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Biodegradable Polymer-Based Sirolimus-Eluting Stents With Differing Elution and Absorption Kinetics

The PANDA III Trial

Bo Xu, MBBS,[a] Runlin Gao, MD,[a] Yuejin Yang, MD,[a] Xuebin Cao, MD,[b] Lei Qin, MD,[c] Yi Li, MD,[d] Zhanquan Li, MD,[e] Xueqi Li, MD,[f] Hailong Lin, MD,[g] Yong Guo, MD,[h] Yitong Ma, MD,[i] Jian'an Wang, MD,[j] Shaoping Nie, MD,[k] Liang Xu, MSc,[a] Eric Cao, MSc,[l] Changdong Guan, MSc,[a] Gregg W. Stone, MD,[m] on behalf of the PANDA III Investigators

ABSTRACT

BACKGROUND Whether the rate of drug elution and polymer absorption affects clinical outcomes of biodegradable polymer-based drug-eluting stents (DES) is unknown. The widely used polylactide polymer-based Excel stent (JW Medical, Weihai, China) elutes sirolimus within 180 days, and the polylactide polymer is completely absorbed within 6 to 9 months. In contrast, the poly-lactide-co-glycolide polymer-based BuMA stent (Sino Medical, Tianjin, China) elutes sirolimus within 30 days, and the poly-lactide-co-glycolide polymer is completely absorbed within 3 months. Thus, both metallic DES elute sirolimus, isolating major differences to the polymer and elution kinetics.

OBJECTIVES The goal of this study was to compare the safety and effectiveness between the BuMA sirolimus-eluting stent (SES) and Excel SES in an "all-comers" population.

METHODS PANDA III was a multicenter trial with few exclusion criteria, powered for sequential noninferiority and superiority testing. The primary endpoint was 1-year target lesion failure (TLF), a composite of cardiac death, target vessel myocardial infarction, or ischemia-driven target lesion revascularization.

RESULTS Between December 2013 and August 2014, 2,348 patients were randomly assigned to treatment with BuMA (n = 1,174) or Excel SES (n = 1,174). The 1-year primary endpoint of TLF occurred in 6.4% of patients in each group (difference: 0.06%; 95% confidence interval: 1.93% to 2.04%; $p_{noninferiority} = 0.0003$; $p_{superiority} = 0.95$). There were no significant between-group differences in any of the secondary endpoints other than the incidence of definite/probable stent thrombosis, which occurred less frequently with the BuMA stent (0.5% vs. 1.3%; log-rank p = 0.048).

CONCLUSIONS The BuMA SES was demonstrated to be noninferior to the Excel SES for 1-year TLF, with a lower incidence of stent thrombosis. (Comparison of BuMA eG Based BioDegradable Polymer Stent With EXCEL Biodegradable Polymer Sirolimus-eluting Stent in "Real-World" Practice [PANDA-III]; NCT02017275) (J Am Coll Cardiol 2016;67:2249–58)

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From the [a]Department of Cardiology, Fu Wai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences, Beijing, China; [b]Department of Cardiology, Chinese PLA 252 Hospital, Baoding, China; [c]Department of Cardiology, Kaifeng Central Hospital, Kaifeng, China; [d]Department of Cardiology, Yunnan St. John's Hospital, Kunming, China; [e]Department of Cardiology, Liaoning Provincial People's Hospital, Shenyang, China; [f]Department of Cardiology, The Fourth Affiliated Hospital of Haerbin Medical University, Haerbin, China; [g]Department of Cardiology, Dalian Municipal Central Hospital, Dalian, China; [h]Department of Cardiology, Dazhou Central Hospital, Dazhou, China; [i]Department of Cardiology, The First Affiliated Hospital of Xinjiang Medical University, Urumqi, China; [j]Department of Cardiology, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China; [k]Department of Cardiology, Affiliated Anzhen Hospital of Capital Medical University, Beijing, China; [l]Research and Development Sino Medical, Tianjin, China; and the [m]Department of Medicine, Columbia University Medical Center, New York-Presbyterian Hospital, and the Cardiovascular Research Foundation, New York, New York. The PANDA III trial was sponsored by Sino Medical, Tianjin, China. Dr. Gao received a research grant from Sino Medical. Mr. E. Cao is an employee of Sino Medical. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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ABBREVIATIONS AND ACRONYMS

AMI = acute myocardial infarction

BP = biodegradable polymer

DES = drug-eluting stent(s)

ID = ischemia-driven

MI = myocardial infarction

OCT = optical coherence tomography

PLA = polylactide

PLGA = poly-lactide-co-glycolide

PoCE = patient-oriented composite endpoint

SES = sirolimus-eluting stent(s)

TLF = target lesion failure

TLR = target lesion revascularization

TV = target vessel

First-generation drug-eluting stents (DES) were associated with an increased risk of stent thrombosis (ST) compared with bare-metal stents (1-4). This is, in part, related to the thick struts and the polymers and drugs used in these devices, which may cause inflammation and hypersensitivity reactions (5,6). As a result, there has been interest in biodegradable polymers to improve the safety profile of DES. A pooled analysis of the ISAR-TEST 3 (Prospective, Randomized Trial of 3 Rapamycin-Eluting Stents With Different Polymer Coating Strategies For The Reduction of Coronary Restenosis), ISAR-TEST 4 (Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting STents), and LEADERS (Limus Eluted From A Durable Versus ERodable Stent Coating) trials, in which biodegradable polymer (BP)-based DES were compared with the durable polymer Cypher (Cordis, Miami Lakes, Florida) sirolimus-eluting stent (SES) found that BP-DES were associated with similar adverse event rates within 1 year, but with a significantly reduced risk of ST and clinically driven target lesion revascularization (TLR) at 4 years (7). In a meta-analysis of 89 trials including 85,490 patients, Palmerini et al. (8) reported similar 1-year and long-term ST and target vessel revascularization (TVR) rates with BP-DES compared with Cypher SES, but higher 1- and 4-year ST rates with BP-DES compared with cobalt chromium durable fluoropolymer-based everolimus-eluting stents (EES), although TVR rates were similar. Finally, in the recent EVOLVE II (A Prospective Multicenter Trial to Assess the Safety and Effectiveness of the SYNERGY Everolimus-Eluting Platinum Chromium Coronary Stent System for the Treatment of Atherosclerotic Lesion) trial, an abluminal bioabsorbable poly(D,L-lactide-co-glycolide) polymer-based EES (with complete polymer absorption within 4 months) had similar 1-year ST and TLR rates compared with a conformal durable polymer-based EES (9). However, the underlying stent platforms varied substantially in this trial. Thus, whether the safety and efficacy profiles of BP-DES and durable polymer DES inherently differ requires additional study.

