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Review

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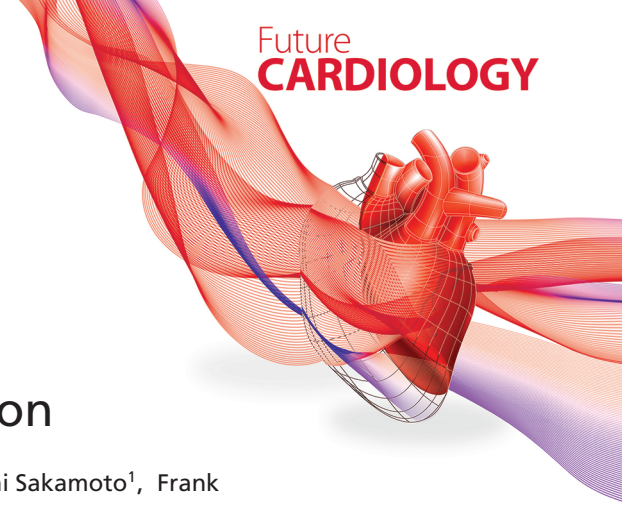

A new category stent with novel polyphosphazene surface modification

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The COBRA-PzF™ (CeloNova BioSciences, Inc., TX, USA) is a new type of coronary stent composed of a cobalt chromium metallic backbone surrounded by a nanothin layer of Polyzene-F (PzF) without any added drug. Evidence from basic studies supports antithrombotic and anti-inflammatory properties for the PzF surface coating. Preclinical studies support the thromboresistance of PzF-coated surfaces and clinical studies have shown good outcomes for patients receiving this device with very low rates of stent thrombosis. COBRA-PzF may be especially useful in patients at high risk for bleeding. Ongoing clinical trials will determine whether shortening the duration of dual antiplatelet therapy to less than 1 month is feasible and these data may represent a new paradigm with regards to patients at high risk for bleeding.

First draft submitted: 17 November 2017; Accepted for publication: 1 March 2018; Published online: 27 March 2018

Keywords: bleeding • drug-eluting stent • polymer • stent • stent thrombosis

Percutaneous coronary intervention (PCI) using drug-eluting stents (DES) is the most frequent strategy used to revascularize patients with obstructive coronary artery disease worldwide [1]. Although DES reduces rates of restenosis compared with bare-metal stents (BMS), they also prolong the arterial repair process. During the process of re-endothelialization of stent struts, patients receiving DES require an extended period of dual antiplatelet therapy (DAPT) with aspirin and an additional adenosine diphosphate receptor P2Y12 inhibitor to mitigate against the risk of stent thrombosis (ST). After BMS implantation, DAPT is generally required for a minimum of 1 month while with DES implantation, this is extended to 6–12 months. Furthermore, some DES such as Xience® and BioFreedom™ have clinical data which suggest safety using shorter durations of DAPT (i.e., 1 month for BioFreedom and 3 months for Xience) [2,3]. Therefore, the duration of DAPT after stent implantation is a moving target with trends toward shorter durations than were previously used.

Additionally, about 5–8% of patients who are treated with PCI also have atrial fibrillation, requiring oral anticoagulation therapy such as a vitamin K antagonist or novel oral anticoagulant to prevent thrombotic events over the longer term [4,5]. When considering duration triple therapy (i.e., combining with DAPT and anticoagulant therapies) the balance between prevention of thrombotic/ischemic events and bleeding is a major concern. Stents equipped with components which make DAPT duration shorter may improve outcomes in patients with atrial fibrillation or other conditions requiring long-term oral anticoagulant therapies.

Since the advent of DES 18 years ago, stent technologies have continued to evolve as our knowledge about how individual components of DES technology influence the vascular responses to these devices as well as short- and long-term clinical outcomes. Each of the three cornerstone design features of DES: metallic stent backbone, antirestenotic drug and polymer coatings, in particular, has undergone evolution as the creation of newer generations of stents with new designs have attempted to improve outcomes.

