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Five-Year Clinical Outcomes of the COBRA Polyzene F NanoCoated Coronary Stent System

Donald E. Cutlip [a,*], Rajiv Jauhar [b], Perwaiz Meraj [b], Kirk N. Garratt [c], Victor Novack [d], Lena Novack [d], Luc Maillard [e], Andrejs Erglis [f], Robert Stoler [g], Mark Barakat [h], Sigmund Silber [i], for the PzF SHIELD Trial Investigators

[a] Cardiology Division, Beth Israel Deaconess Medical Center, Baim Institute for Clinical Research and Harvard Medical School, Boston, MA, United States of America
[b] North Shore University Hospital, Manhasset, NY, United States of America
[c] ChristianaCare, Wilmington, DE, United States of America
[d] Clinical Research Center, Soroka University Medical Center, Beersheba, Israel
[e] GCS ES Axium Rambot, Aix-en-Provence, France
[f] University of Latvia, Riga, Latvia
[g] Baylor Heart and Vascular Hospital at Baylor University Medical Center, Dallas, TX, United States of America
[h] CeloNova BioSciences, San Antonio, TX, United States of America
[i] Department of Cardiology, Heart Center at the Isar, Munich, Germany

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ABSTRACT

Background/purpose: The COBRA Polyzene F™ NanoCoated Coronary Stent System (PzF coated stent) stent demonstrated favorable clinical outcomes at 9 months but late results have not been reported. We sought to assess the late safety and effectiveness of the PzF coated stent for treatment of de novo coronary artery lesions.
Methods: Patients with de novo coronary artery lesions meeting eligibility criteria were enrolled in a non-randomized, prospective clinical trial and followed for 5 years. The primary endpoint was target vessel failure (TVF, cardiac death, myocardial infarction [MI], or clinically-driven target vessel revascularization [TVR]) at 9 months. Secondary endpoints included major adverse clinical events (MACE, cardiac death, MI, or clinically driven TLR), clinically driven target lesion revascularization (TLR) and definite or probable stent thrombosis during 5-year follow-up. Endpoints at 5 years were analyzed as cumulative incidence accounting for competing risk of death.
Results: Of 296 enrolled patients, 290 (98%) were evaluable at 5 years. By 5 years, MACE had occurred in 61 (21.3%), cardiac death in 11 (4.2%), MI in 25 (8.6%), and TLR in 34 (12.0%) subjects. Between follow-up years 1 and 5, a first MACE occurred in 17 (6.2%), including 10 (4.0%) cardiac death, 4 (1.6%) MI, and 7 (2.9%) TLR events. There were no definite or probable stent thromboses.
Conclusions: The PzF coated stent demonstrated continued safety and effectiveness through 5 years with low to very low incident rates of MACE, MI, TLR and stent thrombosis between 1 and 5 years after stent placement.

1. Introduction

The Polyzene F™ NanoCoated Coronary Stent System (PzF coated stent) is a polymer coated thin-strut (71 μm), cobalt-chromium, non-drug-eluting stent for which preclinical data demonstrated reduced thrombogenicity and improved healing compared with control bare metal stents (BMS) and first-generation drug-eluting stents (DES) [1,2]. It was approved for use in the United States based on demonstrating reasonable assurance of safety and effectiveness for 9-month clinical outcomes in the non-randomized COBRA PzF Stent in Native Coronary Arteries for Early Healing, Thrombus Inhibition, Endothelialization, and Avoiding Long-Term Dual Anti-Platelet Therapy (PzF SHIELD) clinical trial [3]. Based on these results, it was postulated that the device may be an alternative to DES, especially for shorter term dual antiplatelet therapy (DAPT) strategies.

Since these results were reported, several studies among subjects with high bleeding risk have confirmed superiority of some DES versus BMS even with DAPT as short as 30 days and have essentially eliminated BMS from clinical use [4,5]. Despite these encouraging short-term results with contemporary DES, a patient-level pooled analysis of randomized clinical trials has shown the risk for major adverse cardiac

* Corresponding author at: Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Boston, MA 02215, United States of America.
E-mail address: dcutlip@bidmc.harvard.edu (D.E. Cutlip).

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events (MACE, defined as cardiac death, myocardial infarction [MI], or clinically driven target-lesion revascularization [TLR]) continues during 5-year follow-up for BMS, first generation DES, and second generation DES [6]. Between 1 and 5 years, MACE was highest for first-generation DES (10.2%) and similar for BMS (7.4%) and second-generation DES (8.5%), such that overall stent-related events occurred between 1 and 5 years in ~2% of subjects per year [7].

