Novel Supreme Drug-Eluting Stents With Early Synchronized Antiproliferative Drug Delivery to Inhibit Smooth Muscle Cell Proliferation After Drug-Eluting Stents Implantation in Coronary Artery Disease Results of the PIONEER III Randomized Clinical Trial

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ORIGINAL RESEARCH ARTICLE

Novel Supreme Drug-Eluting Stents With Early Synchronized Antiproliferative Drug Delivery to Inhibit Smooth Muscle Cell Proliferation After Drug-Eluting Stents Implantation in Coronary Artery Disease

Results of the PIONEER III Randomized Clinical Trial

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BACKGROUND: Accelerated endothelial healing after targeted antiproliferative drug delivery may limit the long-term inflammatory response of drug-eluting stents (DESs). The novel Supreme DES is designed to synchronize early drug delivery within 4 to 6 weeks of implantation, leaving behind a prohealing permanent base layer. Whether the Supreme DES is safe and effective in the short term and can improve long-term clinical outcomes is not known.

METHODS: In an international, 2:1 randomized, single-blind trial, we compared treatment with Supreme DES to durable polymer everolimus-eluting stents (DP-EES) in patients with acute and chronic coronary syndromes. The primary end point was target lesion failure—a composite of cardiac death, target vessel myocardial infarction, or clinically driven target lesion revascularization. The trial was designed to demonstrate noninferiority (margin of 3.58%) of the Supreme DES at 12 months compared with DP-EES (URL: https://www.clinicaltrials.gov; Unique identifier: NCT03168776).

RESULTS: From October 2017 to July 2019, a total of 1629 patients were randomly assigned (2:1) to the Supreme DES (N=1086) or DP-EES (N=543). At 12 months, target lesion failure occurred in 57 of 1057 patients (5.4%) in the Supreme DES group and in 27 of 532 patients (5.1%) in the DP-EES group (absolute risk difference, 0.32% [95% CI, −1.87 to 2.5]; $P_{noninferiority}$=0.002]. There were no significant differences in rates of device success, clinically driven target lesion revascularization, or stent thrombosis at 12 months, and the safety composite of cardiovascular death and target vessel myocardial infarction was 3.5% versus 4.6% (hazard ratio, 0.76 [95% CI, 0.46–1.25]) with Supreme DES compared with DP-EES, although rates of combined clinically and non–clinically driven target lesion revascularization at 12 months were higher with Supreme DES.

CONCLUSIONS: Among patients with acute and chronic coronary syndromes undergoing percutaneous coronary intervention, the Supreme DES proved to be noninferior to the standard DP-EES.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT03168776.

Key Words: acute coronary syndrome ■ drug-eluting stents ■ single-blind method ■ stents

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Clinical Perspective

What Is New?

- This novel biodegradable drug-eluting stent (DES) targets early antiproliferative drug delivery and polymer degradation within 4 to 6 weeks of implantation, leaving behind a permanent electrografted base layer (Supreme DES) to promote endothelial recovery.
- The Supreme DES was compared with durable polymer DES (DP-DES) in a 2:1 randomized trial of 1632 patients with acute and chronic coronary syndromes.

What Are the Clinical Implications?

- The Supreme DES was noninferior to the durable polymer everolimus-eluting stent for the primary end point of target lesion failure at 12 months.
- Superiority of the Supreme DES to durable polymer DES with respect to long-term outcomes will be evaluated at 5-year follow-up.
- Whether this targeted DES therapy affects outcomes in the longer term will be evaluated at 5 years after percutaneous coronary intervention.

Nonstandard Abbreviations and Acronyms

ACS	acute coronary syndrome
cTnI	cardiac troponin I
cTnT	cardiac troponin T
DES	drug-eluting stent
DP-EES	durable polymer everolimus-eluting stent
HR	hazard ratio
MACE	major adverse cardiac event
PCI	percutaneous coronary intervention
PIONEER III	PIONEER III Trial to Assess Safety and Efficacy of the BuMA Supreme Drug Coated Coronary Stent in Patients with Coronary Disease
TLF	target lesion failure
TLR	target lesion revascularization

New or second-generation drug-eluting stents (DESs) reduce device-related adverse clinical outcomes, including target lesion revascularization and stent thrombosis, compared with bare-metal stents,[1] and are the current standard of care for patients undergoing percutaneous coronary intervention (PCI) across the spectrum of coronary syndromes.[2–5] Despite significant improvements, repeated intervention is required at an annual rate of 2% to 3% and life-threatening late and very-late stent thrombosis persists.[6,7] Contemporary DES have emphasized prolonged antiproliferative drug delivery to suppress smooth muscle cell proliferation to mitigate the vasculoproliferative response to arterial injury, which delays endothelialization and may be associated with hypersensitivity reactions and neoatherosclerosis.[8] These contribute to late DES failure including restenosis and stent thrombosis.[9] Even DESs with biodegradable polymer coatings intended to limit the inflammatory response resulting from prolonged polymer degradation have not shown conclusive improvements in clinical outcomes.[10,11] The aim of restoring a more functional endothelial barrier and regaining some physiological vascular functions after DES implantation are likely to minimize the inflammatory response and regulate vascular smooth muscle cell proliferation.[12,13] Important DES characteristics beyond the stent surface itself, including strut thickness, polymer and drug density, and degradation and elution kinetics, are necessary to balance the suppression of vascular smooth muscle cell proliferation and the rapid restoration of a functional endothelium.[14] The Supreme DES (SINOMED, Tianjin, China) is designed to promote healing, rather than suppress vascular smooth muscle cell proliferation over an extended duration, and allow the functional endothelium to recover its biological functions of suppressing thrombosis and smooth muscle proliferation. By design, it targets antiproliferative drug delivery of sirolimus within an early therapeutic window (coinciding with the smooth muscle cell proliferative response that occurs 4 to 6 weeks after DES implantation), after which the polymer matrix degrades to leave behind a stent surface with a biostable ultrathin coating that facilitates complete reendothelialization.[14] PIONEER III (PIONEER III Trial to Assess Safety and Efficacy of the BuMA Supreme Drug Coated Coronary Stent in Patients with Coronary Disease) is designed to evaluate the safety and effectiveness of Supreme DES compared with contemporary durable polymer everolimus-eluting stents (DP-EES).

