A Prospective, Randomized Evaluation of a Novel Everolimus-Eluting Coronary Stent: The PLATINUM (A Prospective, Randomized, Multicenter Trial to Assess an Everolimus-Eluting Coronary Stent System [PROMUS Element] for the Treatment of up to Two De Novo Coronary Artery Lesions) Trial

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EXPEDITED PUBLICATION

A Prospective, Randomized Evaluation of a Novel Everolimus-Eluting Coronary Stent

The PLATINUM (A Prospective, Randomized, Multicenter Trial to Assess an Everolimus-Eluting Coronary Stent System [PROMUS Element] for the Treatment of up to Two De Novo Coronary Artery Lesions) Trial

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New York, New York; La Jolla, California; Clayton, Victoria, Australia; Toulouse, France; Leuven and Genk, Belgium; Ocala, Florida; Tokyo, Japan; and Natick, Massachusetts

Objectives We sought to evaluate the clinical outcomes with a novel platinum chromium everolimus-eluting stent (PtCr-EES) compared with a predicate cobalt chromium everolimus-eluting stent (CoCr-EES) in patients undergoing percutaneous coronary intervention (PCI).

Background Randomized trials have demonstrated an excellent safety and efficacy profile for the CoCr-EES. The PtCr-EES uses the identical antiproliferative agent and polymer but with a novel platinum chromium scaffold designed for enhanced deliverability, vessel conformability, side-branch access, radiopacity, radial strength, and fracture resistance.

Methods A total of 1,530 patients undergoing PCI of 1 or 2 de novo native lesions were randomized at 132 worldwide sites to CoCr-EES (n = 762) or PtCr-EES (n = 768). The primary end point was the 12-month rate of target lesion failure (TLF), the composite of target vessel-related cardiac death, target vessel-related myocardial infarction (MI), or ischemia-driven target lesion revascularization (TLR) in the per-protocol population (patients who received ≥1 assigned study stent), powered for noninferiority.

Results The 12-month rate of TLF in the per-protocol population occurred in 2.9% versus 3.4% of patients assigned to CoCr-EES versus PtCr-EES, respectively (difference: 0.5%, 95% confidence interval: −1.3% to 2.3%, $p_{noninferiority} = 0.001$, $p_{superiority} = 0.60$). By intention-to-treat, there were no significant differences between CoCr-EES and PtCr-EES in the 12-month rates of TLF (3.2% vs. 3.5%, p = 0.72), cardiac death or MI (2.5% vs. 2.0%, p = 0.56), TLR (1.9% vs. 1.9%, p = 0.96), or Academic Research Consortium definite or probable stent thrombosis (0.4% vs. 0.4%, p = 1.00).

Conclusions In this large-scale, prospective, single-blind randomized trial, a novel PtCr-EES was noninferior to the predicate CoCr-EES for TLF, with nonsignificant differences in measures of safety and efficacy through 12-month follow-up after PCI. (A Prospective, Randomized, Multicenter Trial to Assess an Everolimus-Eluting Coronary Stent System [PROMUS Element] for the Treatment of up to Two De Novo Coronary Artery Lesions: NCT00823212) (J Am Coll Cardiol 2011;57:0000–00) © 2011 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

ARC = Academic Research Consortium

CI = confidence interval

CK-MB = creatine kinase-myocardial band

CoCr-EES = cobalt chromium everolimus-eluting stent

DES = drug-eluting stent(s)

ITT = intention-to-treat

MI = myocardial infarction

PCI = percutaneous coronary intervention

PtCr-EES = platinum chromium everolimus-eluting stent

RVD = reference vessel diameter

TLF = target lesion failure

TLR = target lesion revascularization

TVR = target vessel revascularization

Since the introduction of first-generation drug-eluting stents (DES), advances in stent technology have continued to improve the clinical outcomes for patients undergoing percutaneous coronary intervention (PCI). Specifically, the cobalt chromium everolimus-eluting stent (CoCr-EES) (manufactured as XIENCE V by Abbott Vascular, Santa Clara, California, also distributed as PROMUS by Boston Scientific, Natick, Massachusetts) has been shown in a series of randomized trials to reduce the rates of angiographic and clinical restenosis, myocardial infarction (MI), and stent thrombosis compared with a widely used paclitaxel-eluting stent (1–4). Recently, a novel stent based on a new metal alloy has been developed, the platinum chromium everolimus-eluting stent (PtCr-EES) (manufactured as PROMUS Element by Boston Scientific) (5,6), which uses the same durable, biocompatible, inert fluorocopolymer and antiproliferative agent (7) as the predicate CoCr-EES but with a modified scaffold designed to provide improved deliverability, vessel conformability, side-branch access, radiopacity, radial strength, and fracture resistance (Fig. 1, Table 1). The PtCr-EES and CoCr-EES provide comparable everolimus release kinetics, arterial tissue levels, and vascular responses in a noninjured porcine coronary artery model (8). The vascular responses to the PtCr-EES were assessed in 73 patients in whom follow-up angiography at 9 months was performed after PCI of a single coronary lesion with reference vessel diameter (RVD) ≥2.5 to ≤4.25 mm and lesion length ≤24 mm (9). The angiographic in-stent late loss was 0.17 ± 0.25 mm, similar to that previously reported with the CoCr-EES in the SPIRIT First trial (A Clinical Evaluation of an Investigational Device. The Abbott XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Patients With de Novo Native Coronary Artery Lesions) (0.10 ± 0.21 mm at 6 months and 0.24 ± 0.27 mm at 1 year), the SPIRIT II trial (0.11 ± 0.27 mm at 6 months), and the SPIRIT III trial (0.16 ± 0.41 mm at 8 months) (3,4,10,11). By intravascular ultrasound, the percentage volume obstruction with PtCr-EES at 9-month follow-up was 7.2 ± 6.2%, also comparable to that reported with the CoCr-EES (8.0 ± 10.4% and 10 ± 7% at 6 and 12 months, respectively, from the SPIRIT First trial; 2.5 ± 4.7% at 6 months in the SPIRIT II trial, and 6.9 ± 6.4% at 8 months in the SPIRIT III trial) (1,2,10,11).