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Moreover, the optimal rates of drug elution and polymer bioabsorption from BP-DES are unknown. In this regard, the development of 2 DES has enabled assessment of the potential clinical effects of different drug elution and polymer absorption profiles. Specifically, the widely used polylactide (PLA) polymer-based Excel stent (JW Medical, Weihai, China) is a laser-cut 316L stainless steel SES, characterized by complete drug elution within 180 days and complete PLA polymer absorption within 6 to 9 months (10). In contrast, the novel poly-lactide-co-glycolide (PLGA) polymer-based BuMA stent (Sino Medical, Tianjin, China) is a laser-cut 316L stainless steel SES with a unique design that incorporates an electrografting base layer between the polymer and stent strut, allowing for complete elution of sirolimus within 30 days and complete absorption of the PLGA polymer within 3 months (11). A prior single-center, randomized trial showed that the BuMA SES had superior strut coverage at 3 months compared with the Excel SES, as assessed by optical coherence tomography (OCT) (11). However, no clinical study has examined the potential clinical effect of this finding. We therefore conducted the PANDA III (Comparison of BuMA eG Based BioDegradable Polymer Stent With EXCEL Biodegradable Polymer Sirolimus-eluting Stent in "Real-World" Practice) multicenter, randomized trial to determine, in an "all-comers" population, whether the BuMA SES is noninferior or superior to the Excel SES.

METHODS

STUDY DESIGN AND POPULATION. PANDA III was a prospective, multicenter, randomized controlled trial comparing a PLGA polymer-based SES with an electrografting base layer versus a PLA polymer-based SES in patients with coronary artery disease with few exclusion criteria. Patients ≥18 years of age with chronic, stable ischemic heart disease or acute coronary syndromes, including myocardial infarction (MI) with or without ST-segment elevation, were eligible if they had at least 1 coronary lesion with diameter stenosis of >50% in a vessel with visually estimated reference vessel diameter (RVD) ≥2.5 and ≤4.0 mm. There was no restriction on the total number of lesions, number of stents implanted, or lesion location. Exclusion criteria included known hypersensitivity or contraindication to stainless steel, cobalt chromium, rapamycin, PLA, or PLGA polymer, and/or contrast sensitivity that could not be adequately pre-medicated; planned surgery within 6 months after the index procedure; women of childbearing potential; or participation in another investigational drug or device study that had not yet reached its primary endpoint. All patients provided written informed consent. Eligible patients were randomly assigned to receive the BuMA SES or Excel SES (the control device) in a 1:1 ratio in fixed

blocks of 4, stratified by center using a web-based allocation system.

STUDY DEVICES AND IMPLANTATION PROCEDURE. The PLGA polymer-based BuMA and the PLA polymer-based Excel both elute sirolimus from a stainless steel platform, isolating major differences to the polymer and elution kinetics. Specifications of the BuMA SES and Excel SES are provided in Online Table 1.

Stent implantation was performed according to standard techniques. The choice of the appropriate length and diameter of the stents to be implanted and the utilization of intravascular ultrasound or OCT were at the physician's discretion. Use of different stent types was not permitted unless the operator was unable to insert the study stent, in which case use of a commercially available nonstudy device was allowed. Planned staged procedures within 3 months in patients with multivessel disease were permitted using the same study stent.

All patients received ≥100 mg of aspirin and 75 mg of clopidogrel daily for at least 6 days pre-procedure, or received a loading dose of aspirin and 300 mg of clopidogrel on the day of the intervention. Procedural anticoagulation was achieved with unfractionated heparin at a dose of 70 to 100 IU/kg body weight, and the activated clotting time was maintained at ≥250 s; the use of glycoprotein IIb/IIIa inhibitors was left to the operator's discretion. Post-procedure patients were treated with ≥100 mg of aspirin daily for an indefinite period and 75 mg of clopidogrel daily for at least 12 months. Clinical follow-up visits were scheduled at 1, 6, 9, and 12 months, and annually up to 5 years.

ENDPOINT AND ANALYSIS POPULATIONS. The hypothesis of the study was that the BuMA SES would be either noninferior or superior to the Excel SES. The primary endpoint was 1-year target lesion failure (TLF), defined as the composite of cardiac death, target vessel (TV) MI, or ischemia-driven (ID) TLR. Secondary endpoints included acute success; the patient-oriented composite endpoint (PoCE) of all-cause death, all MI, or any revascularization; and the individual components of TLF, PoCE, and ST, defined according to definite or probable Academic Research Consortium criteria (12). Detailed endpoint definitions are provided in the Online Appendix. The primary outcome measures were analyzed in the intention-to-treat (ITT) population, regardless of device crossovers. Analyses in the per-treatment-evaluable (PTE) population, consisting of patients who received only the assigned study device and who had no pre-specified major protocol deviations, are also provided in the Online Appendix.

