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9-Month Clinical and Angiographic Outcomes of the COBRA Polyzene-F NanoCoated Coronary Stent System

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ABSTRACT

OBJECTIVES The aim of this study was to assess the safety and effectiveness of the COBRA Polyzene-F NanoCoated Coronary Stent System (CeloNova Biosciences, San Antonio, Texas) for the treatment of de novo coronary artery lesions.

BACKGROUND Polyzene-F–coated coronary stents have shown reduced thrombogenicity and inflammation in preclinical studies.

METHODS Patients with de novo coronary artery lesions meeting eligibility criteria were enrolled in a nonrandomized, prospective clinical trial. The primary endpoint was target vessel failure (TVF) (defined as a composite of cardiac death, myocardial infarction, or clinically driven target vessel revascularization) at 9 months. A pre-specified subset was planned for routine repeat angiographic follow-up at 9 months. The powered secondary endpoint was mean late lumen loss (LL). The comparator was a performance goal derived from meta-analysis of historical bare-metal stent trials of 19.62% for TVF and 1.1 mm for LL. Other secondary endpoints were clinically driven target lesion revascularization and definite or probable stent thrombosis.

RESULTS Of 296 enrolled patients, 287 (97%) completed primary endpoint analysis; 130 were planned for angiographic follow-up and 115 (88%) completed. At 9 months, TVF had occurred in 33 patients (11.5%; upper 95% confidence boundary: 15.07%), including 1 (0.3%) cardiac death, 20 (7.0%) myocardial infarctions (17 periprocedural), and 17 (5.9%) target vessel revascularizations. LL was 0.84 ± 0.48 mm (upper 95% confidence boundary: 0.92). Target lesion revascularization occurred in 13 patients (4.6%). There were no stent thrombosis events.

CONCLUSIONS The COBRA Polyzene-F stent met performance goals for TVF and LL at 9 months. There was an excellent safety profile, with infrequent late myocardial infarction and no stent thrombosis.
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Bare-metal stents (BMS) have shown improved procedural outcomes and reduced restenosis compared with balloon angioplasty (1,2), but even contemporary BMS have an unacceptably high rate of clinical restenosis. First-generation drug-eluting stents (DES) reduced the risk for restenosis (3,4) but were plagued by an ongoing risk for very late stent thrombosis in routine practice, despite

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12 months of dual antiplatelet therapy (DAPT) (5,6). Although newer generation DES have shown much lower rates of very late stent thrombosis (7), guidelines still recommend a minimum of 6 to 12 months of DAPT after DES (8,9). Circumstances that require shorter term DAPT, such as high bleeding risk, noncompliance, and need for urgent noncardiac surgery have not been adequately addressed. Availability of a coronary stent with lower restenosis risk than historical BMS without a requirement for increased duration of DAPT would be of benefit.

Preclinical studies of a cobalt-chromium coronary stent coated with a nanothin layer of Polyzene-F (PzF) (COBRA Polyzene-F NanoCoated Coronary Stent System, CeloNova Biosciences, San Antonio, Texas) have demonstrated evidence of reduced inflammation, neointimal hyperplasia, and thrombogenicity compared with the Vision BMS (Abbott Vascular, Santa Clara, California) and uncoated COBRA stents (10). In these ex vivo analyses, there were significant reductions in monocyte adherence and platelet aggregation as potential explanations for lower inflammation and thrombogenicity, respectively. Furthermore, early clinical studies of a previous iteration of the COBRA PzF stent showed favorable clinical and angiographic restenosis outcomes with very low stent thrombosis (11,12). We sought to assess clinical and angiographic outcomes of the COBRA PzF stent compared with historical results for BMS currently approved by the U.S. Food and Drug Administration as part of a pre-market approval application.