To further assess the clinical safety and efficacy of the PtCr-EES, we performed the PLATINUM trial (A Prospective, Randomized, Multicenter Trial to Assess an Everolimus-Eluting Coronary Stent System [PROMUS Element] for the Treatment of up to Two De Novo Coronary Artery Lesions), a large-scale, international, multicenter, prospective, single-blind randomized trial in which the PtCr-EES was compared with the CoCr-EES in patients undergoing PCI. The present report describes the principal analyses from the pivotal PLATINUM trial.

Methods

Enrollment criteria. Patients ≥18 years of age with stable or unstable angina pectoris or documented silent ischemia were considered for enrollment. Patients requiring PCI during the index procedure of 1 or 2 de novo native coronary artery target lesions with RVD 2.5 to 4.25 mm, lesion length ≤24 mm, and diameter stenosis ≥50% to <100% with Thrombolysis In Myocardial Infarction flow grade 2 or 3 (by visual estimate) were eligible for inclusion. If only 1 target lesion was to be randomized, an additional nontarget lesion in a different vessel could be treated before the target lesion, and the patient would still qualify as long as PCI of the nonstudy lesion was angiographically successful and uncomplicated. Principal clinical exclusion criteria were acute or recent MI; left ventricular ejection fraction (LVEF) <30%; prior or planned organ transplant; recent or scheduled chemotherapy; autoimmune disease or use of immunosuppressive therapy; platelet count <100,000 or >700,000 cells/mm^3; white blood cell count <3,000 cells/mm^3; liver disease, estimated creatinine clearance <50 ml/min (Cockcroft-Gault formula), or need for dialysis; active peptic ulcer or gastrointestinal bleeding, bleeding diathesis or coagulopathy, warfarin use, or will refuse blood transfusions; stroke or transient ischemic attack within 6 months or any permanent neurologic defect; target vessel treatment with atherectomy, laser, or cutting balloon before stent placement; any planned PCI or coronary artery bypass graft after the index procedure (lesions in nonstudy target vessels could have been treated >24 h before randomization); previous treatment with intracoronary brachytherapy; known allergy to any of the components of the study stent or study medications that could not be adequately premedicated; comorbidity that might reduce life expectancy to <24 months; participation in another investigational drug or device trial that has not reached its primary end point; and inability or unwillingness to comply with all protocol-required procedures. Additional angiographic exclusion criteria included lesion location in an ostial or left main location or in or through a bypass graft conduit; true bifurcation lesion (side branch ≥2.0 mm in diameter by visual estimate or with a significant ostial stenosis); excessive tortuosity, angulation, or calcification proximal to or within the lesion; or presence of thrombus in the target vessel. The study was approved by the institutional review board or ethics committee at each participating center, and all eligible patients signed informed written consent.

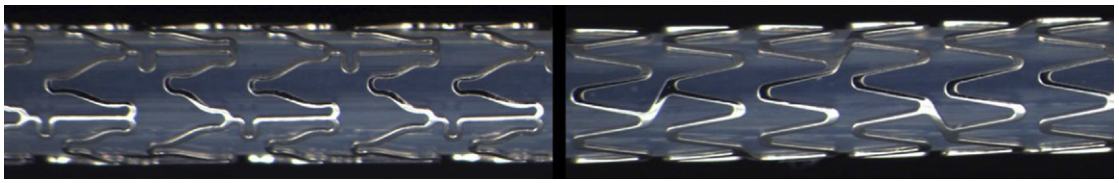

Figure 1 Photograph of CoCr-EES and PtCr-EES

Photograph of the PROMUS cobalt chromium everolimus-eluting stent (CoCr-EES) **(left)** and the PROMUS Element platinum chromium everolimus-eluting stent (PtCr-EES) **(right)** (Boston Scientific, Natick, Massachusetts). Both stents are 3.0 mm in diameter. See text for details.