METHODS

Transparency and Openness Promotion

The trial data were collected in an electronic data capture system and held in a database, accessible by approved individuals of the data management team (Cardiovascular Research Foundation, New York, NY). After all powered trial end points have been assessed at 5-year follow-up, the study publication committee will accept public requests for access to study data and analysis methods for the purposes of reproducing study results or evaluating additional research questions.

Study Design and Participants

PIONEER III is a prospective, randomized, single-blind, multicenter trial conducted at 74 investigational sites in North America, Europe, and Japan (see the Data Supplement). Included were adult male and nonpregnant female patients between the ages of 20 and 99 years with symptomatic ischemic heart disease including chronic coronary syndromes with evidence of ischemia, unstable angina or non–ST-segment elevation myocardial infarction who required elective or urgent PCI. Angiographic criteria were PCI of a de novo major coronary artery or branch target vessel with a reference diameter range of ≥2.25 to ≤4.00 mm and an estimated visual diameter stenosis ≥50% and <100%. ST-segment elevation myocardial infarction, unprotected left main coronary artery disease, known left ventricle ejection fraction <30%, or cardiogenic shock were among the exclusion criteria (Table II in the Data Supplement).

Randomization and Masking

Patients who satisfied both inclusion and exclusion criteria were randomized in a 2:1 ratio to Supreme DES or DP-EES. Randomization was performed using an Interactive Web Response System and stratified by presentation (ACS vs. chronic coronary syndrome), diabetes status, and study center. Patients were randomized after successful treatment, when applicable, of any single nontarget lesion located in a different epicardial vessel from the target lesion. The study was a single-blind study with treatment assignment available to treating physicians. The patient, their family, site personnel conducting follow-up evaluations, members of the clinical events committee, and the angiographic core laboratory were blinded to randomization.

Devices and Procedures

The Supreme DES is a balloon-expandable biodegradable polymer sirolimus-eluting coronary stent system targeting early vascular healing (Figure I in the Data Supplement). The stent platform is a laser cut L605 Cobalt Chromium alloy tube that is electropolished to a nominal strut thickness of 80 μm. Stent struts are covered by a nanometric (≈200 nm), nonerodable brush of poly(n-butyl methacrylate) that is covalently bonded to the metal surface through a proprietary electrografting process (Figure II in the Data Supplement).[15] The durable proprietary electrografting process base layer functions as Velcro to anchor the biodegradable sirolimus-containing topcoat through a process of interdigitation (ie, it secures the adhesion of the topcoat without reactive functions). The nonreactive proprietary electrografting process base layer is designed to (1) secure strong adhesion of the topcoat to prevent polymer cracking and delamination during implantation; (2) accelerate healing after degradation of the topcoat by providing an optimal substrate for rapid endothelialization; and (3) prevent corrosion and heavy metal ion release from the underlying stent. The topcoat (3–10 μm thick) consists of a PLGA (poly[lactic-co-glycolic acid]) biodegradable polymer with sirolimus embedded at a drug density of 1.2 μg/mm^2. The drug release kinetics are designed to be synchronous with the smooth muscle cell proliferation process. By 28 days, >90% of sirolimus is eluted, and both the drug and topcoat are completely resorbed within 4 to 6 weeks.[16,17]

The control DP-EES (Xience; Abbott Vascular, Santa Clara, CA; Promus; Boston Scientific Corporation, Maple Grove, MN) is a laser-cut cobalt chromium stent of 81-μm strut thickness coated with a 7.8-μm durable fluoride–hexafluoropropylene polymer. The everolimus drug density is 1 μg/mm^2 and is released by 120 days. Matching DP-EES sizes were permitted, including lengths of 8 to 38 mm and diameters of 2.25 to 4.0 mm. The design, safety, and efficacy of the DP-EES has been extensively characterized.[18]

Stent implantation was performed according to local standard practice and manufacturer instructions. Nontarget lesions were treated before randomization with regionally approved and commercially available devices. Patients were treated with dual antiplatelet therapy consisting of aspirin and a P2Y12 inhibitor (clopidogrel, ticagrelor, prasugrel) for at least 6 months in chronic coronary syndromes and at least 12 months in patients with acute coronary syndromes (ACSs) in accordance with published guidelines.[19,20] Cardiac biomarkers (cTnI [cardiac troponin I] or cTnT [cardiac troponin T] or creatine kinase myocardial band) were measured within 24 to 48 hours before PCI and within 12 hours after PCI. Patients had follow-up for adverse events at 1, 6, and 12 months after PCI. Planned follow-up will be annually for 5 years.

Outcomes

The primary end point was the device-oriented outcome of target lesion failure (TLF) at 12 months. TLF is defined as the composite of cardiac death, target vessel myocardial infarction, and clinically driven target lesion revascularization (TLR). Secondary end points included the components of the primary end point, death (cardiac and noncardiac), myocardial infarction according to the modified Third Universal Definition,[21] target vessel failure (composite of cardiac death, target vessel myocardial infarction, and target vessel revascularization), major adverse cardiac events ([MACE] composite of all cause death, myocardial infarction, and target vessel revascularization), bleeding complications defined by the Bleeding Academic Research Consortium,[22] and stent thrombosis defined by the Academic Research Consortium[23] at all time points (see Data Supplement). Procedure related secondary outcomes include lesion success, defined as attainment of <30% residual stenosis of the target lesion measured by quantitative coronary angiography, and device success defined as lesion success using the assigned device. All protocol defined end points were adjudicated by an independent clinical event committee (Cardiovascular Research Foundation, New York, NY) (see Data Supplement).

