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Safety and Effectiveness of Second-Generation Drug-Eluting Stents in Patients With Left Main Coronary Artery Disease

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ABSTRACT

BACKGROUND Limited data are available on the relative performances between different types of drug-eluting stents (DES) for obstructive left main coronary artery disease (LMCAD).

OBJECTIVES This study sought to compare effectiveness and safety profiles of various second-generation DES for LMCAD in real-world clinical practice.

METHODS Among 4,470 patients in 3, multicenter, prospective registries (IRIS-DES [Interventional Cardiology Research Incorporation Society-Drug-Eluting Stents] registry, the IRIS-MAIN [Interventional Cardiology Research Incorporation Society-Left MAIN Revascularization] registry, and the PRECOMBAT [PREmier of Randomized COMparison of Bypass Surgery versus AngioplasTy Using Drug-Eluting Stent in Patients with Left Main Coronary Artery Disease] study) treated between July 2007 and July 2015, the authors identified 2,692 patients with significant LMCAD who received second-generation DES; 1,254 with cobalt-chromium everolimus-eluting stents (CoCr-EES), 232 with biodegradable polymer biolimus-eluting stents (BP-BES), 616 with platinum-chromium EES (PtCr-EES), and 590 with Resolute zotarolimus-eluting stent (Re-ZES). The primary outcome was target-vessel failure.

RESULTS The observed 3-year rates of target-vessel failure were not significantly different for the different types of DES (16.7% for the CoCr-EES, 13.2% for the BP-BES, 18.7% for the PtCr-EES, and 14.7% for the Re-ZES; $p = 0.15$). In multiple treatment propensity score analysis, the adjusted hazard ratios (HRs) for target-vessel failure were similar in between-group comparisons of the different DES, except for the PtCr-EES versus the BP-BES (reference; HR: 1.60; 95% confidence interval: 1.01 to 2.54; $p = 0.046$). There were no significant differences in risk of composite of all-cause death, any myocardial infarction, or any revascularization and its individual components according to the different types of DES. Although the 3-year incidence of stent thrombosis was considerably low (≤1.0%) for all types of DES, between-group differences were observed, generally favoring the EES platforms.

CONCLUSIONS In this pooled analysis of 3 prospective registries involving unrestricted use of various second-generation DES for LMCAD, we found no significant between-group differences in 3-year risk of target-vessel failure, except for a higher risk of primary outcome with PtCr-EES compared to BP-BES. (Evaluation of the First, Second, and New Drug-Eluting Stents in Routine Clinical Practice [IRIS-DES]; NCT01186133) (J Am Coll Cardiol 2018;71:832–41)

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The technology and engineering of drug-eluting stents (DES) have continuously advanced (1). Compared with the previous versions, newer-generation DES have been developed that use different antiproliferative drugs with improved drug release kinetics, novel stent materials, thin strut platforms, and biocompatible or biodegradable polymers. In several studies, the newer-generation DES were associated with better safety and efficacy profiles than the first-generation DES and have thus become the default percutaneous coronary intervention (PCI) devices for broad clinical and anatomical subsets including left main coronary artery (LMCA) disease (2,3).

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The cumulative evidence from clinical trials and registries has suggested that PCI using a DES is an acceptable alternative to coronary artery bypass grafting (CABG) in selected patients with LMCA disease (4–8). Recently, the primary results of 2 large randomized trials using second-generation DES have been reported; 1 study found PCI to be noninferior to CABG, whereas another study showed CABG to be superior to PCI (9,10). Although the disparate findings of the 2 trials lead to some uncertainty concerning the optimal revascularization strategy, both studies demonstrate how much PCI with a DES for LMCA revascularization has improved. However, until recently, data for the relative performance of the second-generation DES for the treatment of significant LMCA disease were limited. We therefore evaluated the comparative effectiveness and safety profiles of several second-generation DES for LMCA disease by using a pooled database from 3 large prospective clinical practice registries.

METHODS

STUDY POPULATION, PROCEDURES, AND DATA COLLECTION. The study population that underwent DES implantation for significant LMCA disease between July 15, 2007, and July 29, 2015 was pooled from 3 independent, multicenter observational studies; the IRIS-DES (Interventional Cardiology Research Incorporation Society-Drug-Eluting Stents) registry, the IRIS-MAIN (Interventional Cardiology Research Incorporation Society-Left MAIN Revascularization) registry, and the PRECOMBAT (PREmier of Randomized COMparison of Bypass Surgery versus AngioplasTy Using Drug-Eluting Stent in Patients with Left Main Coronary Artery Disease) registry. The study design and detailed entry criteria of each registry have been described previously (8,11,12), and the key features are summarized in Online Table 1. Briefly, 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 (11). The IRIS-MAIN study was a prospective, multinational registry consisting of a cohort of consecutive Asian patients with significant, unprotected LMCA disease who were treated with PCI, bypass surgery, or medical therapy alone (8). The PRECOMBAT registry involved Korean patients with significant LMCA disease treated with second-generation DES for historical comparison with a patient cohort from the PRECOMBAT randomized trial (12). The current analysis included patients treated with 4 different types of DES: the cobalt-chromium everolimus-eluting stent (CoCr-EES; Xience V, Prime, Xpedition, or Alpine model; Abbott Vascular, Santa Clara, California), the biodegradable polymer-biolimus-eluting stent (BP-BES; BioMatrix model; Biosensors, Newport Beach, California, and Nobori, Terumo Clinical Supply, Kakamigahara, Japan), the platinum chromium-EES (PtCr-EES) (Promus Element or Premier model; Boston Scientific, Natick, Massachusetts), and the Resolute-zotarolimus-eluting stent (Re-ZES; Resolute Integrity model; Medtronic Inc., Santa Rosa, California). These registries were supported by the CardioVascular Research Foundation, Seoul, Korea, and there was no industry involvement in the design, conduct, or analysis of the study findings. The ethics committee of each participating center approved the study protocol, and all patients provided written, informed consent.