Device selection for coronary stents has been a binary choice to date with interventionists either reaching for a BMS or a DES depending upon the clinical situation. However, a recent but improved understanding of polymer technologies in the last decade has changed our understanding of the potential roles of polymers in coronary stents. While polymers selected for first- and even some second-generation DES were associated with increased thrombosis, local inflammation and cell proliferation due to immune cell reactions, more recent studies have shown

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that some polymers have the potential to improve device behavior, especially in situations where device thrombosis or biocompatibility is an issue.

Polyzene-F® (PzF; CeloNova BioSciences, Inc., TX, USA) is one such polymer and consists of a unique formulation of poly[bis(trifluoroethoxy) phosphazene], an inorganic, high-molecular-weight polymer possessing a backbone of alternating nitrogen and phosphorus atoms and trifluoroethoxy side groups that can be used to coat multiple substrates including stents. The COBRA-PzF™ (CeloNova BioScience, Inc.) coronary stent system consisting of a cobalt chromium metallic stent and polymer without drug is the first of its kind and was recently approved for clinical use by the US FDA. In this manuscript, we review the experimental basic and preclinical data, as well as the clinical data that support an important antithrombotic and anti-inflammatory role for this device and suggests this stent might be the device of choice for patients at high risk of bleeding requiring PCI.

Device description

The COBRA-PzF stent combines a unique thin strut (71 μm) cobalt chromium platform with the PzF nanothin (≤50-nm thickness) polymer which consists of poly [bis (trifluoroethoxy) phosphazene], a soft pliable inorganic polymer with a -[p = N] n-backbone and trifluoroethoxy side groups. Stent sizes range in diameter from 2.5 to 4.0 mm and 8 to 30 mm in length. It is premounted on a rapid-exchange balloon delivery catheter.

Impact of strut thickness

The strut thickness is quite thin (71 μm) in the COBRA-PzF stent, which is one of the most important factors determining risk for excessive neointimal proliferation and thrombogenicity [5,6]. A randomized clinical trial (n = 651) comparing a thin strut (50 μm) versus thick strut (140 μm) stent with similar design (ACS RX Multilink® stent or Multi-Link RX Duet® [DT], Guidant, Advanced Cardiovascular Systems, CA, USA) showed lower incidence of 6-month angiographic restenosis (50% diameter stenosis at follow-up angiography) in the thin-strut group (15.0%) versus the thick-strut group (25.8%; risk ration [RR]: 0.58; 95% CI: 0.39–0.87; p = 0.003) [4]. In another randomized clinical trial (n = 611) from the same group, the same thin-strut ACS RX Multilink stent (strut thickness 50 μm, interconnected ring design) was compared with a different design of thick-strut BX Velocity™ stent (Cordis Corp., FL, USA, strut thickness 140 μm, closed cell design) [7]. There was again less angiographic restenosis in the thin-strut group (17.9%) versus in the thick-strut group (31.4%; RR: 0.57; 95% CI: 0.39–0.84; p < 0.001). Additionally, with regard to preventing jailed-side branch and myocardial infarction (MI), thin-strut thickness is important. In SPRIT III trial subanalysis, jailed side branch occlusion and periprocedural MI were significantly greater in thicker TAXUS™ (Boston Scientific, MN, USA) paclitaxel-eluting stent (PES) (132 μm) than in the thinner Xience (Abbott Vascular, CA, USA) everolimus-eluting stent (EES; 81 μm) [8,9]. In preclinical studies assessing thrombogenicity in different types of stents, strut thickness also appeared to have an impact on thrombogenicity [10,11]. Therefore, a thin-strut stent backbone is clinically beneficial regardless of stent design. Currently, Xience and Synergy™ (Boston Scientific) widely used in PCI are also thin-strut stents (81 and 74 μm, respectively). COBRA-PzF (71 μm) has comparable strut thickness to Xience and Synergy.

