, 3,752 (56.5%) were implanted with CoCr-EES, 1,258 (18.9%) with Re-ZES, 864 (13.0%) with PtCr-EES, 437 (6.6%) with UT-SES, and 334 (5.0%) with BP-SES. The proportions of patients with each number of CHIP characteristics according to the type of stents are shown in Supplemental Figure 2.

The baseline clinical and anatomic characteristics of the study population according to the different DES types are shown in Table 1. Significant between-group differences were observed for patient age and several key clinical factors, including the proportions of insulin-dependent diabetes, hypertension, dyslipidemia, smoking, previous PCI or bypass surgery, peripheral vascular disease, chronic renal disease, and clinical indications for PCI. With regard to anatomic characteristics, significant between-group differences were also observed in a proportion of diffuse long lesions, bifurcation lesion, and chronic total occlusion. After adjustment of multiple-treatment propensity score, the standardized effect size was < 0.10 for most of the baseline clinical and anatomic characteristics, indicating only small differences between the multiple groups (Supplemental Table 1).

CLINICAL OUTCOMES. Differential rates of clinical outcomes according to the number of CHIP components are shown in Supplemental Figure 3. With increasing component of clinical or angiographic CHIP criteria, the rates of target-vessel failure and MACE proportionally increased during 12 months of follow-up. Unadjusted (observed) analyses of the primary composite of target-vessel failure and its components at 12 months, are shown in Table 2 and Figure 2, respectively. At 12 months, the observed incidences of target-vessel failure were highest in the Co-Cr-EES group (7.1%) and lowest in the UT-SES group (3.8%), being intermediate in the Re-ZES
Comparison of Several DES for CHIP Patients

TABLE 1 Baseline Characteristics of Groups of Patients Implanted With the 5 Types of DES

| CoCr-EES (n = 3,752) | Re-ZES (n = 1,258) | PtCr-EES (n = 864) | UT-SES (n = 437) | BP-SES (n = 334) | P Value |
|---------------------|-------------------|-------------------|------------------|-----------------|---------|
| Age (y)             |                   |                   |                  |                 |         |
| 68.7 ± 11.5         | 69.7 ± 12.3       | 71.0 ± 11.5       | 68.2 ± 12.3      | 71.3 ± 11.2     | 0.001   |
| Age >75 y           | 928 (24.7)        | 384 (30.5)        | 288 (33.3)       | 118 (27.0)      | 119 (35.5) | 0.001 |
| Male                | 2,605 (69.4)      | 886 (70.4)        | 592 (68.5)       | 309 (70.7)      | 233 (69.8) | 0.88  |
| Body mass index (kg/m²) | 24.5 ± 3.3       | 24.7 ± 3.3        | 24.6 ± 3.4       | 24.6 ± 3.4      | 24.8 ± 3.9 | 0.61  |
| Diabetes mellitus   |                   |                   |                  |                 |         |
| Any                 | 2,243 (59.8)      | 727 (57.8)        | 481 (55.7)       | 238 (54.5)      | 195 (58.4) | 0.07  |
| Requiring insulin   | 297 (7.9)         | 84 (6.7)          | 56 (6.5)         | 19 (4.3)        | 11 (3.3)  | 0.002 |
| Hypertension        | 2,611 (71.2)      | 222 (17.6)        | 222 (17.6)       | 222 (17.6)      | 222 (17.6) | 0.001 |
| Chronic renal disease | 301 (8.0)       | 99 (7.9)          | 79 (9.1)         | 37 (8.5)        | 10 (3.0)  | 0.01  |
| Previous bypass surgery | 143 (3.8)     | 25 (2.0)          | 15 (1.7)         | 15 (3.4)        | 12 (3.6)  | 0.002 |
| Chronic renal disease | 301 (8.0)       | 99 (7.9)          | 79 (9.1)         | 37 (8.5)        | 10 (3.0)  | 0.01  |
| End-stage renal disease | 120 (3.2)      | 46 (3.7)          | 46 (5.3)         | 15 (3.4)        | 6 (1.8)   | 0.01  |
| Previous cerebrovascular disease | 464 (12.4) | 141 (11.2)       | 88 (10.2)        | 46 (10.5)       | 35 (10.5) | 0.30  |
| Peripheral artery disease | 121 (3.2)   | 30 (2.4)          | 33 (3.8)         | 10 (2.3)        | 7 (2.1)   | 0.21  |
| Chronic lung disease | 131 (3.5)        | 50 (4.0)          | 26 (3.0)         | 13 (3.0)        | 8 (2.4)   | 0.56  |
| Ejection fraction (%) | 55.8 ± 11.6     | 55.2 ± 11.4       | 55.8 ± 10.7      | 55.6 ± 12.3     | 56.0 ± 11.0 | 0.54 |
| Ejection fraction <30% | 145 (3.9)       | 42 (3.3)          | 26 (3.0)         | 16 (3.7)        | 11 (3.3)  | 0.74  |