In each registry, PCI was performed according to standard techniques at the discretion of each operator. The registries did not specify stent types according to clinical or anatomical features; therefore each operator was responsible for the choice of a DES. By protocol, the same type of stent implanted for LMCA was used in other non-left main lesions whenever necessary. The maximal available stent diameter was 4.0 mm for all kinds of DES involved in the current study. Periprocedurally, anticoagulant agent was administered according to standard regimens. Administration of glycoprotein IIb/IIIa inhibitors were administered at the discretion of the operator. All patients undergoing PCI received a loading dose of aspirin and $P2Y_{12}$ receptor inhibitor (clopidogrel, prasugrel, or ticagrelor) before or during the intervention. After the procedure, aspirin was continued indefinitely, and $P2Y_{12}$ receptor inhibitors

ABBREVIATIONS AND ACRONYMS

BP-BES = biodegradable polymer-biolimus eluting stent

CABG = coronary artery bypass grafting

CoCr-EES = cobalt-chromium everolimus-eluting stent

DES = drug-eluting stent

LMCA = left main coronary artery

MI = myocardial infarction

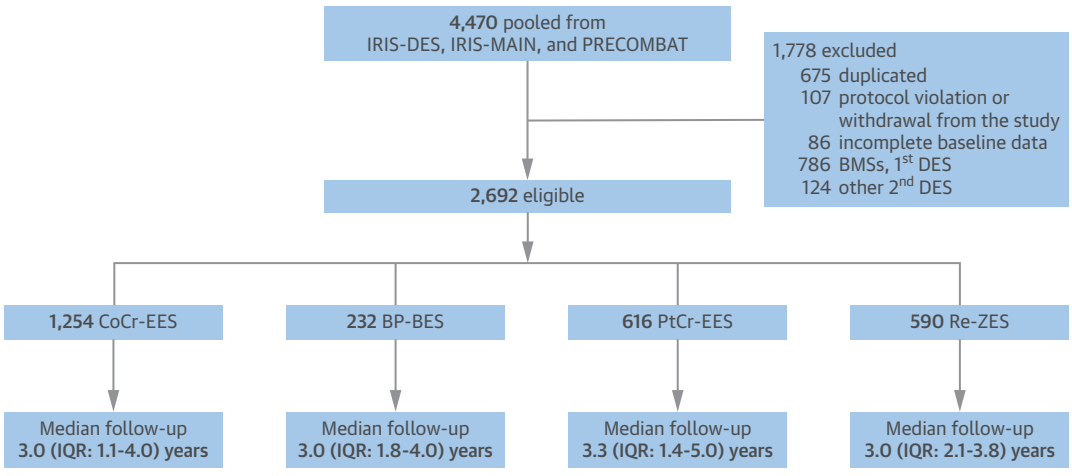
PCI = percutaneous coronary intervention

PtCr-EES = platinum chromium everolimus-eluting stent

Re-ZES = resolute zotarolimus-eluting stent

TVR = target-vessel revascularization

FIGURE 1 Flow Diagram of the Study



BMS = bare-metal stent; BP-BES = biodegradable polymer biolimus-eluting stents; CoCr-EES = cobalt-chromium everolimus-eluting stents; DES = drug-eluting stents; IQR = interquartile range; IRIS-DES = Interventional Cardiology Research Incorporation Society-Drug-Eluting Stents; IRIS-MAIN = Interventional Cardiology Research Incorporation Society-Left MAIN Revascularization; PRECOMBAT = PREmier of Randomized COMparison of Bypass Surgery versus AngioplasTy Using Drug-Eluting Stent in Patients with Left Main Coronary Artery Disease; PtCr-EES = platinum-chromium everolimus-eluting stents; Re-ZES = Resolute zotarolimus-eluting stents.

were prescribed for at least 12 months regardless of DES type. Drugs for secondary prevention were prescribed according to current guidelines.

Clinical follow-up was conducted during hospitalization and at 30 days, at 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 characteristics and outcome data were collected using a dedicated, electronic case report form by specialized personnel at each participating center. This internet-based system provides each center with immediate and continuous feedback for the processes and quality of care measurements. Registry data are periodically monitored and verified in the participating hospitals by members of the academic coordinating center (Clinical Research Center, Asan Medical Center, Seoul, Korea) (11).