TABLE 1 Baseline Characteristics

	BuMA (n = 1,174) (L = 1,605)	Excel (n = 1,174) (L = 1,572)	p Value
Age, yrs	60.8 ± 10.6	61.5 ± 10.6	0.11
Male	828 (70.5)	830 (70.7)	0.93
Body mass index, kg/m^2	24.9 ± 3.4 (1,173*)	24.9 ± 3.3 (1,174*)	1.00
Diabetes mellitus	275 (23.4)	295 (25.1)	0.34
Insulin-requiring	69 (5.9)	86 (7.3)	0.16
Hypertension	724 (61.7)	723 (61.6)	0.97
Hyperlipidemia	368 (31.4)	364 (31.0)	0.86
Renal insufficiency†	9 (0.8)	4 (0.3)	0.09
Family history of coronary artery disease	62 (5.3)	55 (4.7)	0.51
Current tobacco use	437 (37.2)	442 (37.7)	0.83
Previous myocardial infarction	464 (39.5)	483 (41.1)	0.42
Previous stroke	129 (11.0)	139 (11.8)	0.52
Peripheral arterial disease‡	36 (3.1)	35 (3.0)	0.90
Previous percutaneous coronary intervention	122 (10.4)	160 (13.6)	0.02
Prior coronary artery bypass grafting	3 (0.3)	4 (0.3)	1.00
Clinical presentation			
Silent ischemia	48 (4.1)	31 (2.6)	0.05
Stable angina	182 (15.5)	164 (14.0)	0.29
Unstable angina	578 (49.2)	613 (52.2)	0.15
Recent myocardial infarction within 30 days	366 (31.2)	366 (31.2)	1.00
STEMI	170 (14.5)	192 (16.4)	0.21
NSTEMI	196 (16.7)	174 (14.8)	0.21
Left ventricular ejection fraction, %	59.2 ± 9.1 (1,116*)	59.4 ± 8.8 (1,115*)	0.56
Target lesion measures			
Baseline SYNTAX score	14.5 ± 9.2 (1,164*)	14.8 ± 9.3 (1,159*)	0.46
Mean number of target lesions per patient	1.37 ± 0.62	1.34 ± 0.58	0.40
Target vessel location			
Left main artery	20 (1.3)	23 (1.5)	0.60
Left anterior descending artery	729 (45.4)	718 (45.7)	0.89
Left circumflex artery/ramus	342 (21.3)	324 (20.6)	0.63
Right coronary artery	514 (32.0)	507 (32.3)	0.89
Quantitative coronary angiography			
Reference vessel diameter, mm	2.75 ± 0.47 (1,586§)	2.76 ± 0.45 (1,558§)	0.79
Minimal lumen diameter, mm	0.70 ± 0.48 (1,586§)	0.70 ± 0.48 (1,558§)	0.66
Diameter stenosis, %	74.8 ± 16.1 (1,586§)	75.0 ± 16.3 (1,558§)	0.63
Lesion length, mm	19.7 ± 12.1 (1,586§)	19.8 ± 12.1 (1,558§)	0.86
ACC/AHA class B2/C lesions‖	1,325 (82.6)	1,295 (82.4)	0.90
Bifurcation lesion	551 (34.3)	558 (35.5)	0.49
Ostial lesion	59 (3.7)	68 (4.3)	0.35
Total occlusion	210 (13.1)	218 (13.9)	0.52
Severely tortuous or angulated lesion	21 (1.3)	17 (1.1)	0.56
Moderate or heavy calcification	86 (5.4)	79 (5.0)	0.67

Values are mean ± SD or n (%). *Number of patients for whom continuous variables were calculated. †Renal insufficiency was defined as an estimated glomerular filtration rate <30 ml/min/1.73 m^2 of body surface area or the need for dialysis. ‡Peripheral arterial disease includes lower extremity peripheral artery disease, abdominal aortic aneurysm, renal and mesenteric artery disease, and extracranial carotid artery disease. §Number of lesions for which continuous variables were calculated. ‖Patients with B2/C lesions were classified according to the criteria of the ACC/AHA if 1 or more treated lesions met these criteria.

ACC = American College of Cardiology; AHA = American Heart Association; L = number of target lesions; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; SYNTAX = Synergy Between PCI With TAXUS and Cardiac Surgery.

TABLE 2 Procedural Characteristics

	BuMA (n = 1,174) (L = 1,605)	Excel (n = 1,174) (L = 1,572)	Difference (95% CI)*	p Value
During procedure				
Bivalirudin use	4 (0.3)	10 (0.9)	−0.5 (−1.1 to 0.1)	0.11
Glycoprotein IIb/IIIa inhibitor use	69 (5.9)	70 (6.0)	−0.1 (−2.0 to 1.8)	0.93
Transradial approach	1,118 (95.2)	1,123 (95.7)	−0.4 (−2.1 to 1.3)	0.62
Use of IVUS and/or OCT	36 (3.1)	38 (3.2)	−0.2 (−1.6 to 1.2)	0.81
Balloon pre-dilation	1,431 (89.2)	1,423 (90.5)	−1.4 (−3.5 to 0.7)	0.20
Device implantation				
Stents per patient	1.74 ± 0.96	1.70 ± 0.90	0.0 (−0.0 to 0.1)	0.34
Stents per lesion	1.27 ± 0.54	1.27 ± 0.52	0.0 (−0.0 to 0.0)	0.81
Stents diameter, mm	3.03 ± 0.43	3.02 ± 0.42	0.0 (−0.0, 0.0)	0.55
Total stent length per patient, mm	42.6 ± 26.6	42.0 ± 25.4	0.6 (−1.5 to 2.7)	0.60
Total stent length per lesion, mm	31.2 ± 17.8	31.4 ± 17.0	−0.2 (−1.4 to 1.0)	0.71
Post-dilation	849 (52.9)	787 (50.1)	2.8 (−0.6 to 6.3)	0.11
After procedure				
Post-procedural QCA				
Minimal lumen diameter, mm				
In-stent	2.55 ± 0.43 (1,586†)	2.57 ± 0.40 (1,558†)	−0.0 (−0.1 to 0.0)	0.08
In-segment	2.31 ± 0.47 (1,586†)	2.32 ± 0.46 (1,558†)	−0.0 (−0.0 to 0.0)	0.55
Diameter stenosis, %				
In-stent	8.84 ± 5.90 (1,586†)	8.43 ± 5.75 (1,558†)	0.4 (−0.0 to 0.8)	0.05
In-segment	14.5 ± 9.3 (1,586†)	14.7 ± 9.9 (1,558†)	−0.2 (−0.8 to 0.5)	0.64
Post-procedural TIMI 3 flow	1,586 (98.8)	1,550 (98.6)	0.2 (−0.6 to 1.0)	0.59
Residual SYNTAX score	4.64 ± 5.85 (1,164‡)	4.86 ± 5.79 (1,159‡)	−0.2 (−0.7 to 0.3)	0.36
Successful outcome§				
Device success	2,035 (99.8)	1,996 (99.95)	−0.2 (−0.4 to 0.0)	0.22
Lesion success	1,586 (98.8)	1,550 (98.6)	0.2 (−0.6 to 1.0)	0.59
Procedural success	1,117 (95.1)	1,112 (94.7)	0.4 (−1.4 to 2.2)	0.64