Statistical Analysis

PIONEER III is a premarket US investigational device exemption trial designed to test noninferiority of the primary outcome of TLF at 12 months with Supreme DES compared with DP-EES. The event rate in the control group at 12 months was derived from 14 randomized clinical trials representing a total of 13 833 patients treated with commercially available DP-EES (online protocol). Assuming a 6.5% event rate in the control group at 12 months, no difference between groups, a noninferiority margin of 3.58%, a 1-sided type 1 error of 0.025, and an attrition rate of 5% at 12 months, a total sample size of 1632 patients (1088 Supreme DES; 544 DP-EES) would provide 80% power to demonstrate noninferiority of Supreme DES using the Farrington–Manning approach. The noninferiority margin of 3.58% for the primary end point was based on a meta-analysis of historical trials establishing that a conservative estimate (lower bound 90% CI) of the treatment effect of the control comparator (DP-EES) compared with bare-metal stents was 9.0% for the primary outcome of TLF at 1 year.[24]

The selected noninferiority margin of 3.58% therefore preserves >60% of the risk reduction provided by the control using the fixed margin approach, which is more conservative than the usual 50% control effect size used in similar cardiovascular outcomes studies.[25] If the primary end point is met, a planned powered secondary end point will test superiority of TLF between 1- and 5-year follow-up in a landmark analysis, assuming a hazard ratio (HR) of 0.52 in the intervention group compared with control (see the Data Supplement).

The intention-to treat-population, which includes all randomized patients in the assigned treatment group regardless of treatment actually received, is the primary analysis population for the primary safety and efficacy end point and all secondary end points. The per protocol population, defined as randomized patients meeting all major eligibility criteria with an attempt to implant the assigned study stent, was the secondary analysis population for the primary and all secondary end points (see the Data Supplement). A tipping point analysis was performed to assess the impact of loss to follow-up (see the Data Supplement).

Categorical variables are reported as counts and percentages and compared between treatment groups using χ^2 or Fisher exact test. Continuous variables are presented as mean and SD and compared with 2-sample *t* test. If the data failed to meet the assumption for normality per the Shapiro–Wilk test, then the comparisons were made using the Wilcoxon rank-sum test. Time-to-event outcomes were calculated using Kaplan–Meier methods and compared between groups using the log-rank test. Cox proportional hazards analysis was used to calculate HRs with 95% CI and *P* values. Unless otherwise specified, a 2-sided *P* value of less than 0.05 was considered to indicate statistical significance. Statistical analyses were done using SAS software version 9.4 by the Cardiovascular Research Foundation.

Trial Oversight and Role of the Funding Source

The protocol, overall conduct and analysis of the trial were overseen by the Executive Committee (Table I in the Data Supplement). The trial was conducted in compliance with the protocol, the US Food and Drug Administration regulations, the International Conference on Harmonisation Good Clinical Practice guidelines, and the Declaration of Helsinki. All patients provided written informed consent before any study-specific procedures or assessments were administered. The protocol was approved by the applicable institutional review board or ethics committee at each center before subject enrollment. An independent data safety monitoring board oversaw patient safety throughout the trial, an independent clinical events committee adjudicated all potential end point events, an independent statistical analysis (Cardiovascular Research Foundation, NY), and an independent angiographic core laboratory analyzed all the angiograms (Yale Cardiovascular Research, Yale School of Medicine, New Haven, CT). Monitoring was performed by IQVIA (Durham, NC).

Table 1. Baseline Characteristics in the Intention-to-Treat Population

Characteristics	Supreme DES (N=1086 patients)	DP-EES (N=543 patients)
Age, y	64.53±9.83	63.93±10.26
Female, n (%)	258 (23.8)	148 (27.3)
Smoker (current/previous), n (%)	665 (61.2)	322 (59.4)
Diabetes, n (%)	331(30.5)	163 (30.1)
Insulin treatment, n (%)	111 (10.2)	55 (10.1)
Hypertension, n (%)	806 (74.2)	379 (69.9)
Hypercholesterolemia, n (%)	837 (77.1)	413 (76.2)
Family history of CAD, n (%)	377 (34.7)	199 (36.7)
Previous MI, n (%)	189 (17.4)	101 (18.6)
Previous PCI, n (%)	304 (28.0)	166 (30.6)
Previous CABG, n (%)	53 (4.9)	23 (4.2)
Previous stroke, n (%)	46 (4.2)	19 (3.5)
Renal insufficiency, n (%)	86 (7.9)	43 (7.9)
Peripheral arterial disease, n (%)	56 (5.2)	28 (5.2)
Atrial fibrillation, n (%)	22 (2.0)	13 (2.4)
Clinical presentation		
Stable angina, n (%)	536 (49.4)	269 (49.6)
Silent ischemia, n (%)	109 (10.0)	41 (7.6)
Unstable angina, n (%)	218 (20.1)	114 (21.0)
NSTEMI, n (%)	223 (20.5)	118 (21.8)
Number of diseased vessels		
1, n (%)	788 (72.6)	375 (69.2)
2, n (%)	213 (19.6)	128 (23.6)
≥3, n (%)	85 (7.8)	39/542 (7.2)
Procedure characteristics		
Number of vessels treated per patient*	1.11±0.32	1.14±0.34
Multiple vessels treated, n (%)	122 (11.2)	74 (13.7)
Number of lesions per patient*	1.2±0.5	1.3±0.5
1 target lesion, n (%)	889 (81.9)	421 (77.8)
2 target lesions, n (%)	172 (15.8)	104 (19.2)
3 target lesions, n (%)	25 (2.3)	16 (3)
Number of stents per patient*	1.2±0.6	1.3±0.6
Radial/brachial access, n (%)	885 (81.5)	431 (79.6)
Femoral access, n (%)	201 (18.5)	111 (20.5)
Hemostasis device use, n (%)	808 (74.4)	389 (71.8)

CABG indicates coronary artery bypass graft; CAD, coronary artery disease; DES, drug-eluting stent; DP-EES, durable polymer everolimus-eluting stent; MI, myocardial infarction; NSTEMI, non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-segment elevation myocardial infarction.

*Mean±SD.

