Circulation

ORIGINAL RESEARCH ARTICLE

Durable Polymer Versus Biodegradable Polymer Drug-Eluting Stents After Percutaneous Coronary Intervention in Patients with Acute Coronary Syndrome

The HOST-REDUCE-POLYTECH-ACS Trial

Editorial, see p 1092

Hyo-Soo Kim, MD*
Jeehoon Kang, MD*
Doyeon Hwang, MD
Jung-Kyu Han, MD
Han-Mo Yang, MD
Hyun-Jae Kang, MD
Bon-Kwon Koo, MD
Seok Yeon Kim, MD
Keun-Ho Park, MD
Seung-Woon Rha, MD
Won-Yong Shin, MD
Hong-Seok Lim, MD
Kyungil Park, MD
Kyung Woo Park, MD
On behalf of the HOST-REDUCE-POLYTECH-ACS Trial Investigators†

BACKGROUND: Large-scale randomized comparison of drug-eluting stents (DES) based on durable polymer versus biodegradable polymer technology is currently insufficient in patients with acute coronary syndrome (ACS). The present study aimed to prove the noninferiority of the durable polymer DES (DP-DES) compared with the biodegradable polymer DES (BP-DES) in such patients.

METHODS: The HOST-REDUCE-POLYTECH-ACS (Harmonizing Optimal Strategy for Treatment of Coronary Artery Diseases—Comparison of Reduction of Prasugrel Dose or Polymer Technology in ACS Patients) trial is an investigator-initiated, randomized, open-label, adjudicator-blinded, multicenter, noninferiority trial comparing the efficacy and safety of DP-DES and BP-DES in patients with ACS. The primary end point was a patient-oriented composite outcome (a composite of all-cause death, nonfatal myocardial infarction, and any repeat revascularization) at 12 months. The key secondary end point was device-oriented composite outcome (a composite of cardiac death, target-vessel myocardial infarction, or target lesion revascularization) at 12 months.

RESULTS: A total of 3413 patients were randomized to receive the DP-DES (1713 patients) and BP-DES (1700 patients). At 12 months, patient-oriented composite outcome occurred in 5.2% in the DP-DES group and 6.4% in the BP-DES group (absolute risk difference, −1.2%; $P_{noninferiority}<0.001$). The key secondary end point, device-oriented composite outcome, occurred less frequently in the DP-DES group (DP-DES vs BP-DES, 2.6% vs 3.9%; hazard ratio, 0.67 [95% CI, 0.46–0.98]; $P=0.038$), mostly because of a reduction in target lesion revascularization. The rate of spontaneous nonfatal myocardial infarction and stent thrombosis were extremely low, with no significant difference between the 2 groups (0.6% versus 0.8%; $P=0.513$ and 0.1% versus 0.4%; $P=0.174$, respectively).

CONCLUSIONS: In ACS patients receiving percutaneous coronary intervention, DP-DES was noninferior to BP-DES with regard to patient-oriented composite outcomes at 12 months after index percutaneous coronary intervention.

REGISTRATION: URL: https://wwwclinicaltrials.gov; Unique identifier: NCT02193971.

*H-S. Kim and J. Kang contributed equally.

†A list of all HOST-REDUCE-POLYTECH-ACS trial investigators is given in the Data Supplement.

Key Words: acute coronary syndrome ■ drug-eluting stents ■ percutaneous coronary intervention ■ polymers ■ prasugrel hydrochloride ■ thrombosis

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Clinical Perspective

What Is New?

- Newer-generation thromboresistant durable polymer technology has not been tested in a large-scale randomized study against biodegradable polymer technology in patients with acute coronary syndrome receiving percutaneous coronary intervention.
- In this open-label, multicenter, randomized trial of 3413 such patients, we examined whether durable polymer drug-eluting stents were noninferior to biodegradable polymer drug-eluting stents with regard to patient-oriented composite outcomes (death, any myocardial infarction, and any revascularization).

What Are the Clinical Implications?

- Durable polymer drug-eluting stents were noninferior to biodegradable polymer drug-eluting stents for the primary end point of patient-oriented composite outcomes, which were consistent across a broad subgroup of acute coronary syndrome patients, suggesting similar clinical outcomes with contemporary drug-eluting stents, regardless of whether the polymer technology is durable or biodegradable.
- Longer-term follow-up will help elucidate whether the similarity in clinical outcomes between the 2 polymer technologies is sustained.

Drug-eluting stents (DES) have significantly improved outcomes compared with bare-metal stents (BMS) primarily because of the slow elution of the antiproliferative drug mixed with a polymer coated on the stent surface.[1] However, the polymers used in the first-generation DES were considered to be the cause of a chronic inflammatory response that leads to impaired endothelialization of the stent strut and subsequently increases the risk of stent thrombosis (ST).[2] One strategy to mitigate this adverse effect is the development of polymers that are biocompatible. The other is the development of a biodegradable polymer that dissolves with time and leaves only the BMS behind. The former strategy was used for newer-generation durable polymer DES (DP-DES) and the latter was used for biodegradable polymer DES (BP-DES).[1]

BP-DES has the theoretical advantage of leaving behind only the BMS after complete drug elution and polymer degradation, which can lead to reduction of vascular inflammation and decreased risk of late stent-related complications. Early-generation BP-DES showed superior safety and a reduction in patient-oriented outcomes compared with the first-generation DP-DES. However, newer-generation durable polymers have been shown to be thromboresistant and even safer than BMSs. In previous studies of all-comers receiving percutaneous coronary intervention (PCI), which included a significant proportion of stable angina patients, device-oriented outcomes were comparable between BP-DES and DP-DES.[3–6] However, comparison of the 2 polymer technologies in a dedicated acute coronary syndrome (ACS) population who are at heightened risk of thrombosis and delayed vascular healing after PCI has not been previously performed in a large-scale randomized trial. The present study aimed to compare the efficacy and safety of DP-DES and BP-DES in patients with ACS receiving PCI.

METHODS

The HOST-REDUCE-POLYTECH-ACS (Harmonizing Optimal Strategy for Treatment of Coronary Artery Diseases Trial - Comparison of Reduction of Prasugrel Dose and Polymer Technology in ACS Patients) trial will continue follow-up for 3 years, which will be March 2022. Until then, no individual participant data will be available. Any relevant inquiry should be emailed to Dr Hyo-Soo Kim (hyosoo@snu.ac.kr) or Dr Kyung Woo Park (kwparkmd@snu.ac.kr).