Protocol. After successful target lesion pre-dilation, randomization was performed with an automated computerized system in randomly permuted blocks of 2 or 4 patients. Patients were randomized in 1:1 ratio to PtCr-EES or CoCr-EES, stratified by the presence or absence of medically treated diabetes mellitus, by the intent to treat 1 versus 2 target lesions, and by study site. Patients were considered enrolled upon randomization. Both stent types were available in diameters of 2.5 to 4.0 mm; available lengths were 12, 20, and 28 mm for PtCr-EES and 12, 18, and 28 mm for CoCr-EES. The operator performing the procedure was not blinded to the study stent, but patients and hospital caregivers remained blinded.

The PCI was performed with unfractionated heparin, enoxaparin, or bivalirudin as per local practice, and glycoprotein IIb/IIIa inhibitors were permitted per investigator discretion. Loading doses of aspirin (≥300 mg p.o. recommended) and clopidogrel (≥300 mg p.o. required) were required in patients not taking these medications ≥72 h before the index procedure. Post-PCI daily aspirin was required indefinitely, with 162 to 325 mg p.o. daily recommended for at least the first 6 months and 75 to 162 mg p.o. daily thereafter. Clopidogrel 75 mg p.o. daily was required for at least 6 months after stent placement in all patients and for at least 12 months in those not at high risk of bleeding. Ticlopidine was allowed in patients intolerant of clopidogrel, and prasugrel was permitted in non-U.S. sites in accordance with approved country-specific labeling.

After hospital discharge, clinical follow-up was scheduled for 1 month and 6, 12, and 18 months and then annually from 2 to 5 years. Repeat angiographic follow-up was performed only for clinical indications. The primary end point was assessed at 1 year, the timing of the present report.

Data management. Study monitors verified all case report form data on-site. An independent Clinical Events Committee (CEC) blinded to study stent assignment adjudicated all death, MI, target vessel revascularization (TVR), and stent thrombosis events. An independent Data Safety and Monitoring Committee evaluated all reported and adjudicated adverse events at regular intervals, each time allowing the study to continue unchanged. Angiographic data were analyzed by an independent core angiographic laboratory. Study organization and oversight committee membership are provided in the Online Appendix.

End points and definitions. The primary end point was the 12-month rate of target lesion failure (TLF), defined as the composite of cardiac death (any death other than those confirmed to have a noncardiac cause) related to the target vessel, MI related to the target vessel, or ischemia-driven

Table 1 Comparison of Cobalt Chromium and Platinum Chromium Everolimus-Eluting Stents

Parameter	CoCr-EES	PtCr-EES
Drug	Everolimus	Everolimus
Polymer	PBMA and PVDF-HFP*	PBMA and PVDF-HFP*
Polymer thickness (μm)	7	7
Metal composition (%)	Cobalt Chromium (L605)	Platinum Chromium
Iron	3.0 max	37†
Platinum	0	33
Cobalt	52†	0
Chromium	20	18
Nickel	10	9
Tungsten	15	0
Molybdenum	0	2.63
Manganese	1.50	≤0.05 max
Strut width (μm)	91	86
Strut thickness (μm)	81	81
Nominal balloon pressure (atm)	9	12
Balloon rated burst pressure (atm)	16	18
Surface/artery ratio (%)‡§	13.7	15.1
Scaffolding (mm)‖¶	1.07	0.91
Radial strength (N/mm)§	0.14	0.23
Stent recoil (%)§	4.6	3.6
Conformability (N·mm)§#	0.30	0.09
Radiopacity/density (g/cm^3)	9.1	9.9
Trackability (g·cm catheter)**	158	133

Data are for 3.0-mm stents. *Primer layer is poly (n-butyl methacrylate) (PBMA); drug matrix layer is poly (vinylidene fluoride-co-hexafluoropropylene) (PVDF-HFP). †Balance value calculated from nominal values of other elements. Elements listed as maximums (max) are taken at midpoint for this calculation. ‡Percentage of artery wall area covered by the outer surface area of the stent. §n = 15 for platinum chromium everolimus-eluting stent (PtCr-EES); n = 10 for cobalt chromium everolimus-eluting stent (CoCr-EES). ‖Average of the largest circle to fit in each cell. ¶n = 5 for PtCr-EES; n = 10 for CoCr-EES. #Conformability, a measure of the bending moment of the stent, describes ability of a stent to match the natural curvature of a vessel without causing vessel straightening; a lower value reflects better conformability. **16-mm PtCr-EES and 18-mm CoCr-EES, n = 10/group; assessed by measuring the amount of work required to pass the device through a tortuous artery model; a lower value (less work) indicates better trackability.