METHODS

STUDY DESIGN AND POPULATION. The PzF SHIELD (COBRA PzF Stent in Native Coronary Arteries for Early Healing, Thrombus Inhibition, Endothelialization, and Avoiding Long-Term Dual Anti-Platelet Therapy) study was a multicenter, prospective, single-arm, nonrandomized clinical trial conducted at 35 centers within (23 centers) and outside (12 centers) the United States. Eligible patients were older than 18 years and had symptomatic ischemic heart disease due to a single de novo lesion contained within a native coronary artery with reference vessel diameter between 2.5 and 4.0 mm and lesion length ≤24 mm. Clinical exclusion criteria included any previous coronary intervention within 30 days, any previous stent within 15 mm of the target lesion, a previous DES anywhere within the target vessel, myocardial infarction (MI) within 72 h prior to enrollment, left ventricular ejection fraction <30%, comorbid condition limiting participation or life expectancy <12 months, and inability to comply with DAPT for 1 month. Angiographic exclusions included unprotected left main target lesion, nontarget lesions >50% within the target vessel, lesion involving a side branch >2.0 mm diameter, angiographic thrombus within target vessel, excessive tortuosity, and severe calcification. (See the Online Appendix for complete inclusion and exclusion criteria.) Protocol-specified angiographic follow-up was planned in the first 130 consecutive patients who provided consent and was to be scheduled after the completion of 9-month clinical follow-up. A subset of the angiographic follow-up cohort also underwent optical coherence tomographic evaluation (n = 57).

The protocol was approved by the Institutional Review Board or ethics committee at each site. Informed consent was documented for each patient.

ABBREVIATIONS AND ACRONYMS

BMS = bare-metal stent(s)
CI = confidence interval
CKMB = creatine kinase–MB
DAPT = dual antiplatelet therapy
DES = drug-eluting stent(s)
LL = lumen loss
MI = myocardial infarction
PzF = Polyzene-F
QCA = quantitative coronary angiography
TLR = target lesion revascularization
TVF = target vessel failure
TVR = target vessel revascularization

DEVICE DESCRIPTION. The COBRA PzF stent is a balloon-expandable cobalt-chromium alloy coronary stent with strut thickness of 71 μm. It is pre-mounted on a custom rapid-exchange balloon delivery catheter. The surface of the stent is treated with a nanolayer of PzF (poly-bis[trifluoroethoxy]phosphazene). The stent was available for the study in diameters of 2.5 to 4.0 mm and lengths of 8 to 30 mm.

ADJUNCTIVE MEDICAL THERAPIES. All patients were required to receive DAPT beginning not later than the day of stent placement and continuing uninterrupted for 30 days after stent placement. DAPT was to consist of aspirin 75 to 325 mg daily plus a second agent; any oral antiplatelet drug approved for use to prevent stent thrombosis in the country of stent placement was permitted as a second agent, and choice of this drug was at the discretion of the operator. Following 30 days, continued antiplatelet monotherapy with aspirin alone was required, while continuation of a second drug was discretionary. Medical therapies applied at the time of stent placement and during the follow-up period were expected to conform to usual standards of care, but use of other specific drugs were not mandated in the study protocol.

ENDPOINTS AND DEFINITIONS. The primary endpoint was target vessel failure (TVF) at 270 days, defined as a composite of cardiac death, target vessel MI, or repeat revascularization of any segment of the target vessel. All deaths without clear noncardiac cause were considered as cardiac. MI was defined as Q-wave MI in the presence of new pathological

Q waves and any elevation of creatine kinase-MB (CKMB) or non-Q-wave MI if CKMB elevation was >3 times the site-specific upper limit of normal or, in the absence of CKMB, elevation of troponin >3 times the site-specific upper limit of normal. Clinically driven target vessel revascularization (TVR) was considered in the presence of a positive result on a functional ischemia study or ischemic symptoms and an angiographic minimal luminal diameter stenosis ≥50% determined by core laboratory quantitative coronary angiography (QCA) or revascularization of a target vessel with diameter stenosis ≥70% by QCA without either angina or a positive result on a functional study. The powered secondary endpoint was angiographic in-stent late lumen loss (LL), determined by QCA in the subset of patients specified for routine angiographic follow-up at 9 months. Binary angiographic restenosis was defined as a ≥50% diameter stenosis of the stented lesion (in-stent) or the stented lesion plus the 5 mm proximal or distal to the stent (in-segment) at angiographic follow-up. Device success was defined as achievement of <30% diameter stenosis using only the COBRA PzF stent. Secondary clinical endpoints included clinically driven target lesion revascularization (TLR), defined as repeat revascularization of the stented lesion or the 5-mm segment proximal or distal to the stent in the presence of a positive results on a functional ischemia study or ischemic symptoms and an angiographic minimal luminal diameter stenosis ≥50% determined by core laboratory QCA or revascularization of a target vessel with diameter stenosis ≥70% by QCA without either angina or a positive result on a functional study. The protocol was designed for completion of the 9-month clinical follow-up before routine angiographic follow-up to limit angiographic bias. Stent thrombosis was classified as definite or probable according to Academic Research Consortium criteria (13). All clinical endpoints were adjudicated by an independent clinical events committee (Harvard Clinical Research Institute, Boston, Massachusetts). All angiographic endpoints were assessed by an independent core laboratory (Beth Israel Deaconess Medical Center, Boston, Massachusetts).