Study Design and Population

The HOST-REDUCE-POLYTECH-ACS trial is an investigator-initiated, 2×2 factorial, randomized, parallel-group, open-label, adjudicator-blinded, multicenter trial conducted at 35 study sites in Korea, as previously described.[7] Briefly, this study tested 2 independent hypotheses and had 2 arms: the DES arm and the antiplatelet arm. In the antiplatelet arm, we evaluated the noninferiority of prasugrel-based de-escalation therapy compared with conventional therapy in patients with ACS. The results of the antiplatelet arm have been previously published.[8] The present study reports the analysis and findings from the DES arm, which compared the efficacy and safety of DP-DES with BP-DES. Patients 19 years of age or older with a clinical diagnosis of ACS and with at least 1 culprit coronary lesion in a native coronary artery with significant stenosis eligible for stent implantation were screened to participate in the trial. The full inclusion and exclusion criteria and the detailed screening process are described in the Data Supplement. The study complied with the provisions of the Declaration of Helsinki and was approved by the institutional ethics committee of each participating site. All patients provided written informed consent at enrollment. This trial is registered (URL: https://www.clinicaltrials.gov; Unique identifier: NCT02193971).

Randomization

Investigators enrolled eligible patients who were randomized (1:1) to either DP-DES or BP-DES after diagnostic coronary angiography and before PCI (Figure 1). The randomization sequence was generated by a web-based application (Medical Research Collaborating Center Interactive Web Response System; software configuration: Apache 2, PHP 5, and MySQL 5) developed by the Medical Research Collaborating Center (Seoul, Korea), without blocking or

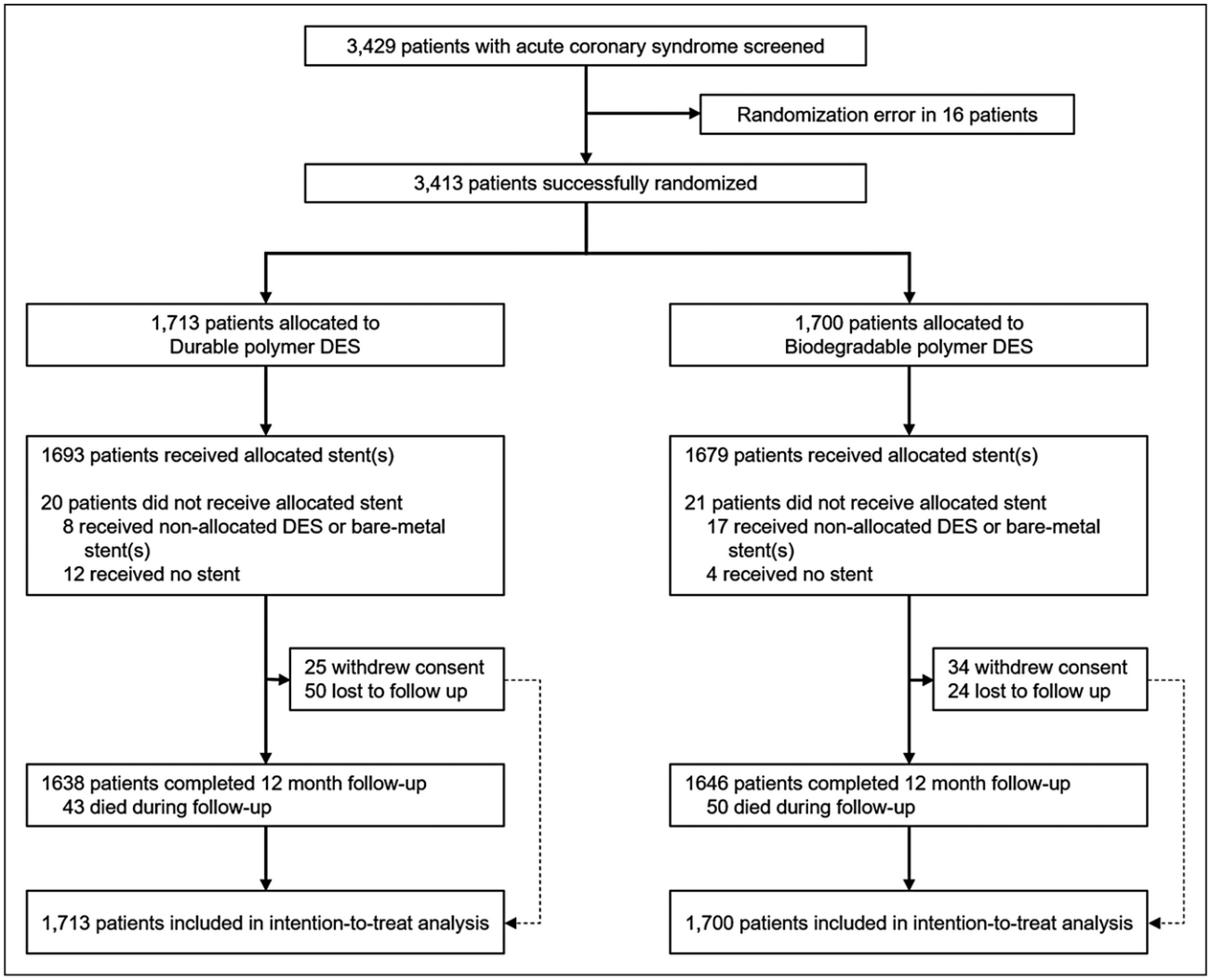

Figure 1. Trial profile.
Patients who were clinically diagnosed as acute coronary syndrome and who had at least 1 culprit coronary lesion in a native coronary artery with significant stenosis eligible for stent implantation were randomly assigned (1:1) to the durable polymer DES group and biodegradable polymer DES group. DES indicates drug-eluting stent.

stratification methods. Screening information for randomization was inputted by an independent research nurse or clinical nurse coordinator, who was not involved with the rest of the trial in each center. An independent committee blinded to the treatment allocations adjudicated all events. This study used a web-based electronic case report form with the Pharmacoepidemiology and Clinical Trial Application X, which was developed by the Medical Research Collaborating Center of Seoul National University Hospital.