N/mm = Newtons/millimeter; N·mm = Newton millimeters.

target lesion revascularization (TLR). Myocardial infarction was defined as: 1) the development of new Q waves in ≥2 leads lasting ≥0.04 s with creatine kinase-myocardial band (CK-MB) or troponin levels elevated above normal; or 2) in the absence of new Q waves, elevation of total CK levels >3× normal (peri-PCI) or >2× normal (spontaneous) with elevated CK-MB, or troponin >3× normal (peri-PCI) or >2× normal (spontaneous) plus at least 1 of the following: 1) electrocardiographic changes indicative of new ischemia (new ST-T changes or left bundle branch block); 2) imaging evidence of new loss of viable myocardium; or 3) new regional wall motion abnormality. Similar criteria were required for the diagnosis of MI after coronary artery bypass graft surgery, with a CK-MB or troponin threshold of >5× normal. Ischemia-driven TLR or TVR was defined as revascularization of the target lesion or vessel with the stenosis ≥50% by quantitative coronary angiography if associated with clinical or functional ischemia (ischemic symptoms, electrocardiographic changes, or positive functional study), or stenosis ≥70% by quantitative coronary angiography without documented ischemia. Additional clinical end points included target vessel failure (defined as the composite of cardiac death, MI, or ischemia-driven TVR); the components of TLF and target vessel failure; stent thrombosis defined according to the definite or probable Academic Research Consortium (ARC) criteria (12), subclassified as acute (<24 h), subacute (24 h to 30 days), and late (>30 days to 1 year); technical success (successful delivery and deployment of the study stent to the target vessel, without balloon rupture or stent embolization); and clinical procedural success (visually assessed lesion diameter stenosis <30% with Thrombolysis In Myocardial Infarction flow grade 3, without in-hospital MI, TVR, or cardiac death).

Sample size determination and statistical methods. The randomized trial was powered for noninferiority testing of PtCr-EES compared with CoCr-EES for the primary end point of 12-month TLF. A 2-group Farrington-Manning test was used to test the 1-sided hypothesis of noninferiority in differences with a noninferiority margin (delta) of 3.5%. A p value <0.05 would indicate noninferiority of PtCr-EES and would correspond to the upper limit of the 1-sided 95% confidence interval (CI) of the difference not exceeding 3.5%. The trial had 89% power to demonstrate noninferiority for TLF (accounting for an expected 1-year attrition rate of 5%), assuming a 1-year TLF rate of 5.5% for both stents (on the basis of the data available at the time of study design for CoCr-EES from the SPIRIT II and SPIRIT III trials [1,2]), with 766 patients enrolled/treatment group.

Treatment groups were compared with a 2-sided chi-square or Fisher exact test for categorical variables and Student *t* test for continuous variables. The Kaplan-Meier product-limit method was used to estimate event rates for time-to-event outcomes; data were compared with the log-rank test. The primary end point was pre-specified to be tested in the per-protocol population (patients receiving 1 or more assigned study stents). All end points were also analyzed in the intention-to-treat (ITT) population (including all patients who underwent randomization, regardless of treatment actually received). All statistical analyses were done with SAS software (version 8.2 or above, SAS Institute, Inc., Cary, North Carolina).

Results

Patient characteristics and procedural outcomes. Between January 27, 2009 and September 4, 2009, 1,530 patients were enrolled at 132 sites in the United States (n = 788), European Union (n = 562), Japan (n = 124), and other Asia Pacific countries (n = 56), and were randomized to CoCr-EES (n = 762) or PtCr-EES (n = 768). The baseline clinical and angiographic features of the randomized study groups were well-matched (Table 2). Mean patient age was 63.5 years, 28.6% were women, 23.5% had medically treated diabetes, and 24.4% presented with unstable angina. Multiple target lesions were treated in 10.7% of patients. The mean lesion RVD was 2.65 mm, and mean lesion length was 12.7 mm. Procedural and angiographic outcomes were also similar between the groups (Table 3), although slightly more CoCr-EES than PtCr-EES were used per lesion, and the maximum dilation pressure was higher for PtCr-EES. Nonetheless, angiographic acute gain and post-PCI target lesion luminal measures were not significantly different between the 2 stent types.

Among patients randomized to CoCr-EES and PtCr-EES, technical success was achieved in 98.8% and 99.4% of patients, respectively (p = 0.14), and clinical procedural success was achieved in 98.2% and 98.3%, respectively (p = 0.83). Unplanned (bail-out) stenting was required in 75 patients (9.8%) treated with CoCr-EES (for procedural complications [n = 36], inadequate lesion coverage [n = 26], or other reasons [n = 13]) compared with 45 patients (5.9%) treated with PtCr-EES (for procedural complications [n = 29], inadequate lesion coverage [n = 11], or other reasons [n = 5]) (p = 0.004). Other performance measures were comparable between the groups.

Clinical outcomes. Patient flow in the study is shown in Figure 2. Follow-up at 12 months was completed in 96.7% of patients. Among patients randomized to CoCr-EES versus PtCr-EES, aspirin was used by 99.6% and 98.7%, respectively, at hospital discharge (p = 0.053) and by 97.4% and 97.6%, respectively, at 1 year (p = 0.84). A thienopyridine (clopidogrel, ticlopidine, or prasugrel) was used by 99.1% and 98.8% of CoCr-EES and PtCr-EES-assigned patients, respectively, at the time of hospital discharge (p = 0.63) and in 89.4% and 90.9% of patients at 1 year, respectively (p = 0.34); prasugrel was taken by only 1 patient at discharge (in the PtCr-EES group) and by 6 patients in each group at 1 year.