In this pre-specified 5-year follow-up of the SHIELD trial, the aim is to assess late outcomes with the PzF coated stent based on the hypothesis that improved early healing as demonstrated with this coated non-DES may reduce late stent-related clinical events.

2. Methods

2.1. Study design and population

The design of the PzF SHIELD trial has been reported previously [3]. Briefly, 296 subjects were enrolled at 35 clinical centers in Europe and United States. Eligible patients 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 mm and 4.0 mm and lesion length ≤ 24 mm. Subjects had chronic stable coronary artery syndrome or had MI >72 h earlier. 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. Following 30 days, continued antiplatelet monotherapy with aspirin alone was required, while continuation of a second anti-platelet drug was discretionary. Routine angiographic follow-up was planned in the first 130 subjects and performed in 115 (88% compliance). Clinical follow-up included annual clinic visits to assess for all adverse events. All deaths, MI, and repeat revascularization procedures were reviewed and adjudicated by an independent clinical events committee. The protocol was approved by the institutional review board or ethics committee at each site. Informed consent was documented for each patient.

2.2. Endpoints and definitions

The primary endpoint was target vessel failure (TVF), defined as a composite of cardiac death, target vessel MI, or repeat revascularization of any segment of the target vessel (TVR) reported at 9 months. The secondary endpoints for this 5-year follow-up analysis included MACE, the individual components of cardiac death, MI, and TLR, and stent thrombosis. All deaths without clear non-cardiac cause were considered as cardiac. MI was defined as Q wave MI in the presence of new pathologic Q waves and any elevation of CKMB or non-Q wave MI if CKMB elevation >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 TLR was defined as repeat revascularization of the stented lesion including the 5 mm segment proximal or distal to the stent in the presence of a positive functional ischemia study or ischemic symptoms AND an angiographic minimal lumen diameter stenosis ≥50% determined by core laboratory quantitative coronary angiography (QCA); or revascularization of a target lesion with diameter stenosis ≥70% by QCA without either angina or a positive functional study. Stent thrombosis was classified as definite or probable according to Academic Research Consortium criteria [8].

2.3. Statistical methods

The primary analysis is based on intention to treat, defined as enrollment in the study and attempted placement of the PzF coated stent. Continuous variables are reported as mean and standard deviation, or median, interquartile range, minimum and maximum values. Categorical variables are reported as numbers and percentages. The primary endpoint of TVF at 9 months was based on calculated rate among all subjects with TVF or completing at least 240 days of follow-up. To assess the impact of routine angiographic follow-up planned after 9 months, TVF at one year was analyzed based on a calculated rate among all subjects with TVF or completing at least 330 days of follow-up. Five-year endpoints were analyzed using cumulative incidence method. Non-fatal endpoints were adjusted for competing risk of mortality. MACE and cardiac death were adjusted for competing risk of non-cardiac mortality. Landmark analysis was performed in the 0- to 1-year and 1- to 5-year periods. Patients with MACE within 1 year were censored from the 1- to 5-year landmark analysis.

All statistical analyses were performed using SAS version 9.4.

2.4. Role of the funding source

The clinical trial sponsor participated in study design, site management and monitoring activities. The authors had complete access to all clinical trial data, drafted the manuscript, and assume full responsibility for the content. The sponsor had opportunity to review the manuscript prior to publication.

3. Results

3.1. Study population, baseline, and procedural characteristics

Between August 21, 2013 and February 18, 2015, 296 patients were enrolled. By 5 years, 290 (98%) were evaluable. Detailed baseline clinical and lesion characteristics were reported previously. [3] The mean age was 66 ± 10 years, 30% were female, and 34% had diabetes. Stable CAD was the presenting indication in 68%. A total of 300 lesions were treated. The reference vessel diameter was 2.74 ± 0.48 mm and lesion length was 12.77 ± 6.75 mm. Bifurcation lesions were excluded and only 13% of lesions had severe calcification. Device success, defined as attaining <30% final residual stenosis using the assigned device, was achieved in 100% of lesions.