Follow-Up and End Points

Clinical follow-up was mandatory at 1 and 12 months after the index procedure. Investigators were strongly recommended to perform the in-person follow-ups as office visits; however, telephone interviews were permitted. The primary end point of the present study was a patient-oriented composite outcome (POCO), defined as a composite of all-cause death, nonfatal myocardial infarction (MI), and any repeat revascularization at 12 months. The key secondary end point was the device-oriented composite outcome ([DOCO] a composite of cardiac death, target-vessel MI, or target lesion revascularization [TLR]). Other secondary end points include the individual components of the primary and key secondary end points (non-TLR, target vessel revascularization, and non–target vessel revascularization) at 12 months. All primary and secondary end points will be analyzed on a per-patient basis.

Statistical Analysis

On the basis of the event rates of previous trials,[9,10] the overall incidence of the primary end point of this study was anticipated to be 6.0% for the DP-DES group and 6.0% for the BP-DES group. A predetermined noninferiority margin of 2.0% and an attrition rate of 5% was estimated. A total of 3384 patients would result in a power of at least 81% with a 1-sided type 1 error of 2.5%.

The Kaplan–Meier estimates were calculated for comparison between treatment allocation. To estimate the adjusted effect of randomization arms on clinical end points, a multivariable Cox proportional hazards regression model was performed. All probability values were 2-sided, and *P* values

<0.05 were considered statistically significant. No imputation methods were used to infer missing values of baseline variables. End points were analyzed on an intention-to-treat basis first, and then on a per-protocol basis. A prespecified subgroup analysis was performed to detect any interaction of the clinical effect of each strategy in various subgroups. Among the definitions of subgroups, the complex PCI group was defined as patients who received bifurcation PCI, left main PCI, multivessel intervention, ≥3 stents implanted, ≥3 treated lesions, total stent length ≥60 mm, and/or those with heavily calcified coronary artery disease. Statistical tests were performed using SPSS version 22 (SPSS Inc.) and R programming language, version 3.4.4 (R Foundation for Statistical Computing).

Role of Funding Source

The funders of this study had no role in study design, collection of data and data analysis, or drafting the article.

RESULTS

From September 2014 through December 2018, 3413 patients with ACS with a total of 4713 lesions were enrolled from 35 centers and randomized to the DP-DES group (1713 patients, 2367 lesions) or the BP-DES group (1700 patients, 2346 lesions). DP-DES included the Promus Premier (922 lesions; 39.0%), Resolute Onyx (690 lesions; 29.2%), Xience Alpine (679 lesions; 28.7%), and DESyne (29 lesions; 1.2%) stents, whereas the BP-DES included the Ultimaster (745 lesions; 31.9%), Orsiro (590 lesions; 25.2%), Biomatrix Flex (503 lesions; 21.5%), Nobori (219 lesions; 9.4%), Synergy (122 lesions; 5.2%), and Biomatrix (98 lesions; 4.2%) stents. Figure 1 shows the trial profile and the flow of the patients. The baseline demographics of randomized patients are shown in Table 1, and the lesion and procedural characteristics are shown in Table 2. The mean age of patients was 63 years, and the clinical conditions were well-balanced between the 2 groups. Approximately 40% of the patients presented with acute MI and 13.1% (447 patients) presented with ST segment elevation MI. More than half of the patients had multivessel coronary artery disease and 30.5% received multivessel intervention. The culprit lesion was located in the left anterior descending artery in 49.4% and at a bifurcation in 18.4%. Intravascular ultrasound was used in 33.4%, and the number of stents implanted per patient was 1.7±1.0. At hospital discharge after the index procedure, 1641 of 1697 (96.7%) patients in the DP-DES group and 1632 of 1687 (96.7%) patients in the BP-DES group were on dual antiplatelet therapy.

At the 12-month follow-up, the primary end point of POCO occurred in 87 patients (Kaplan–Meier estimate, 5.2%) in the DP-DES group and 106 patients (Kaplan–Meier estimate, 6.4%) in the BP-DES group (absolute risk difference, –1.2%; upper margin of the 1-sided 97.5% CI, 0.4%; $P_{\text{noninferiority}}$<0.001) (Figure 2).

Table 1. Baseline Characteristics

	Durable polymer drug-eluting stent (N=1713)	Biodegradable polymer drug-eluting stent (N=1700)
Age, y	63.0±11.1	63.1±11.1
Male	1351/1713 (78.9%)	1337/1700 (78.6%)
Body mass index, kg/m^2	24.9±3.1	25.0±3.2
Hypertension	1092/1713 (63.7%)	1147/1699 (67.5%)
Diabetes	789/1713 (46.1%)	747/1700 (43.9%)
Dyslipidemia	1280/1713 (74.7%)	1247/1700 (73.4%)
Chronic kidney disease	79/1713 (4.6%)	65/1700 (3.8%)
Peripheral vessel disease	24/1713 (1.4%)	25/1700 (1.5%)
Smoking		
Never smoker	854/1713 (49.9%)	860/1700 (50.6%)
Current smoker	515/1713 (30.1%)	475/1700 (27.9%)
Former smoker	344/1713 (20.1%)	365/1700 (21.5%)
Prior myocardial infarction	67/1713 (3.9%)	70/1700 (4.1%)
Prior revascularization	220/1713 (12.8%)	220/1700 (12.9%)
Prior stroke	92/1713 (5.4%)	110/1700 (6.5%)
Family history of coronary artery disease	109/1713 (6.4%)	118/1700 (6.9%)
Left ventricular ejection fraction, %	58.5±10.4	58.7±10.4
Presentations		
ST-segment elevation myocardial infarction	233/1712 (13.6%)	214/1700 (12.6%)
Non–ST-segment elevation myocardial infarction	448/1712 (26.2%)	412/1700 (24.2%)
Unstable angina	1031/1712 (60.2%)	1074/1700 (63.2%)
Medication at discharge		
Aspirin	1665/1697 (98.1%)	1652/1687 (97.9%)
P2Y12 inhibitor		
Clopidogrel	482/1697 (28.4%)	473/1687 (28.0%)
Prasugrel	1091/1697 (64.3%)	1075/1687 (63.7%)
Ticagrelor	132/1697 (7.8%)	151 / 1687 (9.0%)
Antiplatelet randomization arm*		
Prasugrel, de-escalation group	589/1713 (34.4%)	581/1700 (34.2%)
Prasugrel, conventional group	588/1713 (34.3%)	580/1700 (34.1%)
Non-Prasugrel group	536/1713 (31.3%)	539/1700 (31.7%)

*Randomization group of the antiplatelet arm within the HOST-REDUCE-POLYTECH-ACS trial (Harmonizing Optimal Strategy for Treatment of Coronary Artery Diseases Trial - Comparison of Reduction of Prasugrel Dose and Polymer Technology in ACS Patients).