Values are n (%) or mean ± SD. *The value is the difference in the BuMA group compared with the Excel group. †Number of lesions for which continuous variables were calculated. ‡Number of patients for whom continuous variables were calculated. §Definitions for device, lesions, and procedural success are provided for the pre-specified endpoints in the definitions section of the Online Appendix.

CI = confidence interval; IVUS = intravascular ultrasound; OCT = optical coherence tomography; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Table 1.

All adverse events were adjudicated by a blinded clinical events committee, and angiograms were reviewed by a blinded independent core laboratory (CCRF, Beijing, China). Details of the study organization and participating centers are listed in the Online Appendix.

STATISTICAL ANALYSIS. The trial was powered for sequential testing of noninferiority and superiority for the primary endpoint at 1 year. For noninferiority testing, an 8.3% event rate was assumed for both groups on the basis of the event rates from a previously reported all-comers study (13). With a noninferiority margin of 3.5%, enrolling 2,350 patients and anticipating 5% loss to follow-up yielded 85% power to demonstrate noninferiority with a 1-sided type I error of 0.025. Superiority testing was pre-specified if the noninferiority for TLF was met. Assuming a 1-year TLF rate of 8.3% in the Excel group and 5.3% in the BuMA group (a clinically meaningful 36% relative reduction), the study had 80% power to demonstrate superiority with a 2-sided type I error of 0.05.

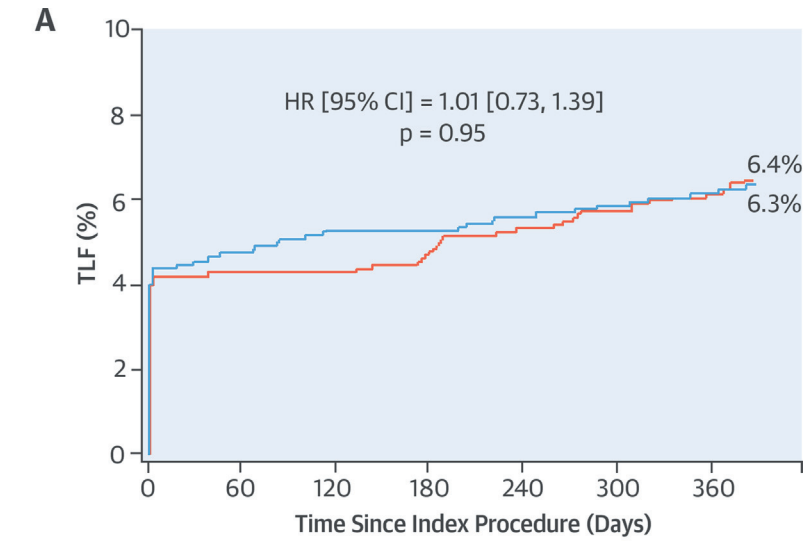
Continuous variables are presented as mean ± SD and were compared by Student *t* test. Categorical variables are presented as counts and percentages and were compared by chi-square or Fisher exact test. The 95% confidence interval (CI) of the difference between the 2 treatment arms was calculated by normal approximation for continuous variables and by the Newcombe score method for binary variables. Noninferiority for the primary endpoint was examined by the Wald asymptotic test. Cumulative event rates and 95% CIs of the differences for 1-year clinical outcomes between the 2 treatment arms were calculated on the basis of Kaplan-Meier estimates. Survival curves for time-to-event variables were compared for superiority with the log-rank test, with hazard ratios (HRs) calculated using Cox proportional hazards regression. We pre-specified analyses of the primary endpoint at 1 year among 13 subgroups, with differences in relative risk determined by interaction testing using a logistic model. All statistical analyses were performed using SAS software version 9.1.3 (SAS Institute, Cary, North Carolina).

RESULTS

PATIENTS AND PROCEDURES. From December 2013 to August 2014, 2,348 eligible patients with 3,177 lesions were randomly assigned at 46 sites in China to receive either the BuMA SES (n = 1,174 patients with 1,605 lesions) or the Excel SES (n = 1,174 patients with 1,572 lesions). A total of 1,169 patients (99.6%) in the BuMA group and 1,164 patients (99.1%) in the Excel group completed 1-year follow-up. Of the 2,348 patients in the ITT population, 85 patients (n = 39 in the BuMA group and 46 in the Excel group) with at least 1 pre-specified protocol deviation did not meet PTE criteria, as shown in Online Figure 1.