3.2. Clinical outcomes

The primary endpoint of TVF at 270 days occurred in 33 (11.5%) subjects. By one year, TVF had occurred in 50 (17.4%) subjects, including 17 additional TVR and 14 TLR immediately after planned 9-month angiographic follow-up. Of these, 16 TVR and 13 TLR occurred in the planned 9-month angiographic follow-up cohort while 1 TVR and 1 TLR occurred in the cohort with clinical follow-up only. The components and rates of TVF reported at 270 days and changes at one year are shown in Table 1.

The composite of MACE and components of MACE at 1 year and 5 years are shown in Table 2. Fig. 1 demonstrates the trends in MACE and the components of MI and TLR during year 1 and the landmark 1 to 5 years. Between 1 and 5 years, the cumulative incidence of a first MACE increased by 17 (7.3%) subjects. This includes increases between 1 and 5 years for cardiac death of 10 (4.0%; average annual hazard 1.0%), MI 4 (1.6%; average annual hazard 0.4%), and TLR 7 (2.9%; average annual hazard 0.7%).

At 5 years, death due to any cause occurred in 34 (12.0%) subjects. There were no definite or probable stent thromboses throughout the 5-year study follow-up. Based on concomitant medication reports, 30% of subjects were taking DAPT for at least 1 day between 1 and 5 years.

4. Discussion

In this prospective, non-randomized clinical trial, the PzF coated stent continued to demonstrate excellent clinical outcomes during 5-year follow-up. The most substantial difference since reporting the 9-month primary endpoint results occurred between 9 months and 1 year with an increase in TVF from 11.5% to 17.4%. Between 1 and 5 years, the secondary endpoint of MACE increased by 7.3%, driven mostly by an average cardiac mortality of ~1% per year with only slight

Table 1
Target vessel failure at 9 months and 1 year.

	$N = 287$[a]
9 Months	
Target vessel failure, N (%)	33 (11.5)
Death, N (%)	6 (2.1)
Cardiac, N (%)	1 (0.4)
Myocardial infarction, N (%)	18 (6.3)
Target vessel revascularization	17 (5.9)
Target lesion revascularization	13 (4.9)
Stent thrombosis	0
One year	
Target vessel failure, N (%)	50 (17.4)
Angiographic follow-up cohort	31/115 (27.0)
Clinical follow-up cohort	19/172 (11.0)
Death, N (%)	7 (2.4)
Cardiac, N (%)	1 (0.4)
Myocardial infarction, N (%)	21 (7.4)
Target vessel revascularization	34 (11.9)
Target lesion revascularization	27 (9.5)
Angiographic follow-up cohort	19/115 (16.6)
Clinical follow-up cohort	8/172 (4.7)
Stent thrombosis	0

Rates calculated based on number of events divided by the denominator including all
subjects with event or completing follow-up.
[a] 287 subjects were evaluable for the primary endpoint as reported previously.

increases in MI and TLR. There were no stent thromboses throughout the 5 years.

The results are helpful for assessment of the overall safety and effectiveness of a PzF nanocoated non-DES and should be interpreted considering the hypothesized improved healing anticipated with this device. The doubling of TLR between 9 and 12 months may raise concerns regarding restenosis and whether the TVF reported at 9 months accurately reflects device effectiveness. In this regard, it should be noted that the study design recognized the concern with bias related to routine angiographic follow-up and incorporated completion of clinical follow-up at 9 months prior to planned angiographic follow-up. As a result, only 6 of 115 subjects in the angiographic follow-up cohort underwent the follow-up angiogram before completing 9-month clinical follow-up [3]. The impact of routine angiographic follow-up has been documented in other studies, with increases in TLR ranging from 30 to 50% with angiographic follow-up versus clinical follow-up despite independent adjudication [9,10]. We observed a similar difference in 1-year TLR between the clinical follow-up and the angiographic follow-up cohort, supporting the argument that apparent decreased effectiveness at 1 year is at least partly due to angiographic follow-up bias. Indeed, only 1 TLR occurred between 9 and 12 months in the cohort with clinical follow-up only, leading to 4.7% TLR at 12 months. This is similar to one year TLR of 4.3% reported by Maillard, et al., from a multicenter registry including 940 patients treated with the PzF coated stent [11].