STATISTICAL METHODS. Performance goal. Using the large volume of data available regarding outcomes following BMS placement, a performance goal based on recent clinical trials including BMS cohorts was selected as the comparator. The performance goal was determined by a meta-analysis of 5 clinical trials reporting TVF at 9 months (see the Online Appendix for details of the studies included). The reported rates of TVF for these studies were adjusted to account for bias introduced by routine angiographic follow-up (14), because our objective was to assess a clinical TVF rate prior to the effect of routine angiography. The TVF rate at 270 days post-procedure derived from the meta-analysis assuming no mandated angiographic follow-up was 10.62% (95% confidence interval [CI]: 9.35% to 11.90%). Notably, MI rates in these studies were based on a historical modified World Health Organization definition of total creatine kinase >2 times the upper limit of normal. Because PzF SHIELD defined MI according to the more sensitive CKMB >3 times normal, the MI rate was adjusted upward by 3% (13). The meta-analysis rate for TVF was determined thus as 13.62%. Because absolute equivalence to a constant cannot be proved statistically, an absolute difference of 6% was established in consultation with the Food and Drug Administration to yield a performance goal of 19.62%. This performance goal represents the value above which the upper 1-sided 95% CI of the observed result must not exceed in order to conclude statistical significance.

Sample size. On the basis of the performance goal, a sample size of 281 patients would provide 85% power to reject the null hypothesis. We planned to enroll 296 patients to allow for 5% loss to follow-up for the primary endpoint. For the secondary endpoint of LL, we assumed a performance goal of 1.1 mm mean LL on the basis of reported rates for BMS and projected a mean LL for the COBRA PzF stent of 0.9 mm. An evaluable sample size of 90 patients would provide 87.6% power with alpha error of 5%. We planned to enroll the first 130 patients to account for 30% noncompliance with planned angiographic follow-up.

Statistical analysis. The primary analysis was based on intention-to-treat, defined as enrollment in the study and attempted placement of the COBRA PzF stent. Continuous variables are reported as mean ± SD or median, minimum, and maximum values. Categorical variables are reported as numbers and percentages. Analysis of the TVF primary endpoint was performed using the exact test of the binomial distribution at the 1-sided 0.05 level of significance. An exact 1-sided upper 95% CI of the primary endpoint rate was calculated for all patients who experienced the primary endpoint or who had follow-up within 30 days of 270 days post-procedure. If this upper interval was <19.62%, the null hypothesis was rejected in favor of the alternative. The late loss endpoint hypothesis test was carried out by comparing the upper bound of the 1-sided 97.5% CI of 270-day in-stent LL with the performance goal of 1.1 mm. Other secondary endpoints are presented as numbers and percentages for all patients having the endpoints or completing follow-up within

30 days of the 270-day period. Analyses for interaction were pre-specified to determine the impact of enrollment within the United States, patient sex, presence of diabetes mellitus, and planned follow-up angiography per protocol.

To test for poolability of the sites, we used a mixed-effects logistic model with TVF to 270 days as an outcome and the clinical site variable added as a random effect. The resulting p value was 0.376, indicating homogeneity among the sites.