PzF coating

Usually polymeric coatings are combined with antiproliferative agents eluted from within the polymer to prevent restenosis. The COBRA-PzF stent is unique in that it consists of a cobalt chromium backbone metallic stent covered by a nanothin layer of PzF, without any added drug. This coating has potential of loading drugs although the thickness of the coating layer would need to be increased.

Polymer coatings became well-known as drug-retention agents in first generation DES (1st-DES). Polymers such as-IBBS (poly[styrene-b-isobutylene-b-styrene]) for PESs (Taxus, Boston Scientific) and polyethylene-co-vinyl acetate (PEVA) and poly n-butyl methacrylate (PBMA) used in sirolimus-eluting stents (SES, Cypher, Cordis, Johnson & Johnson, NJ, USA) were effective at controlling restenosis but probably not ideal from the vascular compatibility standpoint. We reported a number of autopsy cases in which local hypersensitivity reactions seen exclusively within the stented segment seemed consistent with an allergic reaction to the Cypher polymer and usually manifested only after complete release of the drug [12]. Similar though less vehement reactions were seen in the porcine model where SES reduced neointimal formation at 28 days compared with a BMS but later demonstrated inflammation, cell proliferation and late (90 and 180 days) intimal thickening [13]. This porcine model found progressive granulomatous and eosinophilic reactions seen in the SES starting at 90 days and increasing out to 6 months, a time point by which the immunosuppressive drug was no longer present, unmasking the true

biocompatibility of the polymer. This so-called late catch-up phenomenon has been seen both in human pathology DES registries as well as in clinical trials [14].

Thus, conceptually, there is a belief that the bare surface of metal is more biocompatible compared with a durable polymer-coated stent. However, metal itself can cause an allergic reaction (a delayed type hypersensitivity reaction) through the production of metal ions [15]. Metal allergy was associated with recurrent in-stent restenosis of BMSs in some studies [16–18]. Cobalt and chromium used in current metallic stents are important contact allergens, which are under regulation in some countries [15]. Also, metal corrosion of BMS was reported to occur in approximately a third of lesions, resulting in a greater concentration of metal ions in surrounding tissue [19]. Stable and biocompatible polymer coatings may prevent metal corrosion [20]. Every single polymer has a different stability [21,22]. Inflammatory reaction is significantly less in durable polymer Cobalt Chromium EESs (CoCr-EES) 2nd-DES than in durable polymer SES 1st-DES, which is believed to be due to usage of more biocompatible polymer (PVDF-HDF: fluoropolymer) and reduced strut thickness as well as drug dose [23].

PzF is a fluorine-containing polymer, which combines the benefits of inorganic polyphosphazene and fluoropolymer. Fluoropolymer is a general term for fluorocarbon-based polymer with multiple strong carbon–fluorine bonds and is characterized by a high resistance to solvents, acids and bases [24]. Actually, because of its antithrombogenicity, fluoropolymers have been used in a wide variety of blood-contacting medical device applications such as vascular grafts, drug-eluting leads of cardioverter defibrillators, vascular sutures and guide wire coatings [25–32]. Interestingly, suppression of platelet adhesion and activation were stronger as the amount of fluorine was increased [26].

More recently we compared the very long-term vascular responses (i.e., >1 year) to durable polymer SES (PEVA/PBMA polymer), cobalt chromium EESs (CoCr EES, base layer of PBMA encapsulated by a poly(vinylidene fluoride-*co*-hexafluoropropylene) (PVDF-HFP), and bare metal Vision stents in human autopsy specimens [33]. Inflammation score was lowest in fluorinated polymer CoCr-EES versus SES and even Vision BMS. These data suggest that long-term vascular responses are favorable in fluorinated polymer coated BMS and perhaps even superior to BMS.