Using a multivariable Cox proportional hazards regression model, independent predictors of POCO included clinical factors such as older age, clinical diagnosis of acute MI, diabetes mellitus, and chronic renal failure, while the stent type was not an independent predictor of POCO (Table I in the Data Supplement). Regarding the key secondary end point, DOCO occurred less frequently in the DP-DES group compared with the BP-DES

Table 2. Lesion and Procedural Characteristics

Variable	Durable polymer drug-eluting stent (N=1713)	Biodegradable polymer drug-eluting stent (N=1700)
Number of diseased vessels		
1	778//1703 (45.7%)	769/1689 (45.5%)
2	549/1703 (32.2%)	512/1689 (30.3%)
3	376/1703 (22.1%)	408/1689 (24.2%)
Multivessel disease	925/1703 (54.3%)	920/1689 (54.5%)
Anticoagulant agent for percutaneous coronary intervention		
Unfractionated heparin	346/1713 (20.2%)	339/1700 (19.9%)
Enoxaparin	122/1713 (7.1%)	107/1700 (6.3%)
GpIIb/IIIa inhibitor		
Abciximab	15/1713 (0.9%)	16/1700 (0.9%)
Tirofiban	0/1713 (0.0%)	1/1700 (0.1%)
Culprit lesion		
Left main	62/1679 (3.7%)	58/1669 (3.5%)
Left anterior descending artery	837/1679 (49.9%)	845/1669 (50.6%)
Left circumflex artery	307/1679 (18.3%)	308/1669 (18.5%)
Right coronary artery	473/1679 (28.2%)	458/1669 (27.4%)
Lesion complexity		
Multilesion intervention	512/1687 (30.3%)	512/1674 (30.6%)
Heavy calcification	317/2353 (13.5%)	344/2329 (14.8%)
Bifurcation lesion	422/2351 (17.9%)	438/2326 (18.8%)
Thrombotic lesion	204/2353 (8.7%)	208/2328 (8.9%)
Type B2/C lesion	1165/2351 (49.6%)	1215/2328 (52.2%)
In-stent restenosis lesion	56/2353 (2.4%)	42/2328 (1.8%)
Intravascular ultrasound use	706/2360 (29.9%)	752/2339 (32.2%)
Treated lesion number per person	1.4±0.7	1.4±0.7
Stent number per person	1.7±1.0	1.7±1.1
Total stent length, mm	41.7±30.2	42.9±31.9
Procedural success	2358/2366 (99.7%)	2326/2342 (99.3%)

group (hazard ratio [HR], 0.67 [95% CI, 0.46–0.98]; *P*=0.038), which was driven mainly by a significantly reduced risk of TLR (1.0% versus 1.8%; HR, 0.54 [95% CI, 0.29–0.99] *P*=0.049). Other secondary end points, including the individual components of the primary end point, were mostly similar between the 2 groups (Table 3). The per-protocol analyses yielded results similar to the intention-to-treat analyses for the primary study end point (Kaplan–Meier estimate, 5.2% versus 6.2% in the DP-DES and BP-DES groups, respectively; absolute risk difference, −1.0%; upper margin of the 1-sided 97.5% CI, 0.6%; $P_{noninferiority}$<0.001) and for the key secondary end point (Figure I in the Data Supplement). Definite or probable ST occurred in 2 patients (0.1%) in the DP-DES group and 6 (0.4%) in the BP-DES group (Table 3; Figure 3). The details of the 8 cases are shown in Table 4. Sensitivity analyses indicated no substantial influence of competing risks of death for the individual components of the composite outcome (Table II in the Data Supplement), and a restricted mean survival time analysis showed consistent results with the main analysis with regard to POCO and DOCO (Table III in the Data Supplement).

In a prespecified subgroup analysis, the effect of DP-DES compared with BP-DES was consistent across different subgroups with no significant interaction (Figure 4). In particular, when the 2 groups were compared according to the complexity of the procedure, the rate of POCO was similar between BP-DES and DP-DES groups, although DP-DES showed numerically lower but statistically nonsignificant event rates in the complex PCI group (Figure II in the Data Supplement). In addition, because earlier-generation thicker strut stents were included in the BP-DES group, we performed a sensitivity analysis excluding the thick strut (strut thickness >100 μm) stents. The results were mostly similar even after excluding the thick strut stents, and there were no significant differences in the primary outcome (Figure III in the Data Supplement). A post hoc analysis according to individual stents showed no significant outliers (Figure IV in the Data Supplement).

DISCUSSION

In this large-scale, multicenter, randomized trial, DP-DES was noninferior to BP-DES in terms of POCO. Furthermore, the rate of DOCO was significantly lower in the DP-DES group compared with the BP-DES group, which was mainly driven by a reduction of TLR. Even though the study population comprised patients with ACS who have increased risk of thrombotic events, both polymer types showed excellent outcomes with extremely low rates of cardiac death, spontaneous MI, and ST. Sensitivity analyses accounting for the competing risk of death for the individual components of the composite outcome and a restricted mean survival times analysis showed consistent results with the main analysis with regard to POCO and DOCO. A prespecified subgroup analysis showed consistent results in a broad subgroup of patients including complex PCI.