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

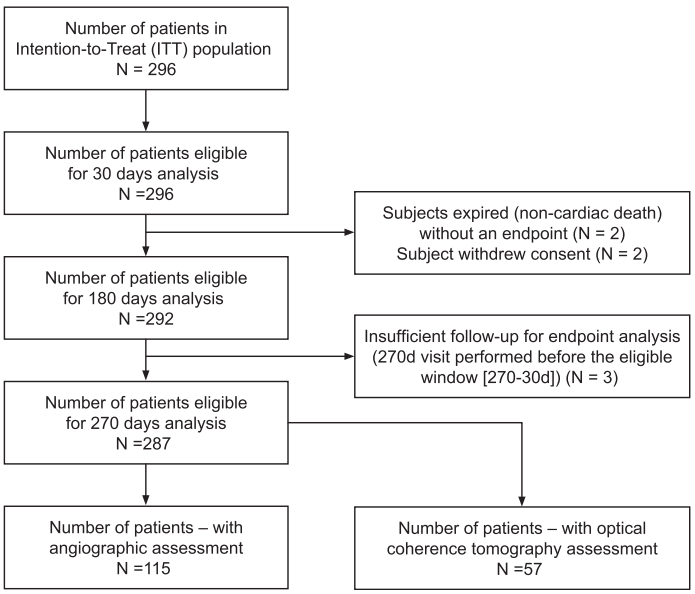
STUDY POPULATION AND BASELINE AND PROCEDURAL CHARACTERISTICS. Between August 21, 2013, and February 18, 2015, 296 patients were enrolled, with 166 (56%) enrolled at sites in the United States. Nine patients (3%) were lost to follow-up or not evaluable at or beyond 9 months of treatment; therefore, 287 patients were assessed for the 9-month primary endpoint analysis (Figure 1). The mean age was 66 ± 10 years, 30% were women, and 34% had diabetes (Table 1). A total of 300 lesions were treated, with complete baseline angiographic data available for 299 lesions and post-procedure analysis available for 297 lesions. The reference vessel diameter was 2.74 ± 0.48 mm, and lesion length was 12.77 ± 6.75 mm. Device success was achieved in 100% of lesions (Table 2).

CLINICAL OUTCOMES. At 30 days, TVF events occurred in 19 patients (6.4%), including 17 MIs (5.8%) (all periprocedural), 1 TVR (0.3%), and 1 cardiac death (0.3%). There were no stent thromboses.

Clinical events to 270 days are shown in Table 3. The primary endpoint of 9-month TVF occurred in 33 patients (11.5%). The upper 1-sided 95% confidence boundary was 15.07%, well below the performance goal of 19.62%. There were no additional cardiac deaths. There were 3 MI events between 30 and 270 days, 2 of which were associated with restenosis and subsequent TLR and 1 in the setting of aortic stenosis and rapid atrial fibrillation without repeat cardiac catheterization. Clinically driven TVR occurred in 17 patients (5.9%) and included clinically driven TLR in 13 patients (4.6%). Of these, 6 underwent TLR after protocol-mandated angiographic follow-up, despite protocol efforts to complete 9-month clinical follow-up prior to planned angiography.

Adherence to DAPT was assessed at 30 days and 9 months. At 30 days, 95% of patients were adherent. By 9 months, 52% of patients remained on DAPT.

FIGURE 1 Patient Flow Diagram



ANGIOGRAPHIC OUTCOMES. Routine angiographic follow-up was planned in 130 patients and was completed in 115 patients (88%) with 117 lesions (Table 4). The powered secondary endpoint of LL was 0.84 ± 0.48 mm. The upper bound of the 1-sided 97.5% CI was 0.92 mm, which was below the performance goal of 1.1 mm. The cumulative distribution frequency for LL is shown in Figure 2A. More than 65% of patients had LL <1.0 mm, and only 2 patients had LL >2.0 mm. The cumulative distribution frequency curves for in-stent percentage diameter stenosis pre- and post-procedure and at follow-up are shown in Figure 2B. In-stent binary angiographic restenosis occurred in 25.6% of patients, including 6 patients (5%) with follow-up diameter stenosis >70% and 1 patient with late total occlusion.