Blood–material interaction

Bare polymer coated or metallic surfaces of stents regularly come in contact with blood elements before neointimal coverage. This first starts with the adsorption of plasma proteins, which leads to the activation of coagulation pathways or the adhesion and activation of platelets, and then the formation of an insoluble fibrin network or thrombus [34–36]. The biomaterial's surface chemistry matters for the adsorbing pattern of specific plasma proteins, which could be either protective or harmful depending on the specifics of the interaction [34–37]. Generally, the prior adsorption of albumin suppresses platelet activation while the adsorption of γ-globulin or fibrinogen may activate platelet activation [38]. In other words, it has been proposed that surfaces with high levels of albumin adsorption could passivate the polymer surface by preventing more reactive proteins such as fibrinogen from adsorbing [39]. Therefore, these initial adsorption processes are important and may influence the clinical performance of both BMS and DES.

Within the polymers used in medical applications, the fluorinated polymers are known to have the ability to reduce platelet adhesion and activation compared with controls [25,28,30,32]. Fluorinated polymers have been used for vascular grafts because they have lower thrombogenicity, with a decreased inflammatory response, and more rapid endothelialization. Graft polymerization with vinylidene fluoride onto polyethylene substrates resulted in a reduction in platelet adhesion and activation as compared with uncoated polyethylene [28]. Suppression of platelet adhesion and activation had a positive correlation with the amount of fluorine dosing [30]. Similarly, modifying polyether urethanes with fluorinated molecules lead to a significant reduction in platelet adhesion as compared with polyether urethanes alone [32]. This was also demonstrated by blending polyvinylidene fluoride into polyacrylonitrile membranes lead to a reduction in protein adsorption, platelet adhesion and thrombus formation [40].

Although these studies are helpful to understand the potential mechanisms behind the pro-thrombotic characteristics of different polymers, *in vivo* thrombosis is a much more complex process. Thus, preclinical studies are necessary to gain greater insight into the behavior of different polymers.

COBRA-PzF stent in preclinical studies

PzF-coated stents have been reported to have less thrombogenicity and less neointimal formation as compared with noncoated BMS in several preclinical studies [41–43]. In an animal study, neointimal formation of a PzF-coated