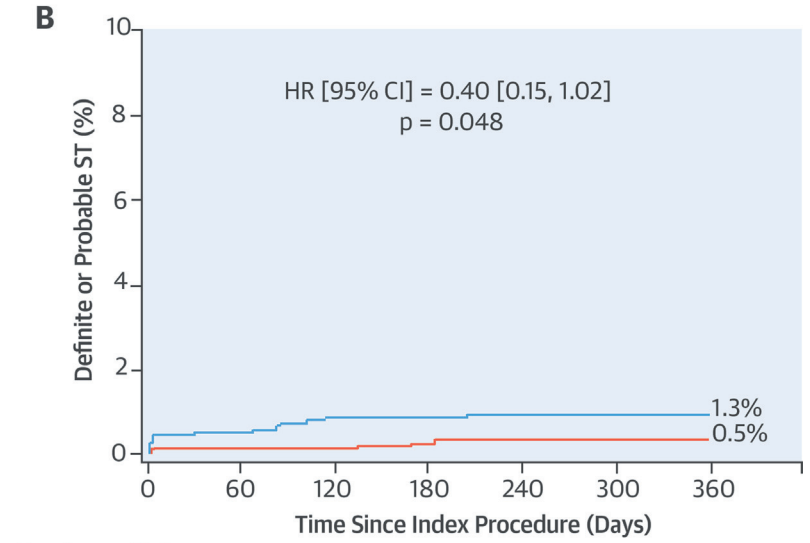
Baseline demographics, risk factors, and lesion and procedural characteristics of the patients were well matched between the 2 groups (Tables 1 and 2, Online Tables 2 and 3), except for a slightly greater rate of previous percutaneous coronary intervention procedures in the Excel group. The mean age was 61.2 ± 10.6 years, 24.3% had diabetes, and 31.2% had acute myocardial infarction (AMI) within 1 month. The total number of stents implanted was 1.72 ± 0.93 per

CENTRAL ILLUSTRATION Comparing 2 Biodegradable Polymer-Based Sirolimus-Eluting Stents: Time-to-Event Curves



Number at Risk:

BuMA	1,174	1,123	1,123	1,118	1,107	1,094	1,089
Excel	1,174	1,116	1,110	1,110	1,104	1,097	1,090



Number at Risk:

BuMA	1,174	1,164	1,164	1,161	1,156	1,146	1,144
Excel	1,174	1,158	1,151	1,151	1,147	1,141	1,136

BuMA Excel

Xu, B. et al. J Am Coll Cardiol. 2016;67(19):2249–58.

Time-to-event curves depict the primary endpoint and definite/probable stent thrombosis through 1 year. Analyses were performed in the intention-to-treat population. Kaplan-Meier curves show the cumulative incidence of **(A)** target lesion failure (TLF) (the primary endpoint); and **(B)** definite/probable stent thrombosis. CI = confidence interval; HR = hazard ratio; ST = stent thrombosis.

TABLE 3 1-Year Clinical Outcomes in the Intention-to-Treat Population*

	BuMA (n = 1,174)	Excel (n = 1,174)	Difference (95% CI)	p Value
Target lesion failure†	75 (6.4)	74 (6.3)	0.1 (−1.9 to 2.1)	0.95
Patient-oriented composite endpoint‡	114 (9.6)	99 (8.5)	1.2 (−1.1 to 3.5)	0.31
All-cause death	27 (2.2)	20 (1.7)	0.5 (−0.6 to 1.6)	0.31
Cardiac	14 (1.2)	15 (1.3)	−0.1 (−1.0 to 0.8)	0.85
Vascular	6 (0.5)	4 (0.3)	0.2 (−0.4 to 0.7)	0.53
Noncardiovascular	7 (0.5)	1 (0.1)	0.4 (0.0 to 0.9)	0.03
All myocardial infarction	52 (4.4)	62 (5.3)	−0.9 (−2.6 to 0.9)	0.33
Target vessel related	50 (4.3)	57 (4.9)	−0.6 (−2.3 to 1.1)	0.48
Q-wave	9 (0.8)	10 (0.9)	−0.1 (−0.8 to 0.7)	0.82
Non-Q-wave	40 (3.4)	46 (3.9)	−0.5 (−2.0 to 1.0)	0.51
Non-target vessel related	2 (0.2)	5 (0.4)	−0.3 (−0.7 to 0.2)	0.26
Q-wave	1 (0.1)	1 (0.1)	0.0 (−0.2 to 0.2)	1.00
Non-Q-wave	1 (0.1)	4 (0.3)	−0.3 (−0.6 to 0.1)	0.18
Periprocedural	44 (3.8)	49 (4.2)	−0.4 (−2.0 to 1.2)	0.59
Post-procedural	8 (0.7)	13 (1.2)	−0.5 (−1.3 to 0.4)	0.26
Any revascularization	52 (4.4)	34 (2.9)	1.5 (−0.1 to 3.0)	0.051
Ischemia-driven TVR	25 (2.2)	15 (1.3)	0.9 (−0.2 to 1.9)	0.11
Ischemia-driven TLR	22 (1.9)	14 (1.2)	0.7 (−0.3 to 1.7)	0.18
Definite/probable stent thrombosis	6 (0.5)	15 (1.3)	−0.8 (−1.5 to −0.0)	0.048
Definite	2 (0.2)	7 (0.6)	−0.4 (−0.9 to 0.1)	0.09
Probable	4 (0.3)	8 (0.7)	−0.3 (−0.9 to 0.2)	0.25
Acute (0 to 24 h)	3 (0.3)	4 (0.3)	−0.1 (−0.5 to 0.4)	0.71
Subacute (>24 h to 30 days)	0 (0)	5 (0.4)	−0.4 (−0.8 to −0.1)	0.03
Late (>30 days to 1 year)	3 (0.3)	6 (0.5)	−0.3 (−0.8 to 0.3)	0.31

Values are n (%). *1-year follow-up includes a window of ± 30 days. †Target lesion failure was defined as a composite of cardiac death, target vessel MI, or ischemia-driven TLR. ‡Patient-oriented composite endpoint was defined as a composite of all-cause death, all MI, or any revascularization. Percentages were Kaplan-Meier estimates from the intention-to-treat analysis. A log-rank test was used to calculate p values.