RESULTS

From October 2017 to July 2019, a total of 1629 (of 1631) consented patients recruited from North America (50.1%), Europe (39.9%), and Japan (10%) were randomly assigned to Supreme DES (1086 patients with 1304 lesions) or DP-EES (543 patients with 677 lesions). Follow-up at 12 months was complete in 96.9% (1036 of 1069) of Supreme DES and

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Table 2. Procedural Characteristics and Angiographic Results (Per-Lesion Analysis)

	Supreme DES (site lesions, N=1304; QCA lesions, N=1283*)	DP-EES (site lesions, N=677; QCA lesions, N=662*)	*P* value
Stent implantation characteristics			
Number of stents per lesion†	1.1±0.3	1.1±0.3	0.23
Stented lesion length, mm†	20.81±8.17	20.44±7.94	0.34
Maximum stent diameter, mm†	2.98±0.40	3.00±0.43	0.42
Procedure characteristics			
FFR performed, n (%)	98 (7.5)	55 (8.1)	0.63
IVUS performed, n (%)	200 (15.3)	100 (14.8)	0.74
Predilation, n (%)	1022 (78.4)	485 (71.6)	0.0009
Postdilation, n/N (%)	678/1296 (52.3)	353/673 (52.5)	0.96
Target vessel location*			
LAD, n (%)	582 (45.4)	290 (43.8)	0.35
LCX, n (%)	334 (26.0)	158 (23.9)	0.50
RCA, n (%)	366 (28.5)	214 (32.3)	0.09
Left main, n (%)	1 (0.1)	0 (0)	1.00
American Colleges of Cardiology/American Heart Association lesion classification*			
A, n (%)	99 (7.7)	65 (9.8)	0.12
B1, n (%)	324 (25.3)	167 (25.2)	0.97
B2, n (%)	342 (26.7)	189 (28.5)	0.38
C, n (%)	518 (40.4)	241 (36.4)	0.11
B2/C, n (%)	860 (67.0)	430 (65)	0.38
Calcification (moderate/severe), n/N (%)	446/1281 (34.8)	218/662 (32.9)	0.54
Eccentric, n/N (%)	323/1281 (25.2)	156/661 (23.6)	0.44
Tortuosity (moderate/severe), n/N (%)	268/1281 (20.9)	153/662 (23.1)	0.29
Bifurcation, n (%)	282 (22)	142 (21.5)	0.80
Bifurcation side branch treatment, n (%)	26 (2)	18 (2.7)	0.32
Baseline QCA results*			
Reference diameter, mm‡	2.78±0.44	2.79±0.44	0.87
Minimal lumen diameter, mm‡	0.93±0.39	0.93±0.39	0.67
Percent diameter Stenosis, %‡	66.62±12.99	66.40±12.96	0.70
Lesion length, mm§	15.28±7.55	14.82±7.04	0.19
Final QCA results*			
In-stent MLD, mm ‖	2.66±0.40	2.68±0.39	0.23
In-stent percent diameter stenosis, % ‖	8.35±4.61	7.95±4.70	0.07
In-stent acute gain, mm ‖	1.74±0.46	1.75±0.46	0.63
Segment MLD, mm¶	2.56±0.42	2.58±0.42	0.26
Segment percent diameter stenosis, %¶	9.93±4.48	9.81±4.34	0.57
Segment acute gain, mm¶	1.63±0.47	1.64±0.47	0.61

DES indicates drug-eluting stent; DP-EES, durable polymer everolimus-eluting stent; FFR indicates fractional flow reserve; IVUS, intravascular ultrasound; LAD, left anterior descending; LCX, left circumflex; LM, left main; MLD, minimal lumen diameter; QCA, quantitative coronary angiography; and RCA, right coronary artery.

*Results reported based on Angiographic Core Laboratory analysis.

†Mean±SD.

‡Total number of lesions is 1281 for Supreme DES and 662 for DP DES.

§Total number of lesions is 1275 for Supreme DES and 662 for DP DES.

‖Total number of lesions is 1268 for Supreme DES and 654 for DP DES.

¶Total number of lesions is 1275 for Supreme DES and 656 for DP DES.

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98.3% (521 of 530) of DP-EES groups (Figure III in the Data Supplement). Baseline clinical and lesion characteristics were matched between groups with 41.3% (673 of 1628) of patients presenting with ACS, 28.6% (465 of 1628) multivessel disease, 12% (196 of 1628) requiring treatment of ≥2 vessels and 19.5% (317 of 1627) had ≥2 lesions treated. Radial access was used in 80.3% (1308 of 1628) of cases (Table 1). PCI guidance with fractional flow reserve (7.7% [153 of 1981]) and intravascular ultrasound (15.1% [300 of 1981]) was used in a minority of cases. Most treated lesions (66.3% [1290 of 1945]) were complex, meeting American College of Cardiology/American Heart Association type B2 or type C criteria for coronary lesions. Stent lengths included in the trial ranged from 10 to 35 mm in increments of 5 mm, and stent diameters for all the available lengths ranged from 2.25 to 4.0 mm in quarter sizes.

Lesions were more commonly predilated in the Supreme DES compared with the DP-EES group, with no difference in postdilation rates or pressures. There were no differences between groups in the final quantitative coronary angiography measures of minimal lumen diameter, percentage diameter stenosis, or acute gain (Table 2). Lesion success for Supreme DES versus DP-EES (99.7% [1271 of 1275] vs. 99.5% [653 of 656], respectively; P=0.62) and device success (97.3% [1212 of 1246] vs. 98.9% [640 of 648], respectively; P=0.07) were no different between groups (Table III in the Data Supplement). Dual antiplatelet therapy duration was no different in the 2 groups. At discharge, 99.0% (1075 of 1086) of Supreme DES and 99.3% (538 of 542) of DP-EES patients were prescribed dual antiplatelet therapy, and at 12 months, 82.8% (869 of 1050) of Supreme DES and 83.0% (436 of 525) of DP-EES remained on dual antiplatelet therapy (Table IV in the Data Supplement).