The primary end point analysis appears in Figure 3. The rate of TLF at 12 months in the per-protocol population occurred in 2.9% of patients assigned to CoCr-EES and

Table 2 Baseline Clinical and Angiographic Features of the Randomized Study Groups

	CoCr-EES (n = 762 Patients, n = 841 Lesions)	PtCr-EES (n = 768 Patients, n = 853 Lesions)	p Value
Demographic features			
Age (yrs)	63.1 ± 10.3 (762)	64.1 ± 10.3 (768)	0.09
Male	542/762 (71.1)	550/768 (71.6)	0.83
Hypertension*	558/762 (73.2)	544/767 (70.9)	0.32
Hypercholesterolemia*	579/760 (76.2)	598/765 (78.2)	0.36
Diabetes*	191/762 (25.1)	169/768 (22.0)	0.16
Insulin treated	48/762 (6.3)	59/768 (7.7)	0.29
Current smoker	131/741 (17.7)	158/751 (21.0)	0.10
Prior myocardial infarction	160/760 (21.1)	160/761 (21.0)	0.99
Unstable angina	188/762 (24.7)	185/767 (24.1)	0.80
Number of target lesions, mean	1.10 ± 0.31 (762)	1.11 ± 0.31 (768)	0.66
1	684/762 (89.8)	683/768 (88.9)	0.60
2	77/762 (10.1)	85/768 (11.1)	0.54
3	1/762 (0.1)	0/768 (0.0)	0.50
Target vessel			
Left anterior descending	343/813 (42.2)	347/824 (42.1)	0.97
Left circumflex	216/813 (26.6)	217/824 (26.3)	0.91
Right	254/813 (31.2)	260/824 (31.6)	0.89
Target lesion measures			
Reference vessel diameter, mm	2.63 ± 0.49	2.67 ± 0.49	0.09
Minimal lumen diameter, mm	0.74 ± 0.34	0.75 ± 0.35	0.40
Diameter stenosis, %	71.9 ± 11.5	71.8 ± 11.5	0.87
Lesion length, mm	12.5 ± 5.5	13.0 ± 5.7	0.10

Values are mean ± SD or n/N (%). *Requiring medication.
Abbreviations as in Table 1.

3.4% of patients assigned to PtCr-EES (difference: 0.5%, 95% CI: −1.3% to 2.3%, $p_{superiority} = 0.60$). The 1-sided 95% Farrington-Manning upper confidence bound was 2.13%, which is less than the pre-specified noninferiority margin of 3.5%. As such, the primary end point of noninferiority for PtCr-EES compared with CoCr-EES for TLF at 12 months was met ($p_{noninferiority} = 0.001$). Similarly, in the ITT population, the 12-month rate of TLF was nonsignificantly different between CoCr-EES and PtCr-EES (3.2% vs. 3.5%, respectively; difference: 0.3%, 95% CI: −1.5% to 2.2%, $p_{noninferiority} = 0.0009$, $p_{superiority} = 0.72$) (Fig. 4).

Additional 12-month outcomes in the ITT population appear in Table 4. There were no significant differences detected in any safety or efficacy measure between the stent types. The 1-year rate of TLR was 1.9% for both groups ($p = 0.96$). ARC definite or probable stent thrombosis through 1 year of follow-up occurred in only 3 patients (0.4%) in each group (1 acute, 2 subacute, and 0 late events with CoCr-EES; and 1 acute, 0 subacute, and 2 late events with PtCr-EES).

Discussion

The principal findings from the present analysis, representing the pivotal 1-year outcomes from the multicenter, multinational, prospective, randomized PLATINUM trial, are that: 1) a novel PtCr-EES has been developed with noninferior 12-month rates of TLF compared with the predicate CoCr-EES; 2) clinical restenosis (ischemia-driven TLR) within 1 year occurred infrequently and to a similar degree with both stents in the patient population tested; and 3) both stents demonstrated an excellent safety profile, with nonsignificantly different 12-month rates of cardiac death, MI, and stent thrombosis.

Prior studies have demonstrated that, across a broad cross-section of patients undergoing PCI, the CoCr-EES results in low rates of TLF, a relatively stent-specific composite measure of safety and efficacy. In large-scale randomized trials, patients treated with the CoCr-EES have been shown to have reduced 1-year rates of TLF, TLR, MI, and stent thrombosis compared with the first-generation paclitaxel-eluting stent (5,6) and nonsignificantly different 1-year rates of TLF, TLR, and MI but less stent thrombosis compared with a second-generation zotarolimus-eluting stent (13). The favorable results with this device likely stem from the properties of its 3 main components: the polymer, the drug, and the metallic stent itself. The thin (7 μm), nonadhesive, durable and inert biocompatible fluorocopolymer has been shown to be resistant to platelet and thrombus deposition in blood-contact applications (14,15), possibly contributing to resistance to stent thrombosis. The polymer controls the release kinetics of the everolimus such that approximately 80% of the drug is released at 30 days, with none detectable after 120 days.