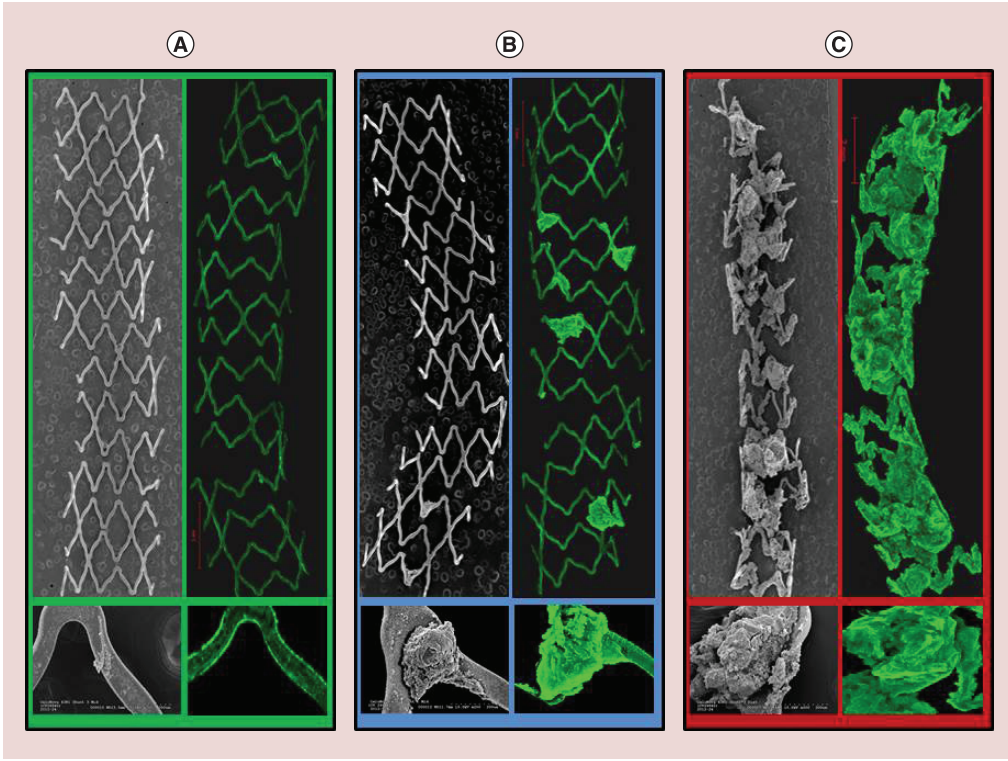

Figure 1. *Ex vivo* arteriovenous porcine shunt model. Representative images derived from confocal microscopy (10× and 20× magnifications) and scanning electron microscopy (15× and 200× magnifications) in a porcine *ex vivo* arteriovenous shunt model. **(A)** Shows the COBRA-PzF™ nano-coated stent. **(B)** Shows the COBRA bare metal stent. **(C)** Shows the Multilink Vision® bare metal stent.
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stent was surprisingly comparable to first generation DES (SES, Cypher, Cordis, NJ, USA; PES, Taxus, Boston Scientific) [44].

We recently reported a preclinical study comparing the COBRA-PzF stent and two types of BMS (noncoated COBRA-BMS which has the same backbone; Vision-BMS, 81 µm thickness, Abbott Vascular) [45]. Porcine arteriovenous shunt and coronary stent implantation models as well as an *in vitro* model were applied in this study.

The porcine arteriovenous shunt model involving a circuit loop consisting of Sylgard elastomer tubing with three in-line tests and control stents was purposed to assess acute platelet adhesion and thrombus formation [10,11]. The circuit was run for 60 min or until flow rate was reduced 50% resulting from blockage by thrombus formation. Bolus and maintenance low dose intravenous heparin (100 IU/kg) was administrated to keep activating clotting time between 150 and 200 s. In the end of each run, stents were gravity perfused with Ringer's lactate until cleared of blood and then fixed in 10% neutral-buffered formalin. The stents were gently cut in half longitudinally. Then, one half underwent immunofluorescent staining with an anti-CD61/CD42b platelet marker cocktail and confocal microscopy. Platelet adhesion and thrombus formation were significantly less in COBRA-PzF than in COBRA-BMS and Vision-BMS (estimated mean percent positive area by confocal, 17, 21 and 62%, respectively, COBRA-PzF vs COBRA-BMS; $p = 0.023$ and COBRA-PzF vs Vision-BMS; $p < 0.0001$; Figure 1).

Porcine coronary stent implantation model was used to pathologically assess different vascular response at 5, 28 and 90 days following either COBRA-PzF or Vision-BMS stent implantation (Figure 2). Overlapping stents were also assessed only at 28 days. Endothelialization of COBRA-PzF reached 98% at 5 days and nearly complete at 28 days. Mean neointimal thickness was significantly less in COBRA-PzF than in Vision-BMS at 28 (both single and overlap) and 90 days, which was consistent with other studies [41–43]). Also, inflammation score was borderline significantly lower in COBRA-PzF than in Vision-BMS at 28 (single) and 90 days and significant differences were observed in the overlap group at 28 days.