Despite the effect of angiographic follow-up on TLR at 1 year, the 5-year cumulative incidence of MACE (21%) and TLR (12%) compare favorably with pooled results for BMS (24% MACE and 19% TLR) and first-generation DES (18% and 11%), although they are higher than for second-generation DES (14% and 7%) [6]. Between 1 and 5 years, however, the observed incidence for MACE and the components of MI and TLR are lower for the PzF coated stent than reported from the pooled analysis for BMS, first- or second-generation DES. Among the cohort treated with second-generation DES in the pooled analysis, MACE continued beyond 1 year for an average annual hazard of slightly over 2%, including MI in 0.6%/year and TLR in 1.1%/year [7]. In the 1 year landmark analyses of our study these corresponding annualized rates were 0.4% and 0.7%, respectively. Additionally, the absence of stent thrombosis at 5 years compared favorably with pooled results at one year and between 1 and 5 years for BMS (1.5% and 0.5%), first-generation of DES (1.6% and 1.8%), and second-generation DES (0.7% and 0.9%) [7].

In the absence of a randomized comparison with second-generation DES, it is not possible to determine if late outcomes of MI and TLR are better after PzF stent or whether the anticipated improved healing after PzF coated stent placement is responsible for any benefit. It must be considered that the earlier penalty due to restenosis at 9 months and additional events after routine angiographic follow-up may have reduced the potential hazard for events beyond 1 year. Nevertheless, among patients remaining at risk beyond 1 year, there was 40% lower risk for TLR between 1 and 5 years than was reported to occur following placement of second-generation DES in the above pooled analysis. Furthermore, the absence of any stent thrombosis also suggests more rapid healing and avoidance of a continued nidus for subsequent thrombus initiation. Notably, Maillard, et al., showed healing as early as 7 days after PCI with the PzF coated stent in a rabbit model [12], and demonstrated safety and effectiveness of single anti-platelet therapy from the time of stent implant in a population with high bleeding risk [13].

Favorable TLR at 5 years relative to BMS and first-generation DES, low risk for TLR beyond 1 year relative to first and second-generation DES, and extremely low risk for stent thrombosis underscore the merit of the PzF nanocoated stent. Nevertheless, it is likely that future study of the PzF stent could benefit from incorporating a strategy to reduce restenosis to a level similar to second-generation DES in the first year. Delivery of an anti-proliferative drug to the treated lesion, either by elution of drug from the PzF stent or pre-stent delivery by a drug-eluting balloon, may allow for such a reduction in restenosis. With either strategy, the improved outcomes beyond 1 year that were demonstrated with the PzF stent without drug would need to be confirmed and substantiated in a randomized comparison of anti-proliferative drug delivery plus PzF stent versus contemporary DES.

In conclusion, the COBRA PzF nanocoated stent demonstrated continued safety and effectiveness through 5 years with low to very low rates of MACE, MI, TLR and zero stent thrombosis between years 1 and 5 following stent placement.

There are several limitations of this study. It was designed for comparison with historical data for BMS and thus included moderate complexity patients and lesions. The sample size was relatively small which limits precision of estimates for outcomes. It was a single arm study which prevents direct comparisons with other device types. In this regard, we await the one-year results of the COBRA REDUCE trial, a randomized comparison of the COBRA PzF stent with 2 weeks of DAPT versus contemporary DES with 3–6 months of DAPT in patients on oral anticoagulant and undergoing PCI.

Table 2
Cumulative incidence of MACE at one and five years.

	$N = 296$
One year	
MACE, N (%)	44 (15.1)
Cardiac death, N (%)	1 (0.4)
Myocardial infarction, N (%)	21 (7.1)
Target lesion revascularization, N (%)	27 (9.4)
Five years	
MACE, N (%)	61 (21.3)
Cardiac death, N (%)	11 (4.2)
Myocardial infarction, N (%)	25 (8.6)
Target lesion revascularization, N (%)	34 (12.0)

Percentages reported based on cumulative incidence and accounting for competing risk.
MACE = major adverse cardiac events.
Components of MACE reported as non-hierarchical and subjects may have more than one MACE component.