Table 3 Procedural and Angiographic Outcomes of the Randomized Study Groups

	CoCr-EES (n = 762 Patients, n = 841 Lesions)	PtCr-EES (n = 768 Patients, n = 853 Lesions)	p Value
Procedural variables			
Stents/patient, n	1.20 ± 0.48	1.16 ± 0.44	0.16
Stents/target lesion, n	1.08 ± 0.35	1.05 ± 0.26	0.01
Maximum stent diameter/lesion (mm)	3.05 ± 0.44	3.09 ± 0.45	0.07
Maximum stent diameter/RVD ratio (mm)	1.18 ± 0.15	1.17 ± 0.15	0.63
Total stent length/lesion (mm)	19.7 ± 8.9	20.5 ± 7.0	0.06
Total stent length/lesion length ratio (mm)	1.7 ± 0.7	1.8 ± 0.7	0.25
Post-stent dilation performed	415/841 (49.3%)	425/853 (49.8%)	0.84
Maximum dilation pressure (atm)*	15.9 ± 3.2	16.3 ± 3.1	0.002
Glycoprotein IIb/IIIa inhibitors used	62/762 (8.1%)	56/768 (7.3%)	0.54
Non-target lesions treated	71/762 (9.3%)	69/768 (9.0%)	0.82
Fluoroscopy time (min)	11.3 ± 10.1	12.2 ± 11.8	0.10
Contrast used (cc)	184 ± 86	185 ± 87	0.85
Post-procedural results (per target lesion)			
Reference vessel diameter (mm)	2.67 ± 0.50	2.70 ± 0.49	0.27
Minimum lumen diameter (mm)			
In-stent	2.54 ± 0.44	2.57 ± 0.42	0.25
In-segment	2.16 ± 0.47	2.19 ± 0.47	0.15
Diameter stenosis, %			
In-stent	4.3 ± 8.7	4.3 ± 9.1	0.95
In-segment	19.2 ± 9.0	18.8 ± 8.6	0.43
Acute gain, %			
In-stent	1.80 ± 0.45	1.81 ± 0.43	0.73
In-segment	1.42 ± 0.47	1.44 ± 0.46	0.45

Values are mean ± SD or n/N (%). *Pre-dilation, stent implantation, or post-dilation balloon.

The dose density of everolimus (100 $\mu g/cm^2$) is lower than with any comparable rapamycin-analogue DES. Finally, the thin (81 μm) CoCr stent struts facilitate rapid re-endothelialization (16) and are fracture-resistant. Preclinical studies have demonstrated more rapid coverage of the CoCr-EES struts with functional endothelialization than with other DES (17).

Through use of a more dense platinum chromium alloy and a modified scaffold architecture, the PtCr-EES was developed to further improve upon several of the mechanical and physical properties of the CoCr-EES (specifically, to enhance trackability, vessel conformability, side-branch access, radiopacity, radial strength, and fracture resistance). A paclitaxel-eluting version of this stent (TAXUS Element,

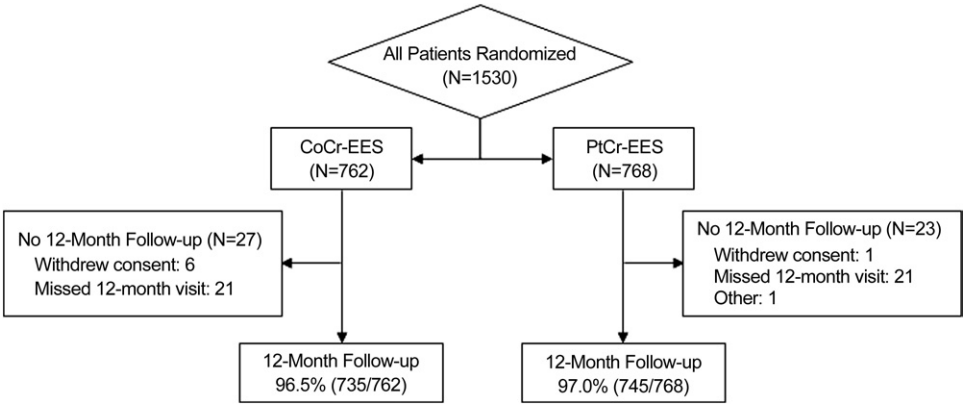

Figure 2 Patient Flow in the Randomized Trial

Abbreviations as in Figure 1.