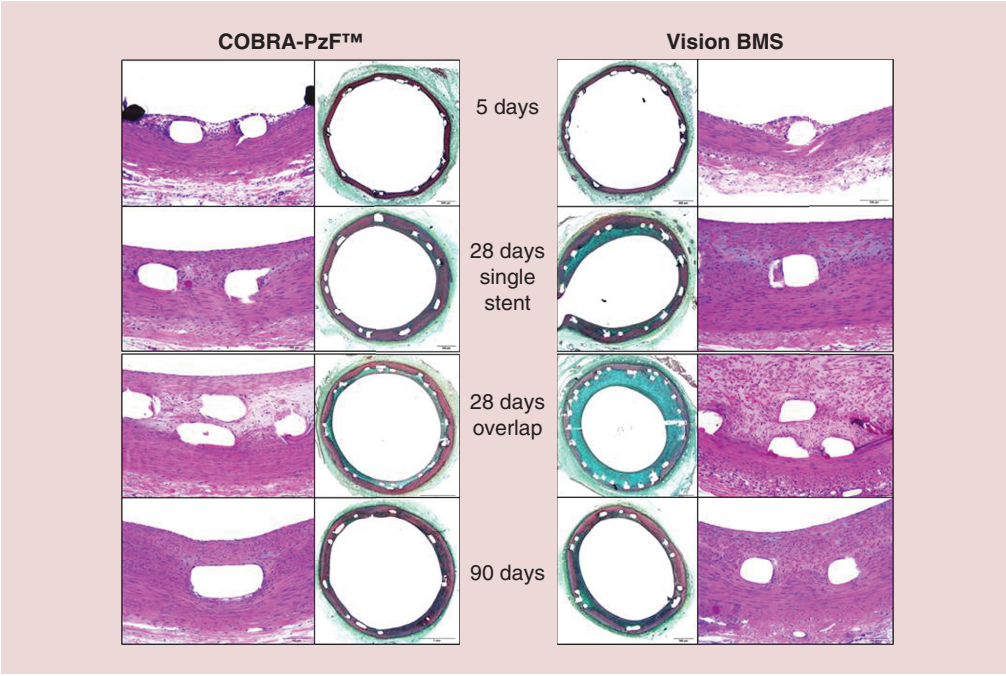

Figure 2. Representative light microscopy images of COBRA-PzF™ and Vision BMS stents at 5, 28, and 90 days implanted in porcine normal coronary arteries, shown at high (hematoxylin and eosin) and low (Movat pentachrome stain) magnification. Low magnification images (2× magnifications) were stained with Movat pentachrome staining and high magnification images (20× magnifications) were stained with hematoxylin and eosin staining.
BMS: Bare metal stent.
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In vitro model assessed the interaction of human monocyte/macrophage on thin cobalt chromium coupons with or without PzF modification after 48 h. The number of adherent monocyte was significantly less in PzF-coated coupon than in noncoated coupon. Human inflammatory cytokine and inflammatory marker (IL-10, IL-12p40, TNFα and IL-4) was also less in PzF-coated coupon than in noncoated coupon.

These data suggest that PzF coating has benefit over bare surface of metals with regards to vascular compatibility.

Clinical studies of COBRA-PzF

There are several clinical studies assessing the first generation stent nanocoated with PzF polymer and COBRA-PzF stent [46–50]. Tamburino *et al.* reported first-in-man 1-year clinical outcomes of the first-generation device coated with PzF polymer in a prospective, single-center, nonrandomized, single-arm study of 55 patients with symptomatic ischemic heart disease with *de novo*, obstructive lesions of native coronary arteries (Assessment of The LAtest Non-Thrombogenic Angioplasty Stent Trial; the ATLANTA Trial) [46]. All patients were advised to maintain lifelong aspirin therapy while thienopyridine therapy (clopidogrel 75 mg.day or ticlopidine 250 mg twice-daily) was discontinued 4 weeks after the procedure. Late lumen loss was 0.60 ± 0.48 mm and the percent neointimal hyperplasia volume was 27.9 ± 16.1% at 6 month follow-up angiography. The incidence of target lesion revascularization (TLR) at 12 months was clinically driven TLR 3.6% and nonclinically driven TLR 7.3%. Substudy using optical coherence tomography at 6 months showed that the rate of covered struts was 99.5% [48].

Tamburino *et al.* also performed the ATLANTA 2 registry to assess the first generation stent coated with PzF polymer in real world clinical practice, which was a prospective, nonrandomized, single-arm study of patients with symptomatic ischemic heart disease and *de novo* lesions of native coronary arteries [49]. In total, 300 patients (396 lesions) with 482 PzF coated stents. Major adverse cardiac events defined as the composite of cardiac death, nonfatal MI or TLR was 8.8%, mainly drive by TLR (6.5%) followed by cardiac death (2.5%) and nonfatal MI (0.7%). Subacute definite or probable ST occurred in 0.7% while no late ST was recorded. When the results are compared with patients treated with DES or BMSs over the same time period, those treated with PzF-coated stent experienced similar outcomes at 1 year.