MI = myocardial infarction; TLR = target lesion revascularization; TVR = target vessel revascularization; other abbreviations as in Tables 1 and 2.

patient, with total stent length of 42.3 ± 26.0 mm. Baseline SYNTAX scores were 14.5 ± 9.2 in the BuMA group and 14.8 ± 9.3 in the Excel group (p = 0.46). Dual antiplatelet therapy (DAPT) utilization rates during hospitalization and at follow-up were high and were comparable in both groups (Online Table 4).

CLINICAL OUTCOMES. At 1 year, TLF occurred in 75 (6.4%) BuMA-assigned and 74 (6.4%) Excel-assigned patients, which was a difference of 0.06% (95% CI: −1.93% to 2.04%), demonstrating noninferiority of the BuMA SES to the Excel SES ($p_{noninferiority}$ = 0.0003; $p_{superiority}$ = 0.95). The Kaplan-Meier estimates for 1-year TLF were 6.4% in the BuMA group and 6.3% in the Excel group (HR: 1.01; 95% CI: 0.73 to 1.39; log-rank p = 0.95) (**Central Illustration**). There were also no significant differences in the individual TLF components of cardiac death, TV-MI, or ID-TLR between the devices (**Table 3**, **Figure 1**). Rates of periprocedural MI were similar between devices, regardless of the threshold used to define MI (Online Table 5). The 1-year relative rates of TLF were consistent across the examined pre-specified subgroups (**Figure 2**). The PoCE at 1 year occurred in 9.6% and 8.5% of patients in the BuMA and Excel groups, respectively (log-rank p = 0.31). The individual components of the PoCE also did not significantly vary between devices, except that patients in the BuMA group had a borderline significantly higher rate of any revascularization (4.4% vs. 2.9%; log-rank p = 0.05). Similar results were found in the PTE population (Online Table 6, Online Figure 2).

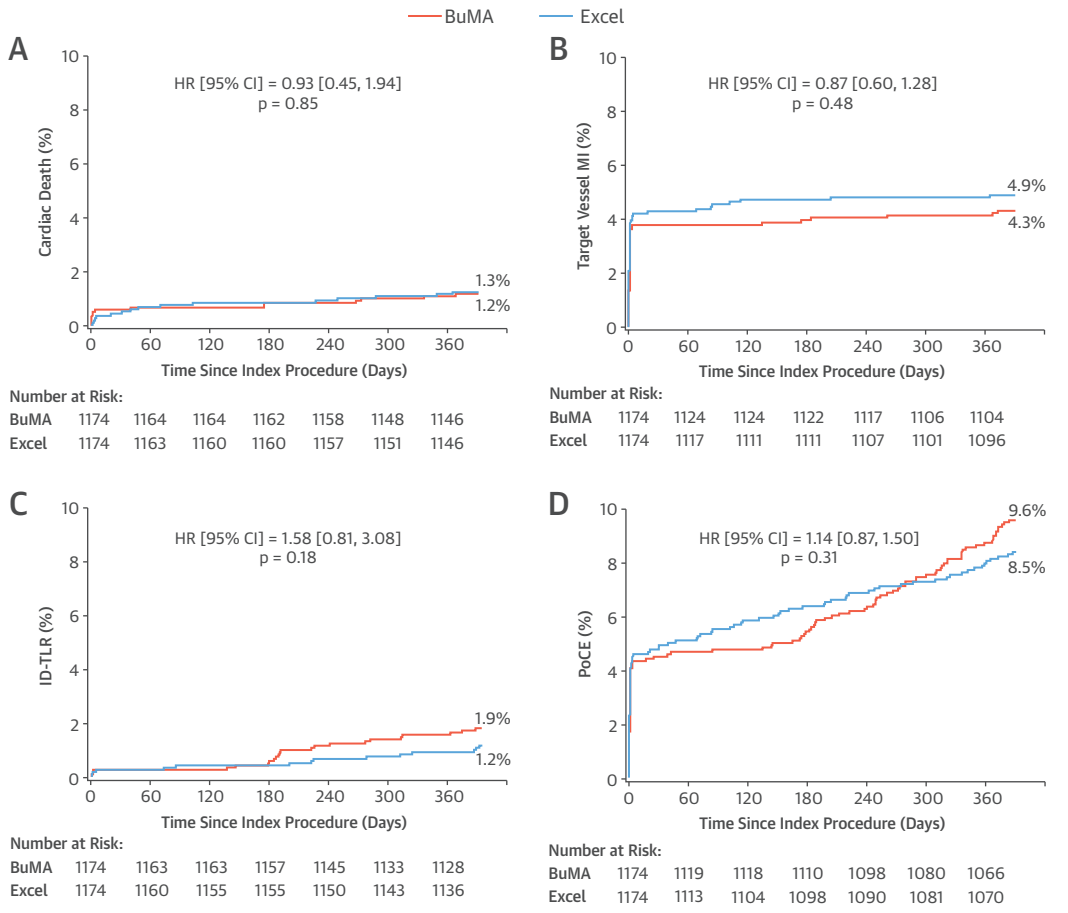
STENT THROMBOSIS. At 1 year, the rate of definite/probable ST was lower in BuMA-assigned patients compared with Excel-assigned patients (0.5% vs. 1.3%; log-rank p = 0.048). The difference in ST favoring the BuMA stent was stronger in the PTE cohort (0.4% vs. 1.3%; log-rank p = 0.01) (Online Table 6). Time-to-event analysis showed that the curves separated principally within the first 3 months (Online Figures 3 and 4), and were significantly different in the subacute period (>24 h to 30 days) (**Table 3**). By ITT, among patients presenting with AMI within 1 month, definite/probable ST occurred within 1 year in 1 patient (0.3%) in the BuMA group and 8 patients (2.2%) in the Excel group (HR: 0.13; 95% CI: 0.02 to 1.00; p = 0.05). In contrast, in patients without AMI within 1 month, the 1-year rates of definite/probable ST were similar with both stents: 0.6% (5 of 806) in the BuMA group versus 0.9% (7 of 801) in the Excel group (HR: 0.71; 95% CI: 0.23 to 2.23; p = 0.55; $p_{interaction}$ = 0.15).