Clinical indication for PCI

| Stable angina or silent ischemia | 1,549 (41.3) | 483 (38.4) | 295 (34.1) | 170 (38.9) | 150 (44.9) | 0.001 |
| NSTE-ACS                        | 1,337 (35.6) | 493 (39.2) | 351 (40.6) | 146 (33.4) | 119 (35.6) | 0.001 |
|STEMI                           | 866 (23.1)   | 282 (22.4) | 218 (25.2) | 121 (27.7) | 65 (19.5)  | 0.06  |
|De novo lesion                  | 3,580 (95.4) | 1194 (94.9) | 828 (95.8) | 426 (97.5) | 319 (95.5) | 0.26  |
|Left main disease               | 407 (10.8)   | 143 (11.4) | 94 (10.9)  | 50 (11.4)  | 31 (9.3)   | 0.86  |
|Multivessel disease             | 2,741 (73.1) | 906 (72.0) | 629 (72.8) | 306 (70.0) | 243 (72.8) | 0.72  |
|Severe calcification            | 280 (7.5)    | 98 (7.8)   | 69 (8.0)   | 37 (8.5)   | 31 (9.3)   | 0.75  |
|Diffuse long lesion (stent length >40 mm) | 985 (26.3) | 258 (20.5) | 178 (20.6) | 49 (11.2)  | 60 (18.0)  | 0.001 |
|Bifurcation lesion              | 1,295 (34.5) | 372 (29.6) | 171 (19.8) | 146 (33.4) | 108 (32.3) | 0.001 |
|Chronic total occlusion         | 1,234 (32.9) | 482 (38.3) | 342 (39.6) | 172 (39.4) | 109 (32.6) | 0.001 |

Procedural characteristics

| Total number of stents per patient | 1.89 ± 1.04 | 1.77 ± 0.98 | 1.81 ± 0.98 | 1.62 ± 0.92 | 1.71 ± 0.94 | 0.001 |
|Total stent length per patient (mm) | 35.47 ± 19.44 | 33.65 ± 18.38 | 33.53 ± 18.01 | 28.46 ± 14.36 | 33.65 ± 17.60 | 0.001 |
|Averaged stent diameter per patient (mm) | 3.17 ± 0.42 | 3.14 ± 0.47 | 3.14 ± 0.46 | 3.09 ± 0.44 | 3.13 ± 0.45 | 0.001 |

Values are mean ± SD or n (%).

BP-SES = biodegradable-polymer, sirolimus-eluting stent (Ultimaster stent); CABG = coronary artery bypass graft; CAD = coronary artery disease; CoCr-EES = cobalt-chromium everolimus-eluting stent (Xience stent); DES = drug-eluting stent; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; PtCr-EES = platinum-chromium everolimus-eluting stent (Synergy stent); Re-ZES = Resolute zotarolimus-eluting stent (Resolute Onyx stent); STEMI = ST-segment elevation myocardial infarction; UT-SES = ultrathin, bioresorbable polymer sirolimus-eluting stents (Orsiro stent).

(5.0%), PtCr-EES (4.6%), and BP-SES (4.2%) groups (overall log-rank P = 0.001). Analysis using the alternative definition of target-vessel failure, which excluded periprocedural enzymatic MI without documented ischemia, yielded less significant between-group differences (Table 2). Also, in a sensitivity analysis of target-vessel failure only including nonprocedural MI, the overall rates of target-vessel failure were not significantly different (overall log-rank P = 0.08) (Supplemental Figure 4).