CLINICAL OUTCOMES AND DEFINITIONS. The primary clinical outcome of the study was target-vessel failure (a composite of cardiac death, target-vessel myocardial infarction [MI], or target-vessel revascularization [TVR]). Secondary clinical outcomes were death (any cause, cardiac, or noncardiac), MI (periprocedural or spontaneous), any revascularization (TVR or non-TVR), stent thrombosis (ST), major bleeding according to the Thrombolysis In Myocardial Infarction definition (13), and major adverse cardiac event (MACE; a composite of all-cause death, any MI, or any revascularization) as a patient-related composite outcome.

Cause of death was considered to be cardiac-related, unless an unequivocal noncardiac cause could be established. The diagnosis of MI was based on clinically relevant MI by the Society for Cardiovascular Angiography and Interventions definition (14). Repeat revascularization included any type of percutaneous or surgical revascularization procedure and was categorized as TVR or non-TVR. Stent thrombosis (definite or probable) was defined according to the Academic Research Consortium definition (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, anatomic and procedural features are described according to the specific types of DES. Stent information for LMCA included all implanted stents that have been overlapped starting from left main stem. Categorical variables are presented as counts (proportions) and continuous variables as mean ± SD. Differences among treatment groups were evaluated by analysis of variance for continuous variables and by the chi-square or Fisher exact test for categorical variables. If differences

were detected, the Tukey test was performed for continuous variables, whereas comparison by Bonferroni correction was applied to categorical variables.

Cumulative events of clinical outcomes were assessed using Kaplan-Meier estimates and compared by using the log-rank test. All analyses were truncated at 3 years of follow-up owing to the different follow-up durations according to DES type and the small number of patients with data thereafter. To minimize confounding and residual selection bias in observational treatment comparisons, a propensity score weighting method was applied to control imbalances in various baseline characteristics across the stent groups. In this study, multiple treatment propensity scores were applied using the TWANG (Toolkit for Weighting and Analysis of Nonequivalent Groups) method, and the corresponding inverse probabilities of treatment weight (the reciprocals of the propensity scores) were estimated by using generalized boosted models through an iterative estimation procedure (n = 3,000), using all related baseline characteristics (16) (Online Appendix). The balance of the pretreatment covariates was assessed, and significant improvement in baseline was achieved after weighting (Online Table 2, Online Figures 1 and 2). To evaluate treatment effects, the PROC SURVEYPHREG procedure of SAS software (Cary, North Carolina) was used to correctly interpret weights as probability weights. All reported p values are two-sided and have not been adjusted for multiple testing. All analyses were performed using SAS software version 9.4 (SAS Institute) and R software version 3.2.2 13 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

STUDY POPULATION AND BASELINE CHARACTERISTICS. A flow diagram of the study is shown in **Figure 1**. Of 4,470 patients identified as receiving stent implants for LMCA disease in the 3 registries, 2,692 patients who received second-generation DES were finally included in the current analysis (1,254 with CoCr-EES, 232 with BP-BES, 616 with PtCr-EES, and 590 with Re-ZES).

Baseline demographics and clinical characteristics of the study population according to the different types of DES are shown in **Table 1** and Online Table 3. Overall, there were no significant between-group differences with regard to age, sex, and several key clinical factors (diabetes, previous PCI, renal failure, peripheral vascular disease, ejection fraction, and clinical indication for PCI). There were, however, significant between-group differences in proportion of hyperlipidemia, family history of coronary artery disease, and history of heart failure or MI.

TABLE 1 Baseline Demographic and Clinical Characteristics of Patient Groups According to Type of Drug-Eluting Stent

	CoCr-EES (n = 1,254)	BP-BES (n = 232)	PtCr-EES (n = 616)	Re-ZES (n = 590)	p Value
Age, yrs	64.4 ± 10.6	63.1 ± 10.8	64.3 ± 10.7	64.8 ± 10.6	0.45
Male	948 (75.6)	177 (76.3)	467 (75.8)	464 (78.6)	0.53
Body mass index, kg/m^2	24.5 ± 3.1	24.6 ± 3.6	24.5 ± 3.0	24.4 ± 2.9	0.41
Diabetes mellitus	435 (34.7)	86 (37.1)	191 (31.0)	201 (34.1)	0.30
Hypertension	774 (61.7)	138 (59.5)	371 (60.2)	393 (66.6)	0.08
Hyperlipidemia	674 (53.7)	145 (62.5)	415 (67.4)	413 (70.0)	<0.001
Current smoker	294 (23.4)	57 (24.6)	136 (22.1)	149 (25.3)	0.61
Family history of CAD	93 (7.4)	30 (12.9)	44 (7.1)	57 (9.7)	0.02
History of MI	82 (6.5)	26 (11.2)	29 (4.7)	38 (6.4)	0.01
History of CHF	79 (6.3)	17 (7.3)	52 (8.4)	63 (10.7)	0.01
Previous PCI	181 (14.4)	40 (17.2)	97 (15.7)	84 (14.2)	0.62
Previous CABG	34 (2.7)	6 (2.6)	13 (2.1)	7 (1.2)	0.22
Renal failure	55 (4.4)	7 (3.0)	28 (4.5)	27 (4.6)	0.77
Cerebrovascular disease	40 (3.2)	6 (2.6)	26 (4.2)	30 (5.1)	0.16
Peripheral vascular disease	55 (4.4)	7 (3.0)	27 (4.4)	27 (4.6)	0.79
Chronic lung disease	27 (2.2)	5 (2.2)	15 (2.4)	17 (2.9)	0.81
Mean ejection fraction, %	58.8 ± 9.6	58.4 ± 9.9	58.4 ± 9.6	58.2 ± 10.3	0.18
Clinical indication for PCI					0.28
Silent ischemia/stable angina	467 (38.9)	110 (48.0)	237 (39.4)	229 (39.8)	
Unstable angina	508 (42.2)	79 (34.5)	257 (42.8)	225 (39.1)	
NSTEMI	154 (12.8)	29 (12.7)	74 (12.3)	80 (13.9)	
STEMI	72 (6.0)	11 (4.8)	33 (5.5)	42 (7.3)	