Comparison of DP-DES and BP-DES have shown mixed results. Several previous studies have reported noninferiority of BP-DES compared with DP-DES. In the COMPARE II (Comparison of the Everolimus Eluting With the Biolimus A9 Eluting Stent) and NEXT (Nobori Biolimus-eluting Versus Xience/Promus Everolimus-eluting Stent Trial) studies, a thick strut Biolimus-eluting BP-DES (Nobori) was noninferior to the everolimus-eluting DP-DES (Xience/Promus stent) in all-comers receiving PCI.[3,4] Other studies have compared the thin strut sirolimus-eluting BP-DES (Orsiro) with everolimus- or Zotarolimus-eluting DP-DES (Xience/Resolute Integrity stent),

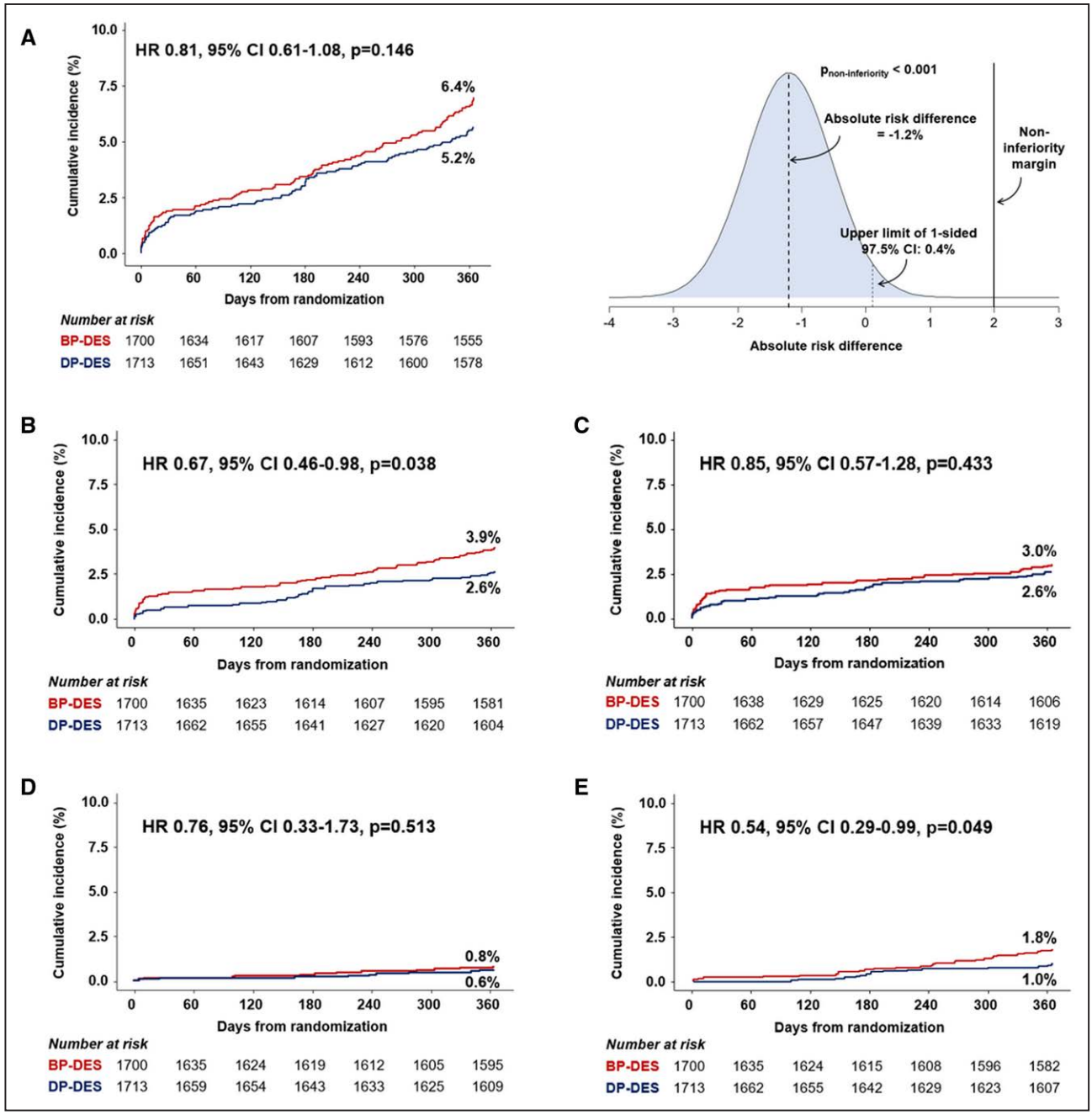

Figure 2. Kaplan–Meier curves in the intention-to-treat population at 12 months' follow-up and the density plot for absolute risk difference between the treatment groups.

A, Left, Kaplan–Meier curve of the primary end point: patient-oriented composite outcome. **A, Right**, The density plot for absolute risk difference between the treatment groups in the incidence of patient-oriented composite outcome confirmed noninferiority of the DP-DES group. Kaplan–Meier curve of the device-oriented composite outcome (**B**), all-cause death (**C**), nonfatal myocardial infarction (**D**), and target lesion revascularization (**E**). BP-DES indicates biodegradable polymer drug-eluting stent; DP-DES, durable polymer drug-eluting stent; and HR, hazard ratio.

which again showed noninferiority of the BP-DES platform.[5,6] However, in the BIOSCIENCE study (Sirolimus-eluting Stents with Biodegradable Polymer Versus an Everolimus-eluting Stents), TLR rates were numerically higher, although statistically insignificant, in the BP-DES group (Orsiro) than in the DP-DES group (Xience Prime/Xpedition) from 4 months with a slight divergence up to 1 year.[6] Furthermore, in the BIONYX trial (Bioresorbable Polymer Orsiro Versus Durable Polymer Resolute Onyx Stents), ST was significantly higher in the thin-strut BP-DES group (Orsiro) compared with the DP-DES group (Resolute Onyx).[11] Because these trials were performed in all-comers, which included a significant proportion of stable angina patients, it remains to be seen how the 2 polymer technology platforms perform in exclusively patients with ACS. Only 1 previous study compared BP-DES and DP-DES in patients with ACS: the BIOSTEMI trial (A Comparison of an Ultrathin Strut Biodegradable