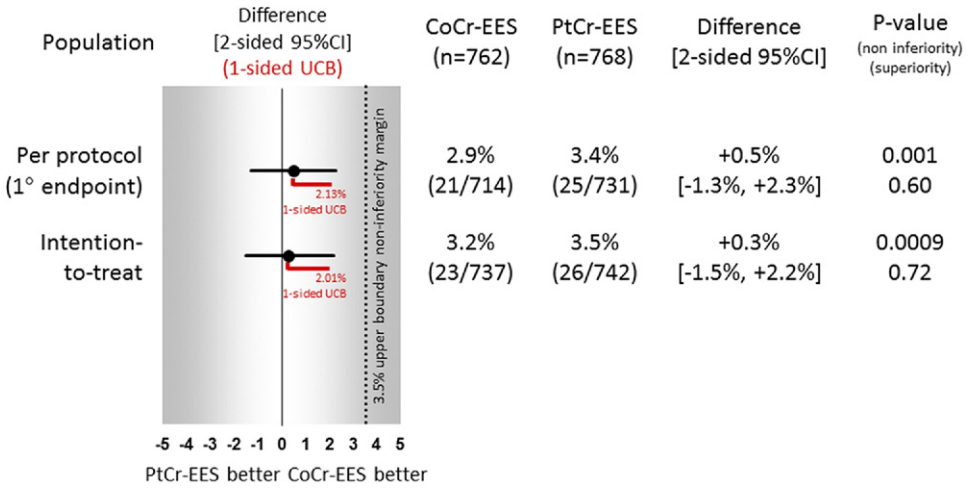

Figure 3 **Primary End Point of TLF at 1 Year**

Primary end point of target lesion failure (TLF) at 1 year for the per-protocol population (primary analysis) and the intention-to-treat (ITT) population (secondary analysis). Plot shows the difference in TLF at 1-year between the CoCr-EES and the test PtCr-EES, with the 2-sided confidence intervals (CIs) **(black line)** and the upper bound of the 1-sided 95% CI **(red line)**. The p values for noninferiority and superiority testing are 1- and 2-sided, respectively. Abbreviations as in Figure 1.

Boston Scientific) has previously been shown to have noninferior clinical outcomes compared with the predicate stainless steel TAXUS Express stent (18). A major design goal for the PtCr-EES was to preserve the clinical safety and efficacy profile of the CoCr-EES by maintaining the same polymer thickness, everolimus concentration, and pharmacokinetics present in the CoCr-EES while improving acute performance. In this regard, comparable everolimus release kinetics, arterial tissue levels, and vascular responses have been reported for the PtCr-EES and CoCr-EES in a noninjured porcine coronary artery model (8), and in a prior nonrandomized clinical study the PtCr-EES was found to have rates of angiographic in-stent and in-segment late loss comparable to those of the CoCr-EES (9). The current results from the large-scale PLATINUM randomized trial demonstrate noninferiority of the PtCr-EES to the CoCr-EES for the composite safety and efficacy measure of TLF at 1 year, with nonstatistically significant different rates present in death, MI, and TLR. Notably, the 0.4% 1-year rate of ARC definite or probable stent thrombosis in both groups in the present trial confirms the low thrombosis rates reported with the EES in prior studies (1–4,10,11,14). Thus, along with stainless steel and cobalt chromium, platinum chromium may now be considered an acceptable metal alloy for use in DES.

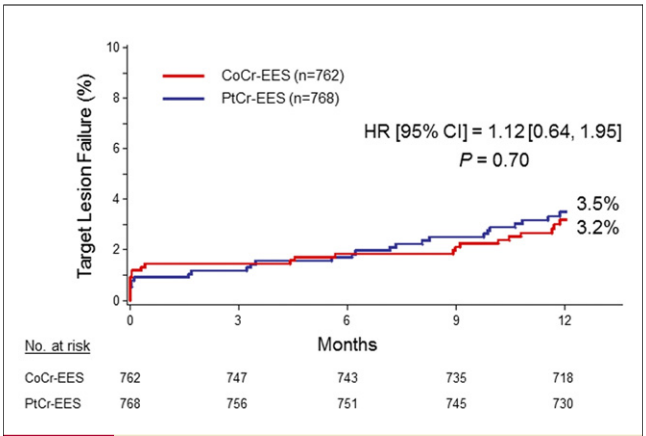

Figure 4 **Time-to-Event Curves for the Primary Endpoint of TLF in the ITT Population**

The event rates presented here were calculated by Kaplan-Meier methodology and compared with the log-rank test. Thus, the p value differs slightly from that in the text and Table 4, which were calculated using categorical variables and compared with the chi-square test. HR = hazard ratio; other abbreviations as in Figures 1 and 3.

Although the rates of technical and clinical procedural success achieved with the 2 stents were similar in the present study, a higher rate of unplanned (bail-out) stenting was observed with CoCr-EES compared with PtCr-EES. The clinical relevance of this finding is uncertain. The present study was not designed to evaluate whether the PtCr-EES is indeed more deliverable, conformable, and/or more radiopaque; affords better side-branch access; is more resistant to recoil; and/or is more fracture resistant than the CoCr-EES. These properties might be difficult to measure in patients, because differences between devices that are detectable on the bench might not be clinically relevant or otherwise perceptible in vivo (19). Typically, extensive multicenter clinical experience in patients with complex coronary anatomy is required to reach a consensus regarding stent deliverability and other ease-of-use characteristics.