Values are mean ± SD or n (%).

BP-BES = biodegradable polymer biolimus-eluting stent(s); CABG = coronary artery bypass grafting; CAD = coronary artery disease; CHF = congestive heart failure; CoCr-EES = cobalt-chromium everolimus eluting stent(s); MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; PtCr-EES = platinum-chromium everolimus-eluting stent(s); Re-ZES = resolute zotarolimus-eluting stent(s); STEMI = ST-segment elevation myocardial infarction.

Table 2 shows the baseline lesion and procedural characteristics of the study population according to the different DES types. Extent of coronary artery disease and LMCA lesion location were similar among the groups. However, there were significant differences across the groups with respect to LMCA stenting techniques, use of final kissing balloon, total stent number used in LMCA, use of intravascular ultrasonography, and use of glycoprotein IIb/IIIa inhibitors. Total number of stents and length per patient did not differ significantly among the DES groups.

CLINICAL OUTCOMES. The median duration of clinical follow-up was 3.1 years (interquartile range [IQR]: 2.0 to 4.5 years), 3.0 years (IQR: 1.1 to 4.0 years) for the CoCr-EES, 3.0 years (IQR: 1.8 to 4.0 years) for the BP-BES, 3.3 years (IQR: 1.4 to 5.0 years) for the PtCr-EES, and 3.0 years (IQR: 2.1 to 3.8 years) for the Re-ZES. Owing to the different follow-up duration for the DES types, analyses were truncated at 3 years of follow-up. Within the 3-year follow-up period, there were 172 deaths (6.4%; 126 cardiac deaths [4.7%] and 47 noncardiac deaths [1.7%]), 153 MIs (5.7%; 122 were periprocedural MIs [4.5%] and 33 were spontaneous

TABLE 2 Baseline Lesions and Procedural Characteristics According to Type of Drug-Eluting Stent

	CoCr-EES (n = 1,254)	BP-BES (n = 232)	PtCr-EES (n = 616)	Re-ZES (n = 590)	p Value
Disease extent					0.40
Left main only	125 (10.0)	26 (11.2)	73 (11.9)	59 (10.0)	
Left main with 1VD	324 (25.8)	52 (22.4)	151 (24.5)	148 (25.1)	
Left main with 2VD	491 (39.2)	90 (38.8)	217 (35.2)	207 (35.1)	
Left main with 3VD	314 (25.0)	64 (27.6)	175 (28.4)	176 (29.8)	
RCA involvement	495 (39.5)	103 (44.4)	259 (42.0)	262 (44.4)	0.17
Left main lesion location					0.20
Ostium or mid-shaft	417 (33.6)	84 (36.2)	219 (35.7)	179 (30.4)	
Distal bifurcation	823 (66.4)	148 (63.8)	395 (64.3)	410 (69.6)	
Stenting technique					<0.001
Left main stenting only	159 (12.7)	44 (19.0)	92 (14.9)	94 (15.9)	
Simple crossover	882 (70.3)	129 (55.6)	391 (63.5)	367 (62.2)	
2-stent technique	213 (17.0)	59 (25.4)	133 (21.6)	129 (21.9)	
Final kissing balloon	338 (27.0)	94 (40.5)	200 (32.5)	184 (31.2)	<0.001
Total stent number per patient	2.2 ± 1.2	2.4 ± 1.3	2.2 ± 1.2	2.1 ± 1.1	0.12
Total stent length per patient	52.0 ± 33.2	52.8 ± 35.1	51.2 ± 32.1	50.8 ± 33.0	0.41
Stent number in left main	1.7 ± 0.9	1.8 ± 1.1	1.6 ± 0.8	1.6 ± 0.8	0.01
Average stent diameter in left main	3.5 ± 0.4	3.3 ± 0.4	3.6 ± 0.4	3.5 ± 0.4	<0.001
Use of intravascular ultrasonography	975 (77.8)	127 (54.7)	466 (75.6)	487 (82.5)	<0.001
Use of Gp IIb/IIIa inhibitors	82 (6.5)	30 (12.9)	46 (7.5)	45 (7.5)	0.01

Values are n (%) or mean ± SD.
Gp = glycoprotein; RCA = right coronary artery; VD = vessel disease; other abbreviations as in Table 1.