The primary 12-month TLF end point occurred in 57 of 1057 (5.4%) patients in the Supreme DES group and 27 of 532 (5.1%) patients in the DP-EES group

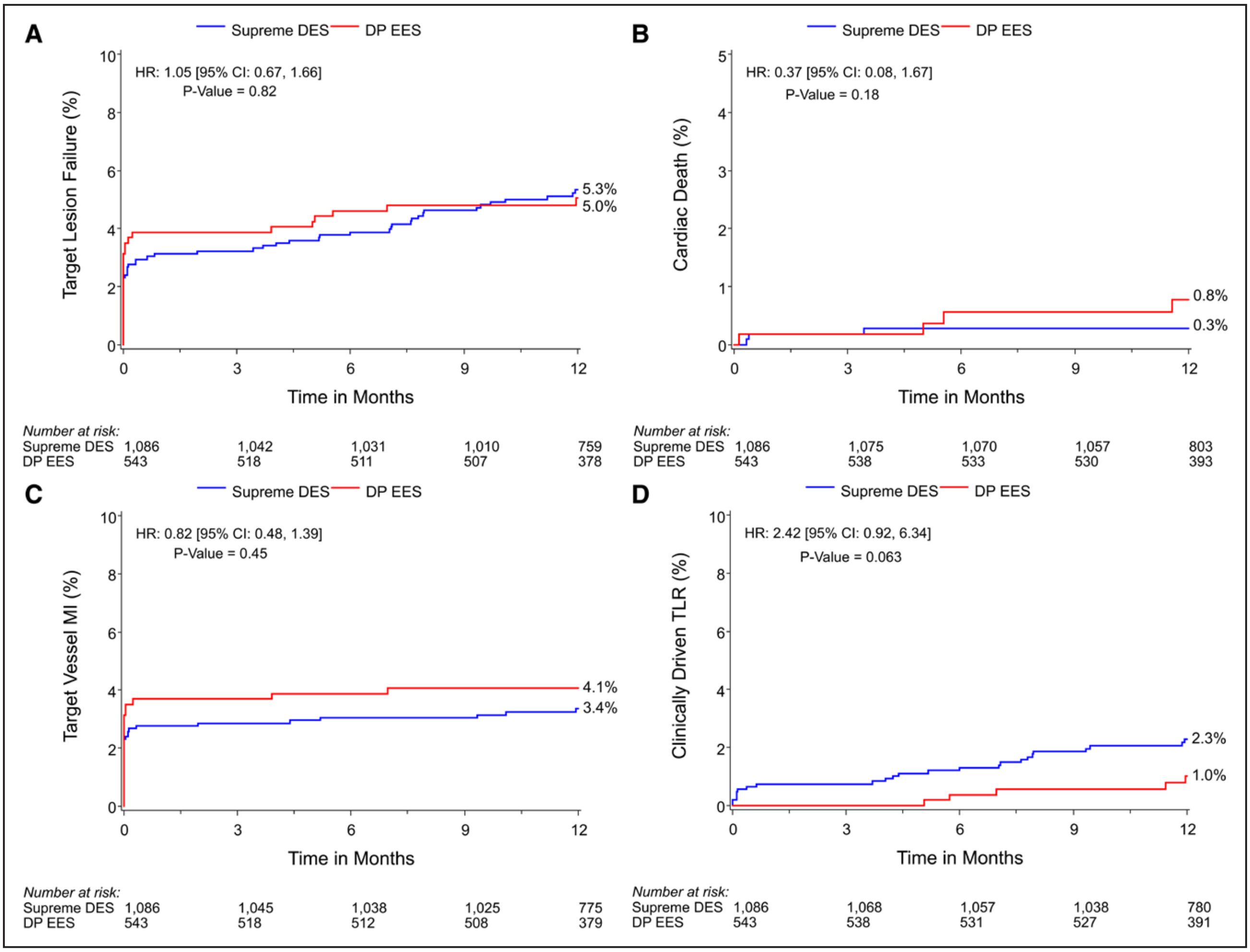

Figure 1. Kaplan–Meier time-to-event curves for the primary outcome and its components.
A, Primary outcome of target lesion failure. **B**, Death from cardiac causes. **C**, Target vessel myocardial infarction. **D**, Clinically driven target lesion revascularization. Data for patients who were lost to follow-up or who withdrew from the trial before 1 year were censored at the end of follow-up. DES indicates drug-eluting stent; DP EES, durable polymer everolimus-eluting stent; HR, hazard ratio; MI, myocardial infarction; and TLR, target lesion revascularization.

(absolute risk difference, 0.32 [95% CI, −1.87 to 2.50]; $P_{noninferiority}$=0.002), meeting the noninferiority criteria (upper bound of 95% CI, 2.50%) for the absolute risk difference (<3.58%) noninferiority margin in the intention-to-treat analysis (Figure 1). In the per-protocol population, TLF occurred in 57 of 1053 (5.4%) Supreme DES patients and in 27 of 531 (5.1%) DP-EES patients (absolute risk difference, 0.33 [95% CI, −1.86 to 2.52]; $P_{noninferiority}$=0.002) (Table V in the Data Supplement).

The components of the primary outcome for Supreme DES versus DP-EES, including cardiac death (0.3% vs. 0.8%; HR, 037 [95% CI, 0.08–1.67]; P=0.18), target vessel myocardial infarction (3.4% vs. 4.1%; HR, 0.82 [95% CI, 0.48–1.39]; P=0.45), and clinically driven TLR (2.3% vs. 0.9%; HR, 2.42 [95% CI, 0.92–6.34]; P=0.06), were not significantly different between the 2 groups (Figure 1). There were no significant between group differences at 12 months in major secondary end points including major

Table 3. Primary and Secondary Clinical Outcomes at 12 Months After Stent Implantation (Intent-to-Treat Population)