PRE-SPECIFIED SUBGROUP ANALYSES. Nine-month clinical and angiographic outcomes were assessed in 4 pre-specified subgroups (Online Tables 1 and 2). For the endpoints of TVF and LL, no significant interactions were observed between patients treated within the United States compared with outside U.S. enrollment sites, male compared with female sex, presence compared with absence of diabetes, or planned angiographic follow-up compared with clinical follow-up (TVF endpoint only). The numerically lower rate of TVF for patients with diabetes compared with patients without diabetes (6.3% vs. 13.8%; p = 0.07) was related mostly to a lower observed

TABLE 1 Baseline Clinical Characteristics (n = 296)

Age, yrs	66.5 ± 10.3
Female	88 (29.7)
History of diabetes	99 (33.7)
Insulin therapy	22 (22.2)
History of hypertension	243 (82.6)
History of hyperlipidemia	237 (80.7)
Chronic kidney disease	17 (5.8)
Current smoking	65 (22.1)
Prior MI	44 (14.9)
Prior coronary bypass surgery	15 (5.1)
History of heart failure	34 (11.6)
Clinical presentation	
Stable angina	162 (54.7)
Positive functional study	40 (13.5)
Unstable angina	87 (29.4)
Acute MI (>72 h)	7 (2.4)

Values are mean ± SD or n (%).
MI = myocardial infarction.

TABLE 2 Baseline Angiographic and Procedural Characteristics (n = 296 Patients, n = 300 Lesions)

Target vessel	
Left anterior descending	108 (36.0)
Left circumflex	64 (21.3)
Right	128 (42.7)
Reference vessel diameter, mm	2.74 ± 0.48
Lesion length, mm	12.77 ± 6.45
Minimum luminal diameter, mm	0.98 ± 0.36
Percentage diameter stenosis	64.95 ± 11.43
Tortuosity, moderate/severe	17 (5.7)
Calcification	
Moderate	86 (28.8)
Severe	40 (13.4)
Total stent length, mm	17.86 ± 5.59
Stent diameter, mm	3.08 ± 0.43
Pre-dilation	284 (96.3)
Post-dilation	142 (48.1)
Final in-stent minimum luminal diameter, mm	2.53 ± 0.42
Final in-stent percentage diameter stenosis	7.68 ± 9.09
Final in-segment percentage diameter stenosis	20.44 ± 7.76

Values are n (%) or mean ± SD.

rate of periprocedural MI (2.0% vs 7.7%; p = 0.06), with no difference in clinically driven TLR (3.2% vs. 5.3%; p = 0.55).

DISCUSSION

In this prospective, nonrandomized clinical trial, the COBRA PzF stent achieved the pre-specified performance goals for both the primary endpoint of TVF and the powered secondary endpoint of LL. These performance goals were based on historical results from contemporary studies that included BMS cohorts, and success on these goals provides evidence that the COBRA PzF stent is safe and effective in the population treated. The successful performance included infrequent (4.6%) clinically driven TLR and an excellent safety profile with no stent thrombosis and about 1% MI beyond the index periprocedural period through 9-month clinical follow-up.

Aside from the formal performance goal statistical comparison, the observed results compare favorably with those of other recently approved BMS. The most recently approved BMS is the REBEL (Boston Scientific, Marlborough, Massachusetts). It is a thin-strut (81 μm), balloon-expandable stent composed of platinum-chromium alloy approved for use in the United States in July 2014. In the pre-market approval study of this device, 9-month target lesion failure occurred in 11.5% of patients, including clinically driven TLR in 7.4%, in the absence of routine angiographic follow-up (15). Definite or probable stent thrombosis was consistent with other BMS and occurred in 2 of 333 studied patients (0.6%).