Study limitations. Several limitations of the present study should be discussed. The 1-year TLF rate with the control

Table 4 1-Year Clinical Outcomes in the ITT Population

	CoCr-EES (n = 762)	PtCr-EES (n = 768)	p Value
All-cause death, MI, TVR	36/732 (4.9)	37/745 (5.0)	0.97
All-cause death or MI	22/732 (3.0)	18/745 (2.4)	0.49
All death	9/732 (1.2)	10/745 (1.3)	0.85
Cardiac death	5/732 (0.7)	7/745 (0.9)	0.58
Related to the TV	3/732 (0.4)	6/745 (0.8)	0.51
Not related to the TV	2/732 (0.3)	1/745 (0.1)	0.62
Noncardiac death	4/732 (0.5)	3/745 (0.4)	0.72
MI	13/732 (1.8)	8/745 (1.1)	0.25
Related to the TV	12/732 (1.6)	6/745 (0.8)	0.14
Not related to the TV	1/732 (0.1)	2/745 (0.3)	1.00
Q-wave MI	5/732 (0.7)	1/745 (0.1)	0.12
Non–Q-wave MI	9/732 (1.2)	7/745 (0.9)	0.59
TVR, overall	21/732 (2.9)	20/745 (2.7)	0.83
TLR, overall	14/732 (1.9)	14/745 (1.9)	0.96
TLR, PCI	12/732 (1.6)	10/745 (1.3)	0.64
TLR, CABG	2/732 (0.3)	4/745 (0.5)	0.67
Non-TLR TVR, overall	8/732 (1.1)	7/745 (0.9)	0.77
Cardiac death or MI	18/732 (2.5)	15/745 (2.0)	0.56
Target lesion failure	23/727 (3.2)	26/742 (3.5)	0.72
Target vessel failure	29/727 (4.0)	31/742 (4.2)	0.85
Stent thrombosis (ARC definite or probable)	3/725 (0.4)	3/735 (0.4)	1.00
Definite	3/725 (0.4)	3/735 (0.4)	1.00
Probable	0/725 (0.0)	0/735 (0.0)	—

Values are n/N (%).

ARC = Academic Research Consortium; CABG = coronary artery bypass graft; ITT = intention-to-treat; MI = myocardial infarction; PCI = percutaneous coronary intervention; TV = target vessel; TLR = target lesion revascularization; TVR = target vessel revascularization; other abbreviations as in Table 1.

CoCr-EES (2.9% in the per-protocol population, and 3.2% in the ITT population) was less than the 5.5% rate assumed during sample size estimation, which was based on prior data from the SPIRIT II and III trials. In the larger SPIRIT IV trial, in which slightly more complex lesions were enrolled than in either of the earlier SPIRIT trials (or the present study), the 1-year TLF rate was only 4.2%, lower than had previously been reported. As such, small absolute differences in event rates between the PtCr-EES and CoCr-EES cannot be excluded by the present study. Nonetheless, the observed 2-sided 95% CI of the difference in the rate of 12-month TLF (−1.3% to 2.3%) ensures that a large absolute difference in TLF between the 2 stent types is unlikely in the lesions tested. Longer-term follow-up and in more complex lesions is required for a comprehensive evaluation between these 2 devices. In this regard, to meet regulatory requirements, the SPIRIT and PLATINUM trials excluded many high-risk patients, such as those with acute or recent MI or visible thrombus, chronic total occlusions, true bifurcations, and lesions in the left main coronary artery or a saphenous vein graft. In contrast, in a large-scale randomized trial in which these patients were actively enrolled, the 1-year rate of TLF with the CoCr-EES was greater (8.2%) than observed in the present study (13). In the future, adoption of the so-called "all-comers" design for regulatory approval stent trials would permit low-frequency but clinically relevant differences between devices to become statistically apparent (or more reliably be excluded), while maintaining reasonable sample size.

Conclusions

In summary, a novel PtCr-EES has been developed and shown to have noninferior 1-year clinical outcomes compared with the predicate CoCr-EES in patients undergoing PCI of up to 2 noncomplex de novo native coronary artery lesions.

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Key Words: angioplasty ■ coronary artery disease ■ restenosis.

APPENDIX

For complete list of the study organization and participating sites and investigators, please see the online version of this article.

A Prospective, Randomized Evaluation of a Novel Everolimus-Eluting Coronary Stent: The PLATINUM (A Prospective, Randomized, Multicenter Trial to Assess an Everolimus-Eluting Coronary Stent System [PROMUS Element] for the Treatment of up to Two De Novo Coronary Artery Lesions) Trial

Gregg W. Stone, Paul S. Teirstein, Ian T. Meredith, Bruno Farah, Christophe L. Dubois, Robert L. Feldman, Joseph Dens, Nobuhisa Hagiwara, Dominic J. Allocco, Keith D. Dawkins, and PLATINUM Trial Investigators

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