The adjusted risks and incidence curves for target-vessel failure and its components after application of multiple-treatment propensity-score weighting are shown in Table 2 and Figure 3, respectively. Compared with the CoCr-EES as a referent group, the adjusted hazard ratios (HRs) for target-vessel failure were lower in the Re-ZES (HR: 0.71; 95% CI: 0.52-0.97), the UT-SES (HR: 0.52; 95% CI: 0.29-0.95), and the BP-SES (HR: 0.33; 95% CI: 0.16-0.70) groups (Figure 4A). When we performed a sensitivity analysis for target-vessel failure only including nonprocedural MI, the overall differences of target-vessel failure according to different DES are shown in Supplemental Figure 5. The adjusted risks for alternatively defined target-vessel failure, which excluded periprocedural enzymatic MI without documented ischemia, was lower in the Re-ZES group (HR: 0.65; 95% CI: 0.43-0.97), and the BP-SES group (HR: 0.41; 95% CI: 0.17-0.98) as...
compared with the referent CoCr-EES group (Figure 4B). All pairwise unadjusted and adjusted comparisons of each DES with regard to target-vessel failure and its components are shown in Supplemental Table 2.

Unadjusted and adjusted analyses of key secondary outcomes are summarized in Supplemental Table 3 and Supplemental Figures 6 and 7. The adjusted risks for all-cause mortality were not significantly different among different DES groups. The observed rates of stent thrombosis were substantially low in each group of different DES. The adjusted risks for MACE, including any death, any MI, and any revascularization, were significantly lower in the Re-ZES, the PtCr-EES, and the BP-SES groups than in the referent CoCr-EES group.

**DISCUSSION**

In a contemporary clinical-practice PCI registry study, we found that the incidences of primary composite outcome of target-vessel failure at 12 months differed significantly according to various types of contemporary DES in patients undergoing PCI for CHIP characteristics (Central Illustration). However, owing to considerable selection bias and inherent limitations of observational studies, current findings should be considered hypothesis-generating, which should be confirmed or refuted through large-sized randomized trials.

Elderly patients, patients with multiple comorbidities (eg, end-stage renal disease, uncontrolled diabetes, peripheral artery disease, or prior stroke), and
hemodynamic unstable patients are usually at substantially higher risks of adverse cardiovascular events and mortality regardless of PCI success (19). In addition, PCI for complex CAD (eg, left main disease, true bifurcation lesion, multivessel disease, heavily calcified lesion, or chronic total occlusion) is associated with an increased incidence of procedure-related complications, leading to periprocedural MI, bleeding, arrhythmia, and decompensated heart failure. For such higher-risk PCI patients, there are still unanswered questions with regard to the relative effectiveness and safety of different contemporary DES in the real-world PCI settings. Over the past 15 years, DES have undergone significant refinement, becoming thinner, more deliverable, and more biocompatible, with the combination of these factors reducing local inflammatory reactions, arterial injury, and thrombogenicity. Although several clinical trials and registries have compared the efficacy and safety of first- and second-generation DES and of different types of newer-generation DES (4,11,20-22), comparative effectiveness research for optimal contemporary DES in CHIP patients is lacking. Therefore, the present findings provide valuable clinical insights on comparative effectiveness of diverse contemporary DES for patients with CHIP characteristics.

In this clinical-practice registry involving unrestricted use of diverse contemporary DES in the real-world setting, we detect differential risks of target-vessel failure among various types of DES in pairwise comparisons. Similar to previous randomized trials of the BIOFLOW V (Safety and Effectiveness of the Orsiro Sirolimus-Eluting Coronary Stent System in Subjects With Coronary Artery Lesions) and BIOSTEMI (A Comparison of an Ultrathin Strut Biodegradable Polymer Sirolimus-Eluting Stent With a Durable Polymer Everolimus-Eluting Stent for Patients With Acute ST-Segment Elevation Myocardial...
Infarction Undergoing Primary Percutaneous Coronary Intervention (20,23), our study found that the rate of target-vessel failure at 1 year was significantly lower in the UT-SES than in the CoCr-EES group, with this difference mainly driven by the difference in periprocedural MI rate. A recent meta-analysis also demonstrated that newer-generation ultrathin strut DES were associated with a lower 1-year rate of target-lesion failure, driven by a lower MI, than contemporary thicker strut second-generation DES (24). Recently, long-term (5-year) report of the BIOSCIENCE trial showed that all-cause mortality was significantly higher in patients treated with UT-SES than in those treated with CoCr-EES (25), which also should be confirmed or refuted through the extended follow-up of this prospective registry as well as other clinical trials. Interestingly, in our study, Re-ZES showed less incidence of cardiac death as compared with CoCr-EES after propensity-score adjustment. Given that there were no significant differences in mortality and target-vessel failure between Re-ZES and CoCr-EES in a previous “all-comer” randomized trial (26), it requires further investigations to determine whether the related findings in the CHIP population may be due to chance. In pairwise comparison of UT-SES and Re-ZES, similar to the results of the BIONYX (Bioresorbable Polymer ORSIRO Versus Durable Polymer RESOLUTE ONYX Stents) and BIORESORT (Comparison of 3 biodegradable polymer and durable polymer-based drug-eluting stents in all-comers) trials (27,28), use of UT-SES was associated with a similar risk of target-vessel failure compared with Re-ZES.