MI [1.2%]), 217 repeat revascularizations (8.1%; 165 were TVR [6.1%] and 70 were non-TVR [2.6%]), and 13 major bleedings. In total, 393 patients experienced at least one target-vessel failure event (14.6%) and 477 patients (17.7%) experienced at least one MACE event.

Kaplan-Meier estimates for clinical endpoints at 3 years are shown in **Table 3 and Figure 2**. The cumulative rates of target-vessel failure did not differ significantly among the groups in an analysis including the entire 3-year period (lowest was for the BP-BES [13.2%] and highest for the PtCr-EES [18.7%]), as well as in a landmark analysis starting 30 days after the index procedure. The cumulative incidences of death (lowest for the BP-BES [6.2%] and highest for the Re-ZES [8.3%]), MI (lowest for the CoCr-EES [5.4%] and highest for the PtCr-EES [7.0%]), or repeat revascularization (lowest for the Re-ZES [7.8%] and highest for the BP-BES [10.4%]) were also comparable among the groups. At 3 years, 11 cases (0.5%) of definite (n = 10) or probable (n = 1) stent thrombosis had occurred (6 for the Re-ZES, 4 for the CoCr-EES, and 2 for the BP-BES), mostly within 30 days (7 cases) of PCI. There were no stent thrombosis events in the PtCr-EES group. Accordingly, significant between-group differences in 3-year rates of stent thrombosis were observed, generally favoring the EES platforms. The cumulative occurrences of any or major bleeding were similar among the groups (Online Figure 3). With regard to patient-related composite outcome, including all deaths, all MIs and any revascularization, 3-year rates of MACE were not significantly different. Restenosis at LMCA occurred in 120 patients (4.5%). Of note, the pattern of restenosis location seemed to be largely attributable to the stenting technique rather than to the type of DES (Online Table 4).

The adjusted hazard ratios for multiple DES comparisons after application of multiple treatment propensity score weighting are shown in **Table 4 and Central Illustration**. With the CoCr-EES as the reference group, the hazard ratios (HRs) for the other types of DES were similar with respect to risk of target-vessel failure as well as to other secondary clinical outcomes. This pattern was consistent for all clinical outcomes in other pairwise comparisons, except that the HR for the risk of target-vessel failure for the PtCr-EES was marginally higher than for the BP-BES (HR: 1.60; 95% confidence interval: 1.01 to 2.54; p = 0.046).

DISCUSSION

In this pooled analysis of 3 multicenter, prospective registries, we did not find significant differences among rates of target-vessel failure at 3 years across different types of second-generation DES for LMCA disease, except that the use of PtCr-EES was associated with a higher risk of primary outcome than BP-BES. Overall, there were no substantial differences in the risks of patient-related outcomes of MACE and its individual components according to different types of DES. The incidence of stent thrombosis was considerably low (≤1.0%) for all types of DES.

Over time, PCI for significant LMCA disease has undergone considerable therapeutic evolution and has rapidly expanded, particularly with the widespread adoption of DES. DES have also undergone significant refinement, becoming thinner, more deliverable, and more biocompatible; and the combination of these factors has resulted in fewer local inflammatory reactions, less arterial injury, and reduced thrombogenicity. Although there has been no randomized trial directly comparing the outcomes of first- and second-generation DES for LMCA disease, observational studies have pointed to comparable or superior clinical outcomes with the newer generation DES (12,17–21). Even though various second-generation DES have completely replaced the first-generation devices, each DES is unique and

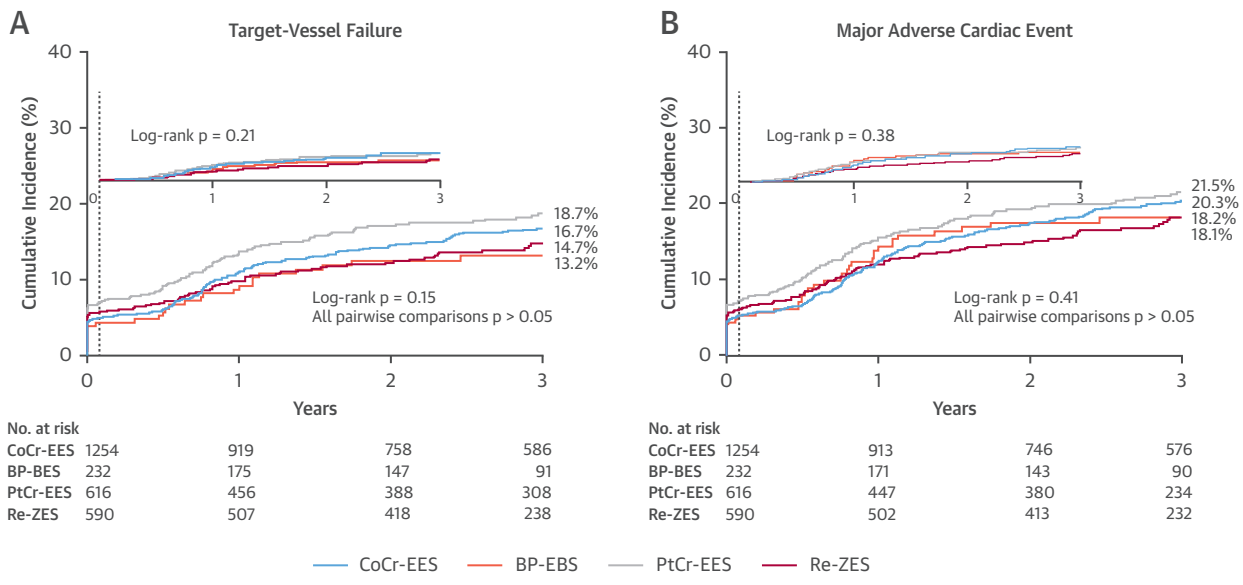
TABLE 3 3-Year Rates of Primary and Secondary Clinical Outcomes According to Type of Drug-Eluting Stent