	Supreme DES (N=1086)	DP-EES (N=543)	Hazard ratio (95% CI)	*P* value
Primary outcome				
TLF, n (%)*	57 (5.4)	27 (5.1)	NA	NA
Components of primary outcome				
Cardiac death, n (%)	3 (0.3)	4 (0.8)	0.37 (0.08±1.67)	0.18
TVMI, n (%)	36 (3.4)	22 (4.1)	0.82 (0.48±1.39)	0.45
Clinically-driven TLR, n (%)	24 (2.3)	5 (1.0)	2.42 (0.92±6.34)	0.06
Secondary outcomes				
TVF, n (%)†	66 (6.2)	34 (6.3)	0.97 (0.64±1.46)	0.87
Cardiac death, n (%)	3 (0.3)	4 (0.8)	0.37 (0.08±1.67)	0.18
TVMI, n (%)	36 (3.4)	22 (4.1)	0.82 (0.48±1.39)	0.45
Periprocedural, n (%)	25 (2.3)	19 (3.5)	0.66 (0.36±1.19)	0.16
Spontaneous, n (%)	12 (1.1)	5 (1.0)	1.20 (0.42±3.41)	0.73
Clinically-driven TVR, n (%)	38 (3.6)	16 (3.0)	1.19 (0.66±2.13)	0.56
Cardiovascular death, TVMI, all TLR, n (%)	60 (5.6)	27 (5.4)	1.11(0.70±1.75)	0.65
All TLR, n (%)	26 (2.5)	5 (1.0)	2.62 (1.01±6.83)	0.040
MACE, n (%)‡	79 (7.4)	39 (7.2)	1.01 (0.69±1.48)	0.82
All death, n (%)	6 (0.6)	8 (1.5)	0.37 (0.13±1.08)	0.059
All MI, n (%)	51 (4.8)	24 (4.4)	1.06 (0.65±1.72)	0.81
Periprocedural, n (%)	27 (2.5)	20 (3.7)	0.67 (0.38±1.20)	0.17
Spontaneous, n (%)	25 (2.4)	6 (1.2)	2.10 (0.86±5.11)	0.10
All TVR, n (%)	40 (3.8)	16 (3.0)	1.25 (0.70±2.24)	0.44
All revascularization, n (%)	55 (5.2)	21 (4.0)	1.32 (0.80±2.18)	0.28
Definite stent thrombosis, n (%)	6 (0.6)	2 (0.4)	1.50 (0.30±7.43)	0.62
Acute (0–30 days), n (%)	5 (0.5)	2 (0.4)	1.25 (0.24±6.44)	0.79
Late (31–365 days), n (%)	1 (0.1)	0 (0.0)	NA	0.48
Definite/probable stent thrombosis, n (%)	8 (0.7)	2 (0.4)	2.00 (0.42±9.42)	0.37
Acute (0–30 days), n (%)	7 (0.6)	2 (0.4)	1.75 (0.36±8.42)	0.48
Late (31–360 days), n (%)	1 (0.1)	0 (0.0)	NA	0.48
Definite stent thrombosis, n (%)	6 (0.6)	2 (0.4)	1.50 (0.30±7.43)	0.62
Any bleeding (BARC definition), n (%)	31 (2.9)	17 (3.2)	0.91 (0.50±1.64)	0.75
BARC 3 or 5, n (%)	24 (2.3)	5 (0.9)	2.41 (0.92±6.32)	0.06

For the primary end point analysis, only patients with appropriate follow-up >335 days postprocedure or those with an event were included in the denominator. Secondary end points are reported using Kaplan–Meier estimates. BARC indicates Bleeding Academic Research Consortium; DES, drug-eluting stent; DP-EES, durable polymer everolimus-eluting stent; MACE, major adverse cardiac event; MI, myocardial infarction; NA, not applicable; TLF, target lesion failure; TLR, target lesion revascularization; TVF, target vessel failure; TVMI, target vessel–related myocardial infarction; and TVR, target vessel revascularization.

*TLF = composite rate of cardiac death, TVMI, and clinically-driven TLR.

†TVF = composite rate of cardiac death, TVMI, and clinically–driven TVR.

‡MACE = composite rate of all-cause death, MI, and TVR.

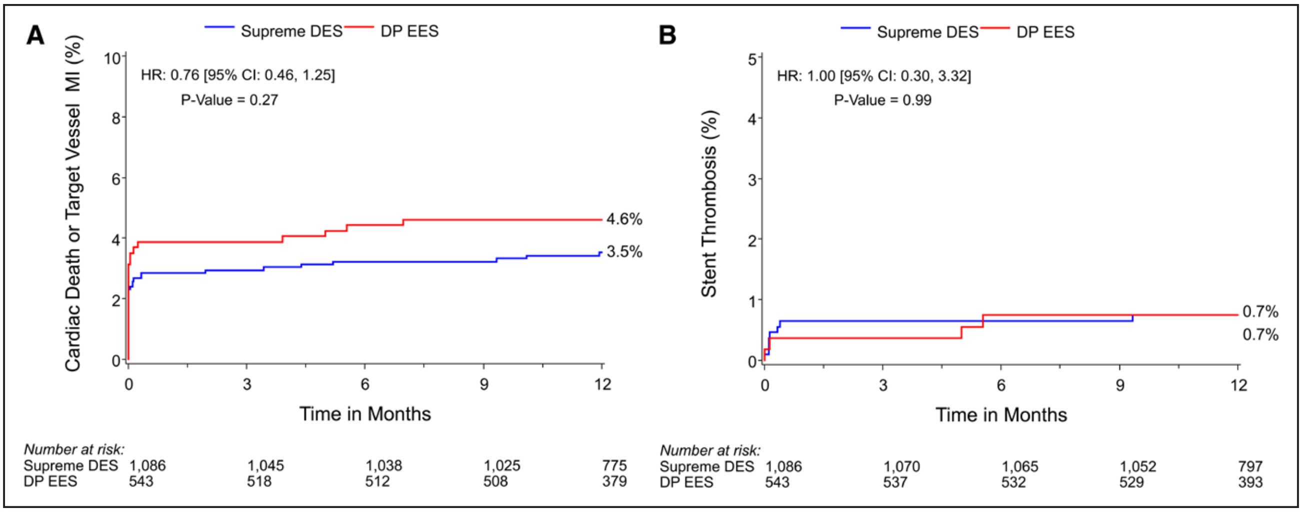

Figure 2. Kaplan–Meier time-to-event curves for the secondary safety outcomes.
A, Composite of cardiac death and target vessel myocardial infarction. **B**, Stent thrombosis (definite, probably, and possible). DES indicates drug-eluting stent; DP EES, durable polymer everolimus-eluting stent; HR, hazard ratio; and MI, myocardial infarction.