In the present study, as compared with CoCr-EES, BP-SES showed a significantly lower risk of target-vessel failure, mainly driven by a lower incidence of periprocedural MI. The BP-SES is a thin strut, cobalt-chromium, biodegradable-polymer, abluminal-coated sirolimus-eluting stent with an open-cell 2-link design and uniform architecture for optimal

**FIGURE 3** Adjusted Kaplan-Meier Curves for Primary Clinical Outcome and Its Component

(A) Primary composite of target-vessel failure, (B) cardiac death, (C) target-vessel-related MI, and (D) clinically driven target-vessel revascularization. Target-vessel failure was a composite of cardiac death, target-vessel MI, or clinically driven target-vessel revascularization. Abbreviations as in Figure 2.
In addition, thin biocompatible, bioresorbable gradient coating was intended to reduce polymer cracking and delamination on the hinges of the stent. However, comparative data on BP-SES as compared with other contemporary DES are still limited. It warrants further observation in an ongoing large-sized clinical trial (eg, the MASTER-DAPT [Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Standard DAPT Regimen] trial) (31).

In our study, it is hard to fully explain why the differences in clinical outcomes after several DES were opposed to previous reports (3-5,10). Although we observed the superiority of Re-ZES, UT-SES, and BP-SES over CoCr-EES in unadjusted and adjusted analyses, we are still doubtful that the true treatment differences among different DES could not be achieved through the current forms of observational studies. There would be many factors affecting these differences and also the heterogeneity of CHIP definition might play important role on observed differences. Therefore, the current findings might be affected greatly by important selection bias, which could not be sufficiently corrected by the propensity-score matching. In this clinical context, the differences in primary clinical outcome in favor of other contemporary DES over CoCr-EES in our study warrant further investigation and should be confirmed or refuted through large, randomized clinical trials.

In our study, the incidence of stent thrombosis was extremely low in the overall population. Although we did not fully explain this phenomenon, as compared with the Western population, a relatively low rate of stent thrombosis might be explained in part by differences in clinical or lesion characteristics, interventional practice (eg, a higher use of intravascular ultrasound), or race or ethnic groups (eg, East-Asian paradox for differential ischemic and bleeding tendency), as previously noted (7,32,33).

There are several limitations in our study. First, this was an observational registry; thus, overall findings should be considered hypothesis-generating. In addition, the P values and confidence intervals were not adjusted for multiple testing and therefore should not be used to infer definitive treatment effects. Second, the choice of the specific stents in our registries was not randomized and thus is subject to selection bias. Although rigorous adjustment was performed with multiple propensity-score analyses, unmeasured confounders cannot be controlled. Third, given that the sample size of each stent group was relatively limited, our study was underpowered to detect clinically relevant differences in hard
clinical endpoints. Fourth, the composite primary end point is sensitive to the protocol definition of MI, which varied among several studies. To diminish uncertainty and to minimize ascertainment bias for MI, further research and consensus are warranted to implement a more applicable definition of peri-procedural MI (34). Last, the follow-up duration was relatively short. Therefore, further studies with longer-term follow-up are required to examine whether differences in late-occurring events between DES emerge over time.

**CONCLUSIONS**

In this contemporary PCI cohort of patients with CHIP features, we found the differential risks of target-vessel failure according to various types of contemporary DES. However, considering the inherent limitations of observational study, the small absolute differences in primary composite outcome in favor of specific types of DES warrant further investigations with large-sized randomized clinical trials.

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Comparison of Several DES for CHIP Patients

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APPENDIX For supplemental tables and figures, please see the online version of this paper.