	CoCr-EES (n = 1,254)*	BP-BES (n = 232)	PtCr-EES (n = 616)	Re-ZES (n = 590)	p Value
Primary outcome					
Target-vessel failure†	16.7 (15.5–17.9)	13.2 (10.8–15.6)	18.7 (17.0–20.4)	14.7 (13.1–16.3)	0.15
Secondary outcomes					
Death from any cause	7.7 (6.8–8.6)	6.2 (5.5–7.9)	6.9 (5.8–8.0)	8.3 (7.1–9.5)	0.83
Cardiac	5.8 (5.1–6.5)	3.4 (2.1–4.7)	5.7 (4.7–6.7)	6.0 (4.9–7.1)	0.70
Noncardiac	2.1 (1.6–2.6)	3.4 (2.1–4.7)	1.4 (0.9–1.9)	2.5 (1.8–3.2)	0.23
Myocardial infarction	5.4 (4.7–6.1)	5.5 (3.9–7.1)	7.0 (6.0–8.0)	6.0 (5.0–7.0)	0.55
Periprocedural	4.1 (3.5–4.7)	3.9 (2.6–5.2)	5.7 (4.8–6.6)	4.6 (3.7–5.5)	0.43
Spontaneous	1.5 (1.1–1.9)	1.7 (0.7–2.7)	1.5 (1.0–2.0)	1.4 (0.9–1.9)	0.99
Any revascularization	10.1 (9.1–11.1)	10.4 (8.2–12.6)	10.2 (8.9–11.5)	7.8 (6.6–9.0)	0.43
TVR	7.8 (7.0–8.6)	8.0 (6.0–10.0)	8.0 (6.8–9.2)	5.4 (4.4–6.4)	0.34
Non–TVR	3.2 (2.6–3.8)	2.0 (1.0–3.0)	4.0 (3.2–4.8)	2.3 (1.6–4.0)	0.24
Definite or probable stent thrombosis	0.2 (0.1–0.3)	1.0 (0.3–1.7)	0.0 (0.0–0.0)	1.0 (0.6–1.4)	0.02§
Early, 0 to 30 days	0.2 (0.1–0.3)	0.4 (0.0–0.8)	0.0 (0.0–0.0)	0.7 (0.4–1.0)	0.10¶
Late, 30 days to 1 yr	0.1 (0.0–0.2)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.4 (0.1–0.7)	0.30
Very late, 1 to 3 yrs	0.0 (0.0–0.0)	0.6 (0.0–1.2)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.01#
MACE‡	20.3 (19.1–21.5)	18.1 (15.4–20.8)	21.5 (19.7–23.3)	18.2 (16.5–19.9)	0.41

Values are cumulative rate (95% confidence interval). *Cumulative rates (95% confidence interval) of events are based on Kaplan-Meier estimates. †Target-vessel failure was defined as death from cardiac causes, target-vessel MI, or TVR. ‡MACE was defined as the composite of all-cause death, any MI, or any repeat revascularization. §Pairwise comparisons are significant between CoCr-EES and Re-ZES (p = 0.03), BP-BES and PtCr-EES (p = 0.02), and PtCr-EES and Re-ZES (p = 0.01). ¶Pairwise comparisons are significant between PtCr-EES and Re-ZES (p = 0.04). #Pairwise comparisons are significant between CoCr-EES and BP-BES (p = 0.02).

CI = confidence interval; MACE = major adverse cardiac events; TVR = target-vessel revascularization; other abbreviations as in Table 1.

FIGURE 2 Cumulative 3-Year Incidence of Clinical Outcomes According to Type of Drug-Eluting Stent



Cumulative-incidence curves for target-vessel failure **(A)** and major adverse cardiac events **(B)**. p values were calculated using the log-rank test. Target-vessel failure was defined as death from cardiac causes, target-vessel myocardial infarction, or target-vessel revascularization. Major adverse cardiac events were defined as the composite of all-cause death, myocardial infarction, or any revascularization. Abbreviations as in Figure 1.