DISCUSSION

In the present study, the BuMA SES was shown to be noninferior (but not superior) to the Excel SES for the primary endpoint of TLF at 1 year. Both devices had similar rates of cardiac death, TV-MI, ID-TLR, and most other measures of safety and efficacy. However, the 1-year rate of definite/probable ST was lower with the BuMA stent than the Excel stent.

Animal and human studies have linked polymer coatings to inflammation, hypersensitivity reactions, and abnormal healing, all of which predispose to ST (5,14). Biodegradable coatings were therefore designed to improve DES safety and potentially reduce the long-term requirement for DAPT. In the LEADERS trial, a biolimus A9-eluting BP-DES resulted in lower rates of very late ST from 1 to 5 years compared with the first-generation durable polymer Cypher SES (15), although ST rates within 1 year were not significantly different. Conversely, other studies have demonstrated higher 1-year and long-term ST rates with the biolimus A9-eluting BP-DES compared

FIGURE 1 Time-to-Event Curves for Selected Secondary Endpoints Through 1 Year



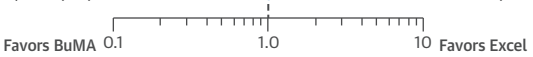
Analyses were performed in the intention-to-treat population. Kaplan-Meier curves show the cumulative incidence of **(A)** cardiac death; **(B)** target vessel MI; **(C)** ID-TLR; and **(D)** the PoCE. CI = confidence interval; HR = hazard ratio; ID-TLR = ischemia-driven target lesion revascularization; MI = myocardial infarction; PoCE = patient-oriented composite endpoint.

with contemporary durable polymer DES, especially the cobalt chromium EES (8). The causes of ST are multifactorial, however, and comprise numerous stent-related factors beyond the polymer, including strut thickness and metal composition as well as antiproliferative drug type and dose. The 1-year rates of ST have been shown to be comparable with a contemporary BP-EES and durable polymer EES with different stent platforms (9). Moreover, it is conceivable that the rate of drug elution and polymer bioabsorption can affect healing and ST rates. Sorting out which of these variables is most strongly related to ST ideally requires animal and large-scale clinical studies in which most components of the 2 stents are kept constant while varying only 1 factor.

Although there is a small difference between the 316L stainless steel BuMA and Excel stent in strut thickness (~10 μm), the major differences between these devices are the type of bioabsorbable polymers used and the method of bonding the polymers to the underlying stent surface, resulting in different rates of drug elution and polymer bioabsorption. Specifically, the PLGA polymer on the BuMA stent elutes sirolimus completely within 1 month, and the polymer is completely absorbed by 2 to 3 months (11). In contrast, the PLA polymer of the Excel stent elutes sirolimus completely within 6 months, and the polymer is completely absorbed by 9 months (10). In an 80-patient randomized trial, the primary endpoint of the percentage of covered stent struts, as assessed by OCT at 3 months, was significantly higher with the BuMA SES than the Excel SES (94.2% vs. 90.0%; $p < 0.01$), and the proportion of lesions with >10% uncovered struts was significantly lower with the

FIGURE 2 Subgroup Analysis of Target Lesion Failure at 1 Year

	Target Lesion Failure, - *Events/Total (%)*		Relative Risk (95% CI)	P-Value for Interaction
	BuMA, N = 1174	Excel, N = 1174		
Age				
<61 years	18/553 (3.3)	24/529 (4.5)	0.72 (0.39-1.31)	0.17
≥61 years	57/616 (9.3)	50/635 (7.9)	1.18 (0.82-1.69)	
Sex				
Female	22/345 (6.4)	25/343 (7.3)	0.87 (0.50-1.52)	0.54
Male	53/824 (6.4)	49/821 (6.0)	1.08 (0.74-1.57)	
Diabetes				
Present	21/274 (7.7)	18/293 (6.1)	1.25 (0.68-2.29)	0.43
Absent	54/895 (6.0)	56/871 (6.4)	0.94 (0.65-1.35)	
Recent MI within 30 days				
Present	20/363 (5.5)	30/363 (8.3)	0.67 (0.39-1.15)	0.07
Absent	55/806 (6.8)	44/801 (5.5)	1.24 (0.85-1.82)	
Number of target lesions				
1	40/815 (4.9)	48/829 (5.8)	0.85 (0.56-1.28)	0.21
≥2	35/354 (9.9)	26/335 (7.8)	1.27 (0.78-2.07)	
SYNTAX Score				
<13	23/570 (4.0)	19/547 (3.5)	1.16 (0.64-2.11)	0.60
≥13	52/589 (8.8)	55/602 (9.1)	0.97 (0.67-1.39)	
Reference vessel diameter				
<2.71 mm	51/646 (7.9)	51/626 (8.1)	0.97 (0.67-1.41)	0.77
≥2.71 mm	24/521 (4.6)	23/534 (4.3)	1.07 (0.61-1.87)	
Lesion length				
<16.4 mm	34/518 (6.6)	33/494 (6.7)	0.98 (0.62-1.56)	0.89
≥16.4 mm	41/649 (6.3)	41/666 (6.2)	1.03 (0.67-1.56)	
ACC/AHA lesion class				
B2/C	69/1025 (6.7)	72/1009 (7.1)	0.94 (0.69-1.30)	0.14
A/B1	6/144 (4.2)	2/155 (1.3)	3.23 (0.66-15.7)	
LAD lesion				
Yes	54/672 (8.0)	44/670 (6.6)	1.22 (0.83-1.80)	0.10
No	21/497 (4.2)	30/494 (6.1)	0.70 (0.40-1.20)	
Bifurcation lesion				
Yes	43/491 (8.8)	34/497 (6.8)	1.28 (0.83-1.97)	0.13
No	32/678 (4.7)	40/667 (6.0)	0.79 (0.50-1.24)	
Total occlusion				
Yes	15/203 (7.4)	17/206 (8.3)	0.90 (0.46-1.74)	0.69
No	60/966 (6.2)	57/958 (5.9)	1.04 (0.73-1.48)	
Total stent length per patient				
<35 mm	21/531 (4.0)	20/561 (3.6)	1.11 (0.61-2.02)	0.65
≥35 mm	54/638 (8.5)	54/603 (9.0)	0.95 (0.66-1.36)	
All patients	75/1169 (6.4)	74/1164 (6.4)	1.01 (0.74-1.38)	