adverse cardiac events, target vessel failure, periprocedural myocardial infarction (2.5% vs. 3.7%; HR, 0.67 [95% CI, 0.38–1.20]; P=0.17), composite cardiovascular death and target vessel myocardial infarction (3.5% vs. 4.6%; HR, 0.76 [95% CI, 0.46–1.25]; P=0.27), definite or probable stent thrombosis (0.7% vs. 0.4%; HR, 2.00 [95% CI, 0.42–9.42]; P=0.37), and any stent thrombosis (0.7% vs. 0.7%; HR, 1.00 [95% CI, 0.30–3.32]; P=0.99). There was no difference in early stent thrombosis (≤30 days; 0.6% vs. 0.4%; P=0.48) or late stent thrombosis (0.1% vs. 0.4%; P=0.22) with Supreme DES compared with DP-EES (Table 3, Figure 2; Figures IV and V in the Data Supplement). Clinically and non–clinically driven TLR at 12 months favored the control DP-EES (2.5% vs. 1.0%; HR, 2.62 [95% CI, 1.01–6.83]; P=0.04). There were no differences in the primary end point in any of the prespecified high-risk subgroups (Figure 3). The composite of cardiac death, target vessel myocardial infarction, and all TLRs was not different between groups (Table 3).

DISCUSSION

This large, prospective, multicenter, randomized trial conducted internationally across 3 regions demonstrated that the Supreme DES was noninferior to the well-established DP-EES for TLF at 1 year, with consistent results across all subgroups. All adjudicated component safety measures including cardiac death, myocardial infarction, and stent thrombosis rates were equally low in both treatment groups. Clinically driven TLR was numerically, but not significantly, higher with Supreme DES, whereas combined clinically and non–clinically driven TLR was higher with Supreme DES. Acute success rates with this first introduction of the Supreme DES, using mostly radial access, matched the widely available DP-EES benchmark.

PIONEER III confirms previous evidence that, in an expanded population comprised of 41% ACS, 28% multivessel disease, and 66% complex lesions, the Supreme DES performed as well as the best-in-class DP-EES. The previous European PIONEER trial, in which 170 patients with mostly chronic coronary syndromes and less complex lesions were randomized to Supreme DES or Resolute Integrity DES (Medtronic, Minneapolis, MN), demonstrated no difference in TLF rates (4.9% vs. 5.7%; P=0.72) between groups.[17] The PIONEER III trial is the first Chinese-designed and -manufactured DES to undergo the evaluation rigors of a US and Japanese approval study, validating the previous clinical evaluation performed in both China and Europe—and representing a growing trend in globalization of medical devices across markets.

The Supreme DES is designed to address the shortcomings observed in both durable polymer and biodegradable polymer drug-eluting stents, namely a ≈2 to 3% annual accrual of device-related clinical events.[7] These late stent-related events have been attributed, in part, to hypersensitivity reactions, neoatherosclerosis (≈50% with DP-EES vs. <20% with bare-metal stents), or thrombosis related to delayed endothelial healing.[26–28] Biodegradable polymer DESs gradually degrade polymer to biostable water and carbon dioxide to reduce or eliminate polymer-related long-term inflammation. However, most biodegradable polymer DESs have prolonged polymer degradation times ranging from 3 to 15 months which may delay healing and explain the general lack of clinical benefit with this class of devices in the longer 3- to 5-year term.[29–34]

The Supreme DES is specifically designed to minimize polymer exposure by early synchronized delivery of antiproliferative drug and polymer degradation, leaving behind a biostable base layer to restore endothelial function and vascular homeostasis early as a prereq-