TABLE 4 Adjusted HR for Clinical Outcomes Between Different Pairs of Drug-Eluting Stents in a Multigroup Propensity Score Analysis

	HR (95% CI)				
Stent Comparison	Target-Vessel Failure*	Death	MI	TVR	MACE†
BP-BES vs. CoCr-EES	0.72 (0.46–1.12)	0.62 (0.33–1.17)	1.02 (0.53–1.95)	0.95 (0.52–1.74)	0.85 (0.58–1.23)
p Value	0.62	0.14	0.95	0.87	0.38
PtCr-EES vs. CoCr-EES	1.15 (0.90–1.47)	0.88 (0.59–1.32)	1.36 (0.92–2.02)	1.00 (0.69–1.47)	1.08 (0.86–1.36)
p Value	0.28	0.55	0.13	0.98	0.50
Re-ZES vs. CoCr-EES	0.88 (0.67–1.15)	1.13 (0.77–1.67)	1.11 (0.73–1.71)	0.68 (0.44–1.04)	0.91 (0.71–1.16)
p Value	0.35	0.53	0.62	0.08	0.43
PtCr-EES vs. BP-BES	1.60 (1.01–2.54)	1.43 (0.72–2.84)	1.33 (0.68–2.63)	1.05 (0.56–1.99)	1.28 (0.86–1.90)
p Value	0.046	0.30	0.41	0.87	0.23
Re-ZES vs. BP-BES	1.23 (0.76–1.98)	1.83 (0.93–3.60)	1.09 (0.54–2.20)	0.71 (0.36–1.39)	1.07 (0.71–1.61)
p Value	0.40	0.08	0.80	0.31	0.74
Re-ZES vs. PtCr-EES	0.77 (0.57–1.04)	1.28 (0.81–2.02)	0.82 (0.51–1.31)	0.67 (0.42–1.09)	0.84 (0.64–1.10)
p Value	0.08	0.29	0.41	0.11	0.21

*Target-vessel failure was defined as death from cardiac causes, target-vessel MI, or TVR. †MACE was defined as the composite of all-cause death, any MI, or any revascularization.

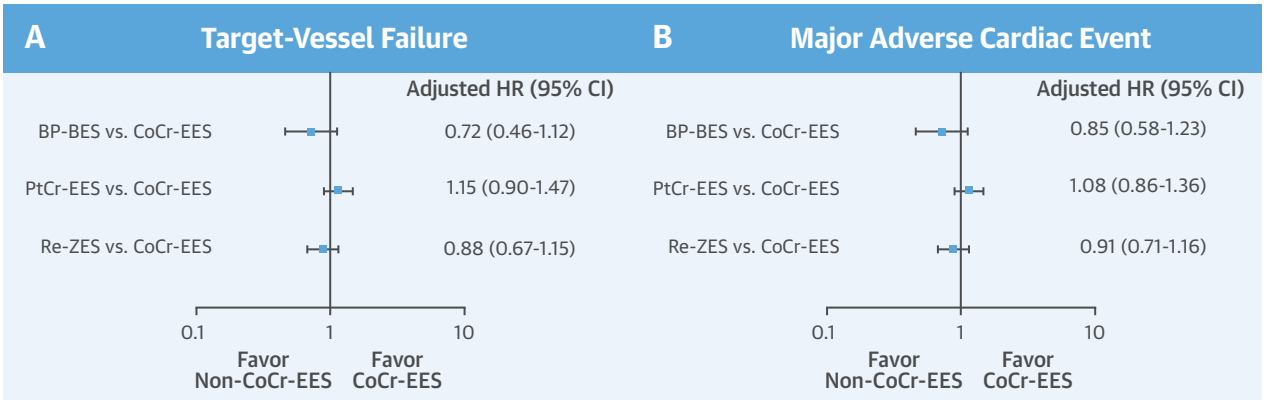
DES = drug-eluting stent; HR = hazard ratio; other abbreviations as in Tables 1 and 3.

has a different profile with respect to stent platform, polymer coating, and anti-proliferative drug. However, there has been little systematic comparative evaluation of the performances of the second-generation DES for LMCA disease, and thus, the present findings should provide valuable clinical information and help clinicians make the optimal choice of DES in patients undergoing PCI for LMCA disease.

In this pooled analysis of clinical practice registries involving unrestricted use of several second-generation DES for LMCA disease, the overall adjusted risk of target-vessel failure was comparable for the different types of DES in pairwise comparisons, except for the PtCr-EES versus BP-BES. Although the lipophilicity of the biolimus and biodegradable polymer of the BP-BES might have affected the device-oriented outcome, this would not be consistent with the general idea that the influence of the various components of DES on clinical outcome is minimal in LMCA of relatively large caliber. Because the differences in frequency of target-vessel failures in the 2 types of DES mostly involved the immediate period after the procedure, it is reasonable to assume that other clinical or procedural factors contributed to this disparity. Indeed, the differences in cumulative incidence of target-vessel failures in the PtCr-EES versus the BP-BES was less in the landmark analysis starting 30 days after the index procedure. In addition, although our propensity score estimates for multiple treatments using generalized boosted models might have allowed a fair examination of the causal treatment effects of the multiple treatment conditions, the method at best only eliminated confounding by the observed variables. Thus, unknown or unmeasured confounders, which may be especially implicated in early events such as cardiac deaths or periprocedural MIs, might have affected our results. Finally, the risk of longitudinal stent deformation would be highest in the PtCr-EES group (the Promus Element model used 82% within the group) and it may have contributed to the future risk of stent failure, particularly in our cohort involving LMCA disease (22). Unfortunately, procedural information regarding the occurrence of longitudinal stent deformation for each stent group was not available in the current study.