Analyses were performed in the intention-to-treat population. The p value for interaction represents the likelihood of interaction between the variable and the relative treatment effect. Subgroups for continuous data were selected by median. Patients with multiple lesions were placed in the historically high-risk group if 1 or more treated lesions met these criteria (e.g., B2/C vs. A/B1 lesions, small vessel, long lesion, and so forth). ACC = American College of Cardiology; AHA = American Heart Association; LAD = left anterior descending artery; SYNTAX = Synergy Between PCI With Taxus and Cardiac Surgery; other abbreviations as in Figure 1.

BuMA stent (8.1% vs. 46.3%; $p < 0.01$) (11). More complete strut coverage by OCT has been associated in at least 1 study with a decreased rate of subsequent cardiovascular death, MI, or ST (16). The OCT findings of enhanced early strut coverage with the BuMA stent are consistent with the results of the present study, in which the 1-year rate of ST was lower with the BuMA than the Excel stent, a difference that emerged within the first month after implantation. The more rapid rates of drug elution and polymer absorption with the BuMA stent may allow for accelerated and more complete healing to occur within the first several months after stent implantation, a critical period for vascular restoration to prevent later complications (17).

The 1-year rates of ID-TLR were similar with the BuMA and Excel stents, consistent with the findings from the earlier randomized trial, which reported comparable mean neointimal thickness with both devices (11). Moreover, the 1-year rates of TLF and the PoCE were similar with both stents, consistent with overall similar safety and effectiveness. The fact that

these rates did not vary between the 2 devices, although ST was lower with the BuMA stent, reflects the multifactorial etiology of stent- and patient-related outcomes. Similarly, in the Resolute All-comers trial, the cobalt chromium EES and the slow-release zotarolimus-eluting stent had nearly identical rates of TLF at 1 year, despite a lower rate of definite ST with the EES (13).

STUDY LIMITATIONS. First, although our inclusion and exclusion criteria were less restrictive than most comparative DES trials, selection bias cannot be ruled out. A universal screening log was not kept, and thus, we cannot state with certainty how generalizable the results are. Specifically, ~80% of all enrolled patients presented with an acute coronary syndrome; the extent to which the present results therefore apply to patients with stable ischemic heart disease is uncertain. Second, because we used the modified Academic Research Consortium definition of MI, the incidence of this event is likely over-represented compared with a more clinically relevant definition of MI (18). However, the relative incidence of periprocedural MI did not vary according to the biomarker threshold used to define its occurrence. Third, the 1-year rate of TLF was slightly lower than assumed (6.4%, rather than 8.3%), and thus, the 3.5% noninferiority margin is relatively wider than desired. However, we can state with 95% confidence that the 1-year TLF rate with the BuMA stent is not >2.0% more than with the Excel stent. Fourth, the present study was not powered to evaluate low frequency safety endpoints, such as ST. We also only recorded events for which the patient sought care; therefore, the incidence of silent MI and angiographic restenosis may be underestimated. Fifth, we currently have only 1 year of follow-up data; comprehensive evaluation of the safety and efficacy of these devices will require long-term evaluation, which is ongoing through 5 years. Finally, because most patients received 1 year of DAPT, we cannot speculate whether the more rapid drug elution, polymer bioabsorption, and strut coverage with the BuMA stent would safely enable a shorter duration of DAPT with this device.

CONCLUSIONS

In the multicenter, randomized PANDA III trial, the PLGA polymer-based BuMA SES was noninferior to the PLA polymer-based Excel SES for the primary endpoint of TLF at 1 year in an all-comers population. The BuMA SES was associated with a lower incidence of ST compared with the Excel SES, consistent with previous findings of enhanced early strut coverage with this device.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Runlin Gao, Fu Wai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences, A 167, Beilishi Road, Xicheng District, Beijing 100037, China. E-mail: gaorunlin@citmd.com.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:

In patients undergoing percutaneous coronary intervention, the BuMA BP-DES, a device with more rapid drug elution and polymer absorption kinetics, was associated with a lower incidence of ST, possibly due to enhanced early strut coverage.

TRANSLATIONAL OUTLOOK: Further studies are warranted to determine whether accelerated drug elution and polymer absorption allow for earlier withdrawal of DAPT after BP-DES deployment and to compare clinical outcomes with these devices to those achieved with durable polymer DES and fully resorbable vascular scaffolds.

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KEY WORDS coronary artery disease, drug-eluting stents, randomized controlled trial, thrombosis

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