Table 3. Primary and Specified Secondary Outcomes

Variable	Durable polymer drug-eluting stent (N=1713)	Biodegradable polymer drug-eluting stent (N=1700)	Hazard ratio (95% CI)	*P* value
Patient-oriented composite outcome (primary end point)				
All-cause death, nonfatal myocardial infarction, repeat revascularization	87 (5.2%)	106 (6.4%)	0.81 (0.61–1.08)	0.146
Key secondary end point				
Device-oriented composite outcome				
Cardiac death, target vessel myocardial infarction, target lesion revascularization	44 (2.6%)	65 (3.9%)	0.67 (0.46–0.98)	0.038
Other secondary end points				
All-cause death	43 (2.6%)	50 (3.0%)	0.85 (0.57–1.28)	0.433
Cardiac death	27 (1.6%)	38 (2.3%)	0.70 (0.43–1.15)	0.160
Non–cardiac death	16 (1.0%)	12 (0.7%)	1.32 (0.62–2.78)	0.472
Any myocardial infarction	10 (0.6%)	13 (0.8%)	0.76 (0.33–1.73)	0.513
Target vessel myocardial infarction	5 (0.3%)	8 (0.5%)	0.62 (0.20–1.89)	0.396
Non–target vessel myocardial infarction	5 (0.3%)	5 (0.3%)	0.99 (0.29–3.41)	0.985
Stent thrombosis				
Definite/probable	2 (0.1%)	6 (0.4%)	0.33 (0.07–1.63)	0.174
Definite/probable/possible	4 (0.2%)	6 (0.4%)	0.66 (0.19–2.34)	0.519
Acute (<24 h)	1 (0.1%)	1 (0.1%)		
Subacute (1 d≈1 mo)	1 (0.1%)	2 (0.1%)		
Late (1 mo≈1 y)	0	2 (0.1%)		
Any repeat revascularization	48 (2.9%)	58 (3.6%)	0.82 (0.56–1.20)	0.298
Target vessel revascularization	21 (1.3%)	38 (2.3%)	0.54 (0.32–0.93)	0.025
Target lesion revascularization	16 (1.0%)	29 (1.8%)	0.54 (0.29-0.99)	0.049
Non–target vessel revascularization	32 (1.9%)	27 (1.7%)	1.17 (0.70-1.96)	0.541

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).[12] In this trial, the Orsiro stent was statistically superior to the Xience stent in terms of DOCO. It is interesting to note that the main driver of the difference, which was TLR, occurred much more frequently in the DP-DES group within the first 3 months and was mostly similar between the 2 stent types thereafter. In real-world experience, a recent analysis from a database of more than 95 000 stents showed that BP-DES was not associated with an incremental clinical benefit over DP-DES at 2 years follow-up.[13]

In our study, the risk of POCO was similar between the 2 groups, whereas the risk of DOCO was lower in the DP-DES group, driven by a lower risk of TLR. It is notable that we could observe a slight increase of TLR in the late phase, from 6 months from index PCI, which is a finding similar to what was seen in the BIOSCIENCE study.[6] Because BP-DES becomes similar to BMS after full drug elution and polymer degradation, there may be a chance for increased risk of late restenosis after the initial drug elution and polymer degradation periods. In particular, the Orsiro stent that was used in the BIOSCIENCE study has a drug release duration of 4 months after PCI, and it was after this period that an increase of TLR was observed. In addition, all BP-DES used in our study, excluding the Orsiro stent, have an abluminally coated polymer, which leaves a bare metal in the intraluminal side, immediately after PCI, which may also contribute to the risk of restenosis.[1]

The overall incidence of spontaneous nonfatal MI (0.7%) and definite or probable ST was extremely low (0.2%) in our study, suggesting the excellent safety profile of both BP- and DP-DES. This may be attributable to the fact that the study was performed in an East Asian population who, in other trials, have been reported to have lower rates of thrombotic events.[14] Another reason may be the high rate of intravascular imaging in the present study (up to 30% in our study), which was higher than in previous studies (1.2% in the BIONYX study[11]). It is well known that intravascular ultrasound–guided PCI significantly reduces the risk of ST by achieving higher rates of optimal stent dilatation, which is not always possible by angiography alone.[15] However, the ultralow rates of nonfatal events compared to fatal events may suggest underascertainment

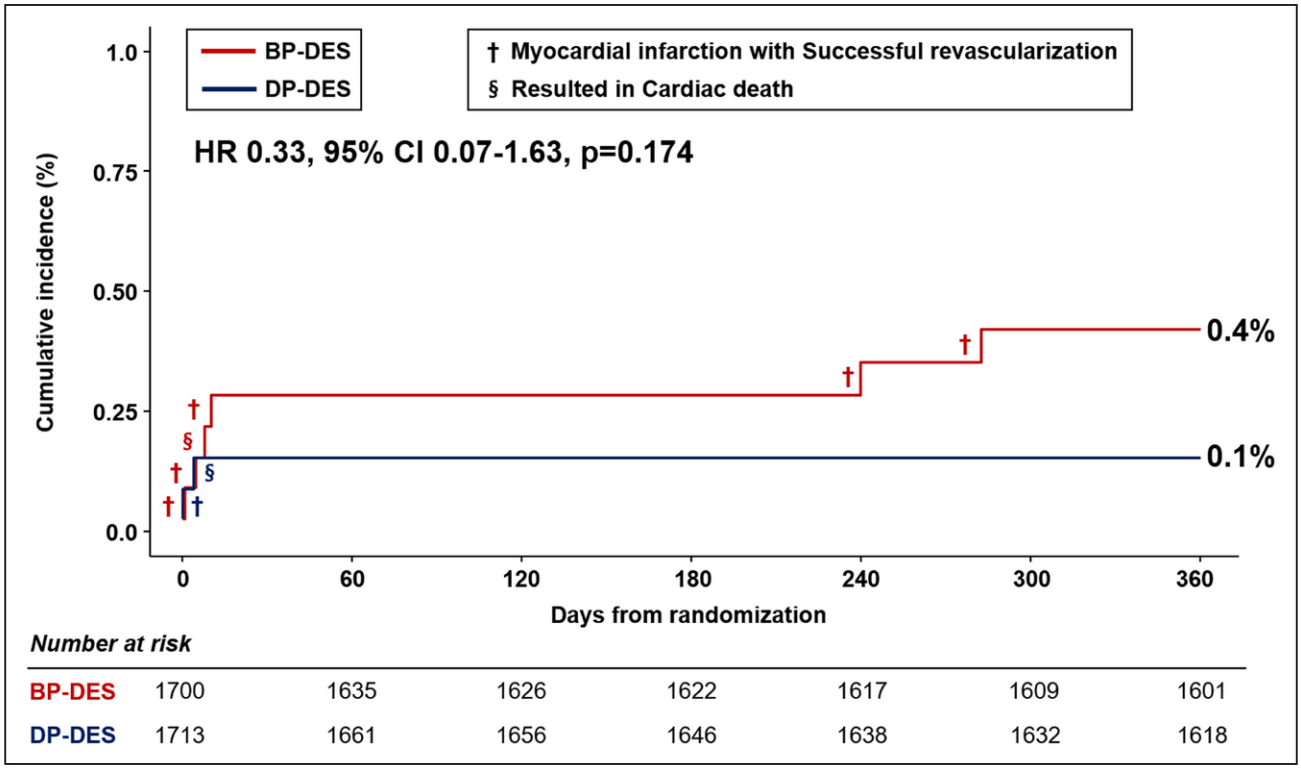

Figure 3. Cumulative incidence of definite or probable stent thrombosis at 12 months' follow-up.
Definite or probable stent thrombosis with clinical consequences are shown. BP-DES indicates biodegradable polymer drug-eluting stent; DP-DES, durable polymer drug-eluting stent; and HR, hazard ratio.