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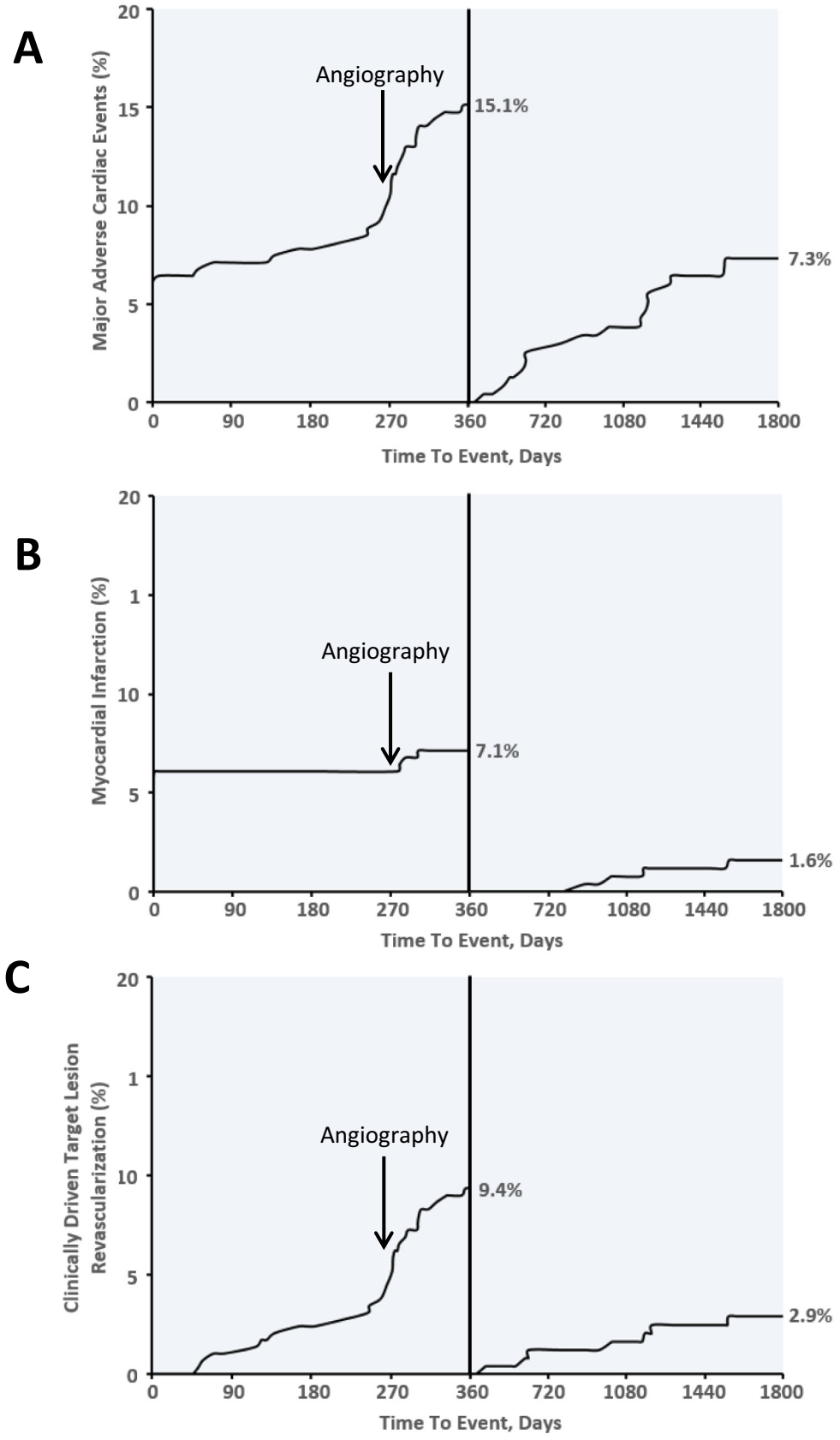

Fig. 1. Cumulative incidence curves within 1 year and the landmark period of 1 to 5 years.
(A) Major adverse cardiac events; (B) myocardial infarction; (C) clinically driven target lesion revascularization.

CRediT authorship contribution statement

Study Design: Cutlip, Barakat, V Novack.

Data Collection: Cutlip, Jauhar, Meraj, Garratt, Maillard, Erglis, Stoler, Silber.

Statistical Analysis: L Novack; V Novack.

Drafting of Manuscript: Cutlip.

Critical review and revision of manuscript: Jauhar, Meraj, Garratt, V. Novack, L. Novack, Maillard, Erglis, Stoler, Barakat, Silber.

Declaration of competing interest

Drs. Cutlip, Jauhar, Meraj, Garratt, Maillard, Erglis, and Silber report receiving institutional research funding from Celonova.

Dr. Victor and Dr. Lena Novack report statistical consulting fees from Ceonova.

Dr. Stoler reports receiving institutional research funding from Celonova and serves as a member of the Advisory Board or as a proctor for Medtronic, Boston Scientific, Edwards Lifesciences, and Biotronik.

Dr. Barakat is a paid employee of Celonova.

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