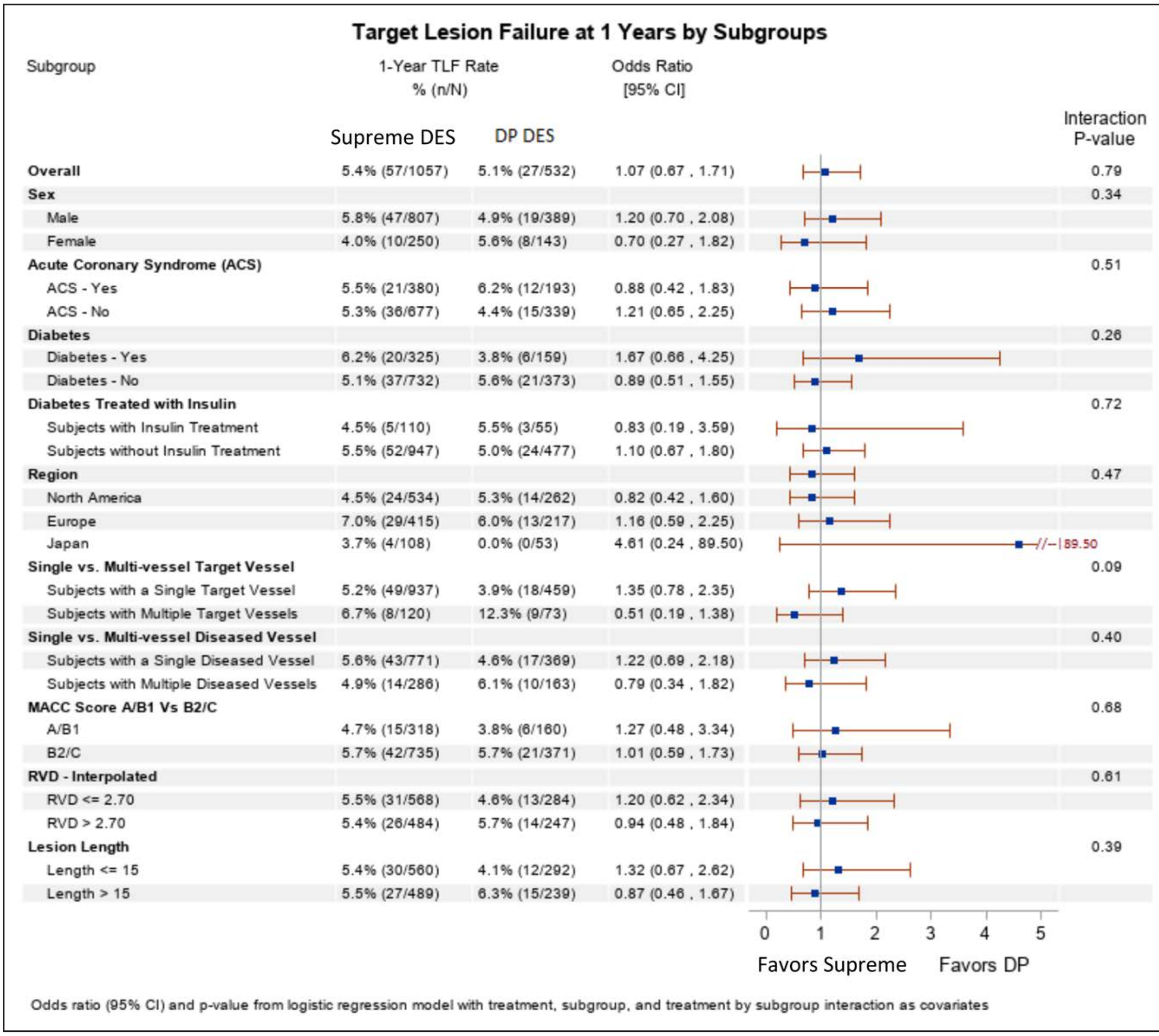

Figure 3. Subgroup analysis of primary outcome of target lesion failure for predefined patient and lesion characteristics.
DES indicates drug-eluting stent; DP DES, durable polymer everolimus-eluting stent; MACC, Modified American College of Cardiology Criteria; RVD, reference vessel diameter; and TLF, target lesion failure.

uisite to improved long-term event-free survival.[35,36] An in vivo porcine study using Evans Blue and P120/VE-cadherin costaining demonstrated reduced endothelial permeability with Supreme DES compared with DP-EES.[37] These findings, along with optical coherence tomography demonstrating more complete stent strut coverage after 1 month with Supreme compared with DP-EES (83.8±10.4% vs. 73.0±17.5%; P=0.037),[38] provide evidence for earlier healing and restoration of endothelial function with Supreme DES. Whether these findings translate into superior long-term clinical outcomes remains to be proven.

By design, the PIONEER III trial demonstrated noninferiority of TLF with the Supreme DES compared with the DP-EES, with low rates of target vessel failure, target vessel myocardial infarction, and stent thrombosis. These results, combined with the safety measures of the composite of cardiovascular death and target vessel myocardial infarction at 12 months (Figure 2), and late stent thrombosis numerically favoring Supreme DES, are aligned with an early endothelial healing concept. These findings were consistent across subgroups, including higher-risk groups such as patients with diabetes or patients presenting with ACS, multivessel disease, and complex lesions. However, demonstration of clinical benefit (superiority) derived from early endothelial healing is expected to require longer-term follow-up and will be tested in a planned powered secondary landmark analysis evaluating superiority of TLF with Supreme DES compared with controls between 1 and 5 years.

The difference in combined clinically and non–clinically driven TLR favoring the control group in our study (2.5%

vs. 1.0%; P=0.04), should be interpreted with caution. Whether this represents a clinically meaningful difference in effectiveness related to the early drug release kinetics of Supreme DES is plausible but remains speculative, and will be further evaluated with longer-term follow-up and use in higher-risk patients. Our study showed no significant difference when clinically relevant TLR was adjudicated by the blinded Clinical Events Committee, minimizing potential bias of TLR in an open-label study. It is well recognized that all revascularization (comprising both clinically driven and non–clinically driven revascularization) is inherently subject to bias, particularly when operators are not blinded to subject treatment assignment. In addition, because non–clinically driven revascularizations are, by definition, considered to be unjustified by the lack of existence of objective evidence of ischemia, the clinical significance of these events is questionable. Furthermore, the lower-than-previously-reported overall TLR rates of 1.0% in the control DP-EES group (where other randomized trials consistently have reported rates of 2%–5% at 12 months using the same definitions), is significantly underpowered and not prespecified to make this comparison reliable.[39–45] While between-trial differences are difficult to ascertain, one important factor in our study is that a significant proportion of clinical follow-up was performed between January and July 2020 at the peak of the coronavirus disease 2019 (COVID-19) pandemic. Whether possible pandemic-related hospital presentation delays or avoidance contributed to lower-than-expected TLR rates cannot be fully evaluated.[46] Last, the more frequent predilation with the Supreme DES likely represents early operator response to a novel DES compared with the experienced use of familiar device in an open-label trial.

Limitations

The trial was powered for noninferiority of the primary composite TLF end point and was not powered for superiority. Therefore the 12-month primary outcome was not designed to evaluate differences between treatments. Long-term results will test whether the Supreme DES offers clinical benefit compared with DP-EES. Although the study showed a significant difference in overall TLR between groups, clinically driven TLR was not different; this may be a play of chance as the trial was not powered to evaluate any secondary end point and did not adjust for multiplicity testing. Therefore, caution should be used when comparing low frequency events and outcomes. Furthermore, while the study enrolled a population with increased clinical risk, including ACS and multivessel disease, the sample size in high-risk subgroups is variable and interaction testing is inherently underpowered. Last, the trial did not include all-comers (eg, ST-elevation myocardial infarction, left main disease, or chronic total occlusion lesions), therefore limiting generalizability of results to all patients.

Conclusion

This international prospective randomized trial confirms the noninferiority of this novel DES compared with DP-EES in patients with acute and chronic coronary syndromes undergoing PCI. Whether the Supreme DES differentiates into clinical benefit will be assessed at 5-year follow-up.

ARTICLE INFORMATION

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