Recently, the EXCEL (Evaluation of XIENCE Everolimus Eluting Stent Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) and NOBLE (Nordic-Baltic-British Left Main Revascularization Study) trials yielded conflicting primary results. The use of different types of second-generation DES in the 2 trials has been proposed as 1 of the main reasons for this discrepancy (23). The EXCEL study used a thin strut, fluoropolymer-based CoCr-EES, which was associated with the lowest risk of stent thrombosis of all available DES in previous studies (24). In contrast, the NOBLE study used a first-generation stent, with a thicker strut, the sirolimus-eluting stent (11%) or the BP-BES (Biomatrix Flex) (89%). There was a substantial difference in rate of definite stent thrombosis between the 2 trials (0.7% in the EXCEL and 3% in the NOBLE). In our study, definite or probable stent thromboses occurred in 3 patients (0.2%) treated with the

CENTRAL ILLUSTRATION **Comparison Between Outcomes of Different Types of Drug-Eluting Stents in the Propensity-Score Analyses: Adjusted HR**



Lee, P.H. et al. J Am Coll Cardiol. 2018;71(8):832–41.

Adjusted hazard ratios are given for different types of stents compared with the CoCr-EES: **(A)** target-vessel failures and **(B)** major adverse cardiac events. Target-vessel failure was defined as death from cardiac causes, target-vessel myocardial infarction, or target-vessel revascularization. Major adverse cardiac events were defined as the composite of all-cause death, myocardial infarction, or any revascularization. BP-BES = biodegradable polymer biolimus-eluting stents; CI = confidence interval; CoCr-EES = cobalt-chromium everolimus-eluting stents; HR = hazard ratio; PtCr = platinum-chromium everolimus-eluting stents; Re-ZES = Resolute zotarolimus-eluting stents.

CoCr-EES and in 2 (0.9%) treated with the BP-BES. The exact reasons for the differing rates of stent thrombosis between the NOBLE trial and our findings remain unclear but may be explained in part by differences in clinical or lesion characteristics, interventional practice or specific expertise in left main PCI, or to the mixture of first-generation DES used in the NOBLE trial (25).

Biodegradable polymer-based DES were developed to mitigate the risk of thrombotic events related to use of permanent polymers. The BP-BES is one of the formed devices that has undergone extensive investigation and is in general use (26). A comprehensive network meta-analysis of clinical trials detected no significant difference in the rate of definite or probable stent thrombosis between other second-generation DES and the BP-BES (3,27). Therefore, it remains unclear whether the use of different stent types (CoCr-EES or BP-BES) contributed to the contradictory findings of the EXCEL and NOBLE trials. However, it is also worth mentioning that there seemed to be a differential risk of stent thrombosis favoring the EES platforms over the others in our study, raising concerns of relatively thick struts of BP-BES. Unfortunately, owing to the low numbers of thrombotic events, our study could not provide reliable real-world clinical evidence with regard to the relative safeties of the second-generation DES for LMCA disease.

STUDY LIMITATIONS. First, this study was observational and therefore the overall findings should be considered hypothetical and hypothesis-generating only. Second, the choice of the specific stents in our registries was not randomized and thus was subject to selection bias. Also, baseline clinical and procedural characteristics varied between the groups treated with the different DES. Although potentially confounding clinical covariates were adequately adjusted, the comparative results may be vulnerable to unknown confounders. Third, similar to previous analyses (3,27), Biomatrix and Nobori stents were included in a group of BP-BES in our study, but some differences between the 2 stent platforms existed and might have affected the results. In addition, we should also consider the technical evolutions undergone for each DES with modification of stent design, platform, and delivery system during the last years. Fourth, the sample size of each stent group was relatively small, and thus the analysis was underpowered for detecting clinically relevant differences of stent thrombosis rates between devices. Finally, longer-term follow-up is required to examine whether differences in late-occurring events between

DES emerge over time; a final 5-year follow-up is currently being undertaken in each registry.

CONCLUSIONS

There were no significant differences between stent-related and patient-related outcomes at 3-year follow-up among different types of newer generation DES for LMCA disease, except that the use of the PtCr-EES was associated with a higher risk of target-vessel failure than that of the BP-BES. Our findings should be confirmed or refuted through large, randomized clinical trials with long-term follow-up.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Although 3-year clinical outcomes after PCI of LMCA lesions with various second-generation DES were otherwise similar, PtCr-EES were associated with a higher risk of target-vessel failure than BP-BES.

TRANSLATIONAL OUTLOOK: Further research is needed to clarify the mechanisms underlying differences in vascular outcomes with various types of DES.

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KEY WORDS drug-eluting stent, left main coronary artery, percutaneous coronary intervention

APPENDIX For an expanded Methods section as well as supplemental tables and figures, please see the online version of this article.