of clinical events which may be an important concern. Also, the higher-than-usual percentage of patients with biomarker-negative ACS and the inclusion of patients in whom PCI was suitable may suggest selection bias toward lower-risk patients in the enrollment of patients and may explain the low rates of clinical outcomes. Therefore, the external validity of our findings to higher-risk patients with ACS and ethnicities beyond East Asians may need to be verified in future studies.

The incidence of ST by groups showed numerically lower rates in the DP-DES group (0.1%) than in the BP-DES group (0.4%). It is notable that all of the late ST cases (2 cases) occurred in those receiving thick-strut BP-DES stents (Biomatrix Flex and Nobori). Previous studies have shown that the thrombogenicity of coronary stent has been related to strut thickness, by areas of recirculation that are created behind thick struts.[16] This turbulence delays neointimal coverage and

Table 4. Specific Stent Type, Lesion Location, Onset Time, and Clinical Result of Definite or Probable Stent Thrombosis Events

No.	DES group	Stent name, size	Lesion location	Definite or probable	Time from index percutaneous coronary intervention	Clinical result
1	DP-DES	Xience Alpine 3.0×33 mm	Proximal left circumflex coronary artery	Definite	Acute (day 0)	Successful revascularization
2	DP-DES	Promus Premier 2.75×32 mm	Proximal left anterior descending coronary artery	Probable	Subacute (day 4)	Cardiac death
3	BP-DES	Ultimaster 2.75×24 mm	Proximal left anterior descending coronary artery	Definite	Acute (day 1)	Successful revascularization
4	BP-DES	Orsiro 2.5×35 mm	Mid left anterior descending coronary artery	Definite	Subacute (day 5)	Successful revascularization
5	BP-DES	Ultimaster 2.75×24 mm	Mid left anterior descending coronary artery	Probable	Subacute (day 8)	Cardiac death
6	BP-DES	Ultimaster 4.0×28 mm	Proximal right coronary artery	Definite	Subacute (day 10)	Successful revascularization
7	BP-DES	Biomatrix Flex 2.5×14 mm	Proximal right coronary artery	Definite	Late (day 243)	Successful revascularization
8	BP-DES	Nobori 3.0×28 mm	Proximal right coronary artery	Definite	Late (day 286)	Successful revascularization

BP-DES indicates biodegradable polymer drug-eluting stent; and DP-DES, durable polymer drug-eluting stent.

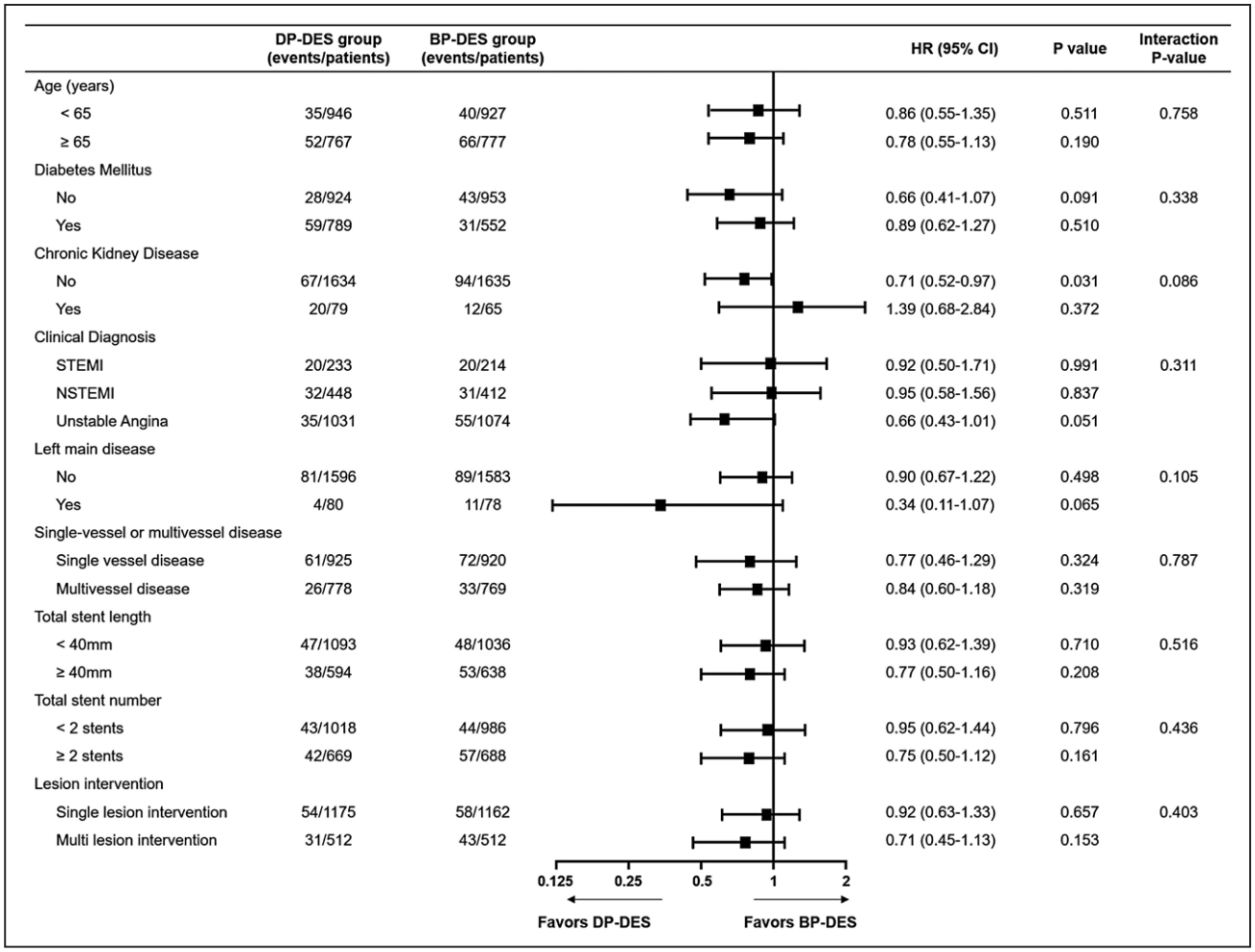

Figure 4. Subgroup analyses.
Subgroup analyses of the primary end point in the DP-DES and BP-DES groups. $P_{interaction}$ represents the likelihood of interaction between the subgroup variable and the treatment strategy. BP-DES indicates biodegradable polymer drug-eluting stent; DP-DES, durable polymer drug-eluting stent; HR, hazard ratio; and STEMI, ST-elevation myocardial infarction.