Perhaps more important than relative comparisons between BMS is the question of whether any BMS should have a role in coronary stenting. Until recently, BMS have been used in approximately 15% of patients in the United States and more frequently in some countries, with preference over DES mostly related to concerns over prolonged DAPT and costs (16). Studies with newer generation DES that indicate potential safety of DAPT duration as short as 3 months and the DAPT (Dual Anti-Platelet Therapy) study that showed similar risk and benefit for DES and BMS with continuation of therapy for 12 versus 30 months have reduced further the enthusiasm for current BMS as an alternative (17–19). Furthermore, in the LEADERS FREE (Prospective Randomized Comparison of the BioFreedom Biolimus A9 Drug-Coated Stent Versus the Gazelle Bare-Metal Stent in Patients at High Bleeding Risk) trial, a contemporary biolimus coated stent with no polymer was superior to a BMS for both the primary effectiveness endpoint of clinically driven TLR (5.1% vs. 9.8%; p < 0.001) and a composite safety endpoint of cardiac death, MI, or stent thrombosis (9.4% vs. 12.9%; p = 0.005), despite only 30 days of DAPT in both groups (20). Notably, overall TLR frequency with the thicker strut Gazelle BMS was 10% in the absence of routine angiographic follow-up, and much of the difference in the safety endpoint was also related to restenosis manifest as MI presentation, so-called type 4c MI. Definite or probable stent thrombosis was relatively high in both groups early (1.0% vs. 1.2%) and late (1.1% vs. 1.0%).

TABLE 3 Clinical Outcomes at 270 Days (n = 287*)

Target vessel failure	33 (11.5)
Death	6 (2.1)
Cardiac	1 (0.4)
Myocardial infarction	20 (7.0)
Periprocedural (type 4a)	18 (6.1)
Spontaneous (type 1)	1 (0.3)
Restenosis-related (type 4c)	2 (0.7)
Target vessel revascularization	21 (7.3)
Clinically driven	17 (5.9)
Target lesion revascularization	16 (5.6)
Clinically driven	13 (4.6)
Stent thrombosis	0
Stroke	1 (0.3)

Values are n (%). *Denominator for each endpoint includes all patients with event or completing at least 240 days of follow-up.

TABLE 4 Results of 9-Month Angiographic Follow-Up (n = 115 Patients, n = 119 Lesions)

In-stent minimum luminal diameter, mm	1.78 ± 0.63
In-stent percentage diameter stenosis	36.89 ± 18.30
In-segment percentage diameter stenosis	38.34 ± 17.03
In-stent late luminal loss, mm	0.83 ± 0.48
In-stent binary angiographic restenosis	30 (25.6)
In-segment binary angiographic restenosis	34 (28.6)

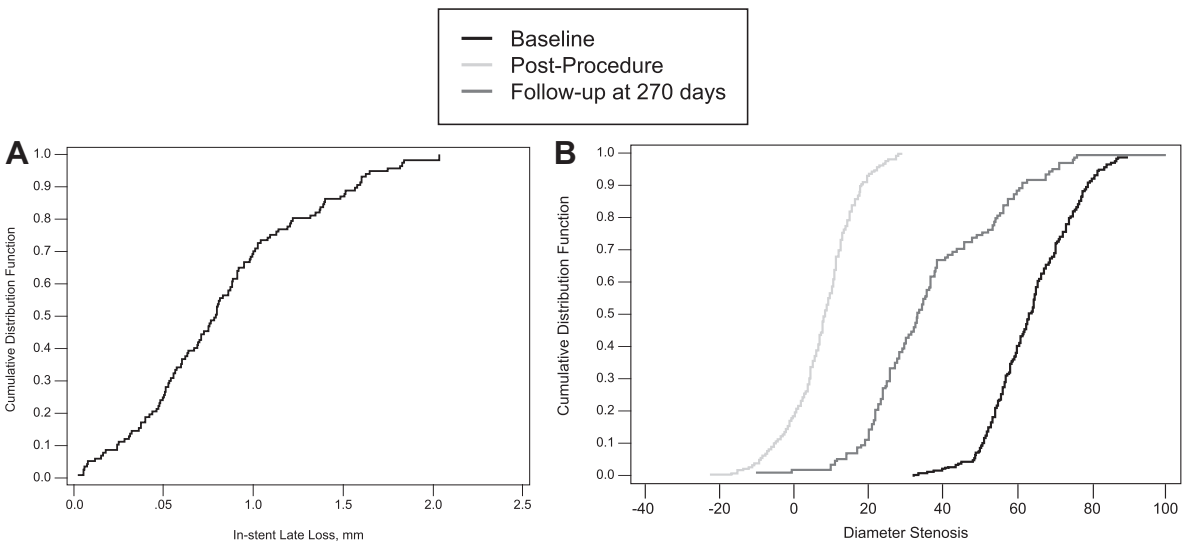
Values are mean ± SD or n (%).

In the present study, the frequency of clinically driven TLR was low, and the safety hazards associated with severe restenosis were infrequent, with only 2 patients having type 4c MIs. The distribution of LL also shows that the frequency of severe or occlusive restenosis was low, including only 1 patient with >90% diameter stenosis at follow-up. This result is consistent with preclinical studies showing decreased neointimal response, decreased inflammation, and improved healing for the PzF surface modified COBRA PzF stent compared with other BMS and first-generation DES (10,21,22).

The absence of stent thrombosis in our study also supports findings from preclinical work that showed markedly reduced platelet adherence and thrombogenicity for stents with a nanolayer of PzF (10,21). To date, among the published results including more than 650 patients receiving either the Catania or COBRA PzF stent, there have been only 2 subacute stent thrombosis events and no late stent thrombosis (11,12). It should be noted that the results of our study reflect continued DAPT at 9 months in more than 50% of patients.

STUDY LIMITATIONS. Analyses were dependent on historical data, and unmeasured or unaccounted differences in treated populations, procedural methods, or other variables that may have influenced observations cannot be excluded. Patients with higher risk features, such as acute MI, prior restenosis, long

FIGURE 2 Distributions of Late Loss and Diameter Stenosis



(A) Cumulative frequency distribution curve for late lumen loss at 9 months and **(B)** cumulative frequency distribution curves for percentage diameter stenosis pre-procedure, post-procedure, and at 9-month follow-up.

lesions, multivessel treatments, and bifurcation lesions, were not represented in this study. As a single-arm study, it was not possible to blind investigators, adjudicators, or the angiographic core laboratory. The patient sample size limited our ability to perform additional subset analyses to determine if certain populations may receive greater benefit, or be exposed to greater risk, with placement of COBRA PzF stent. It is not known whether continuation of DAPT for 9 months in about 50% of patients affected late safety outcomes, and thus extrapolation of the excellent safety profile observed to shorter durations of DAPT is not possible. Additionally, because the protocol mandated 30 days of DAPT, this study does not provide information about safety of even shorter duration DAPT after placement of this stent, despite the apparent unmet clinical need for shorter durations of DAPT in patients at very high risk for bleeding (23). The ongoing COBRA-REDUCE (COBRA PzF Stenting to Reduce Duration of Triple Therapy) randomized clinical trial will compare the safety and effectiveness of the COBRA PzF stent and 2 weeks of DAPT with a DES and 6 months of DAPT (NCT02594501).

CONCLUSIONS

We observed favorable results with respect to TVF, restenosis, and stent thrombosis events in this nonrandomized comparison of the COBRA PzF stent with historical BMS performance. Further evaluation of this unique device for percutaneous treatment of coronary artery disease is warranted.

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PERSPECTIVES

WHAT IS KNOWN? BMS have high restenosis and are not associated with lower risk for stent thrombosis. A cobalt-chromium coronary stent coated with a nanothin layer of PzF (the COBRA PzF) has shown reduced neointima hyperplasia and thrombogenicity compared with uncoated stents.

WHAT IS NEW? This study showed the COBRA PzF meets a performance goal for an effectiveness endpoint of 9-month TVF with an excellent safety profile, including low risk for MI beyond the periprocedural period and no stent thrombosis.

WHAT IS NEXT? An ongoing study will compare safety and effectiveness of the COBRA PzF and 2 weeks of DAPT with second-generation DES and 6 months of DAPT among patients at high risk for bleeding.

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KEY WORDS restenosis, stent(s), thrombosis

APPENDIX For inclusion and exclusion criteria, PzF SHIELD study organization, study definitions, performance goal and sample size justification, a list of PzF SHIELD participating study sites and principal investigators, as well as supplemental results and tables, please see the online version of this article.