promotes fibrin deposition and thrombus in the microenvironment around the struts.[17] On the other hand, there is also evidence to suggest that polymers used in the newer DP-DES can be thromboresistant.[18] The fluoropolymer has been shown to reduce the risk of thrombus formation when compared with BMSs. Furthermore, preclinical evidence suggests superior thromboresistance of the fluoropolymer when compared with other biodegradable polymers.[19] However, intravascular imaging studies have not been able to detect any meaningful differences in terms of ST between different polymer technologies.[20,21] Because the risk of ST is affected by both stent-related and -nonrelated factors, the association of polymer technology and the risk of ST is difficult to prove.

Our study has several limitations. First, the present analysis is 1 major arm of the HOST-REDUCE-POLYTECH-ACS, which is a trial with a 2×2 design.[7] Although the 2 arms were independent, such a design carries the risk of power limitation because of multiple testing. Also, our study was an open-label trial where the investigator and patient were not blinded. However, the adjudicators were blinded to the treatment allocation, and the clinical end points were assessed by an independent clinical event adjudication committee. Second, as mentioned previously, the rate of nonfatal events was surprisingly low relative to death. Although we performed active follow-up, periodic site monitoring, and auditing of the source document in at least 50% of cases in each individual center to ensure that all information was properly entered in the electronic case report form, we cannot rule out the possibility of underascertainment of events. This could have critical implications such as making the treatment look safer and more effective than it really is and driving the results of the trial toward noninferiority. Third, the study population was a low-risk ACS population with a large proportion of patients with biomarker-negative ACS (ie, unstable angina). This limits the generalizability of our findings to higher-risk patients with ACS. Fourth, we randomized only the polymer type, and, therefore, various stents were included in each group. Various

stent-related factors, such as the stent design, architecture, strut thickness, type of the antiproliferative drug, and release kinetics are potential factors that may affect clinical outcomes. Especially for the BP-DES group, early-generation BP-DES such as the Biomatrix and Nobori stents were included, whereas the DP-DES group included only second-generation DESs. Although we performed a sensitivity analysis that excluded first-generation BP-DESs with thick stent struts (strut thickness >100 μm) to test whether this had a major effect on outcome and observed consistent results, the heterogeneity of stents remains a major limitation. Fifth, the analysis is limited to only 12 months' follow-up. The true difference in stent performance because of differences in polymer technology may not be apparent at the 12-month follow-up period and may require longer-term follow-up. Considering the pathophysiology of neoatherosclerosis and the fact that the degradation time of biodegradable polymer can extend up to 15 months, a longer duration of follow-up will be necessary to confirm the durable safety and efficacy of DP and BP-DESs. Therefore, we are planning to continue clinical follow-up for at least 3 years. Sixth, although our study was a comparison between DESs, our primary end point was patient-oriented outcomes rather than device-oriented outcomes. Although the rate of DOCO was significantly lower in the DP-DES group, our study was not adequately powered to test this outcome nor the individual components and thus, caution is required in interpreting the results. Last, our primary analysis was based on intention-to-treat. One may argue that a per-protocol analysis may be preferred as the main analysis for noninferiority testing given that it tends to be more conservative. However, the protocol deviation rate was low and balanced between the 2 groups, and we confirmed consistency between intention-to-treat and per-protocol analysis.

Conclusion

In patients with ACS receiving PCI, DP-DESs were noninferior to BP-DESs for POCOs at 12 months. Although the 2 polymer types showed excellent safety and efficacy profiles at 12 months, there was a slightly increased incidence of target lesion revascularization in the BP-DES group.

ARTICLE INFORMATION

Received September 22, 2020; accepted November 3, 2020.

The Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/circulationaha.120.051700.

Correspondence

Kyung Woo Park, MD, PhD, MBA, Department of Internal Medicine, Cardiovascular Center, Seoul National University Hospital, 101 Daehak-ro, Jongro-gu, Seoul 03080, Korea. Email kwparkmd@snu.ac.kr

Affiliations

Seoul National University Hospital, Korea (H-S.K., J.K., D.H., J-K.H., H-M.Y., H-J.K., B-K.K., K.W.P.). Seoul Medical Center, Korea (S.Y.K.). Chosun University Hospital, Gwangju, Korea (K-H.P.). Korea University Guro Hospital, Seoul, Korea (S-W.R.). Soon Chun Hyang University Cheonan Hospital, Cheonan, Korea (W-Y.S.). Ajou University School of Medicine, Suwon, Korea (H-S.L.). Dong-A University Hospital, Busan, Korea (K.P.).

Acknowledgments

J-K.H., H-M.Y., H-J.K., B-K.K., K.W.P., and H-S.K. conceived and designed the study. All authors participated in enrollment of patients and performed clinical follow-up. J.K., D.H., and K.W.P. acquired the data and participated in data analysis and data interpretation. H-S.K., J.K., and K.W.P. wrote the first draft and reviewed and revised the article. All authors approved the final version of the article.

Sources of Funding

This study was supported by Daiichi Sankyo, Boston Scientific, Terumo, Biotronik, Qualitech Korea, and Dio.

Disclosures

H-S.K. has received research grants or speaker's fees from Daiichi Sankyo, Boston Scientific, Terumo, Biotronik and Dio, as well as Medtronic, Abbott Vascular, Edwards Life Science, AmGen, and Behringer Ingelheim. K.W.P. reports fees from Daiichi Sankyo, Astra Zeneca, Sanofi, Bristol-Myers Squibb, Bayer AG, and Pfizer outside of the submitted work. The other authors declare no competing interests.

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