More recently, Cutlip *et al.* published the nonrandomized, prospective clinical trial enrolling 296 patients implanted with COBRA-PzF stent, in which the COBRA-PzF stent was compared with BMS from a historical cohort in 9 month clinical outcomes and routine follow-up angiography was performed at 9 months [50].

The primary endpoint was defined as target vessel failure including cardiac death, MI and clinically driven target vessel revascularization at 9 months. Target vessel failure occurred in 19.62% in historical cohort BMS group and 11.5% in COBRA-PzF group at 9 months. Late lumen loss at 9 months follow-up angiography was 1.1 mm in BMS group and 0.84 mm in COBRA-PzF group. Surprisingly, no ST occurred in COBRA group in which the rate of continuation for DAPT was 52% at 9 months.

Furthermore, the e-COBRA Registry evaluated the safety and efficacy of the COBRA-PzF nanocoated coronary stents at 30 day follow-up, which is a consecutive, prospective study and enrolled 1027 all comers high risk of bleeding and thrombotic patients who were not indicated to receive conventional DES in 17 sites in France [51]. In this study, patients' population have comorbidities and at high risk for complications and as a result 13% patients were required very short DAPT (<30 day). Even in this population including, COBRA-PzF stents showed the excellent safety and efficacy with a low rate of ST and TLR at 30 days (0.8 and 0.5%, respectively).

These clinical data show safety of COBRA-PzF stent. However, randomized data comparing COBRA-PzF stent versus BMS are lacking. More importantly, preclinical and clinical data suggest that the utility of the COBRA-PzF stent may be seen in patients with high bleeding risk in whom DAPT is best continued for a very short period of time and who may benefit from the intrinsic antithrombotic nature of the PzF coating. To this end the COBRA-REDUCE trial (NCT02594501) has been initiated to assess its safety and efficacy in patients who require anticoagulation treated with COBRA-PzF with DAPT duration of 14 days as compared with current standard DES with DAPT duration of 3–6 months. The primary endpoints are defined as major adverse cardiac events including all cause death, MI, ST or ischemic stroke and Bleeding Academic Research Consortium class ≥2 at 6 months. As discussed below, DAPT duration for DES is currently a moving target with multiple stent makers conducting 1 month clinical trials. Thus, the utility of the COBRA-PzF system may only become apparent if DAPT duration less than 1 month can be shown to be safe with this system.

Polymer free drug-coated stent

Polymer free drug-coated stent is another possibility for the patients at high risk bleeding or the patients requiring noncardiac surgery [3,52–55]. In a randomized, double-blind trial (n = 2466), polymer free drug-coated stent (BioFreedom polymer free umirolimus-coated stent, Biosensors Interventional Technologies, Jalan Tukang, Singapore) and BMS were compared in the patients with a high risk of bleeding. All patients received 1 month of DAPT. The primary safety endpoint (cardiac death, MI or ST) had occurred in 9.4% in the drug-coated stent group and in 12.9% in the BMS group (hazard ratio: 0.71; 95% CI: 0.56–0.91; p = 0.005). Clinically driven target lesion revascularization was needed in 5.1% in the drug-coated stent and in 9.8% in the BMS (hazard ratio: 0.50; 95% CI: 0.37–0.69; p < 0.001). In subanalysis focusing on acute coronary syndrome (ACS) patients, polymer free drug-coated stent showed better safety endpoint (cumulative incidence of cardiac death, MI or definite or probable ST 9.3 vs 18.5%) [53]. The trend was also similar at 2 year follow-up while major bleeding occurred in 8.9% of drug-coated stent and 9.2% of BMS patients (p = 0.95) [54]. Therefore polymer free DES is likely to be more beneficial than BMS for the patients at high risk bleeding as long as patients can tolerate 1 month of DAPT.

Toward shorter duration for DAPT

In the early history of coronary stents, a major issue was balancing ST and procedure-related bleeding [56,57]. DAPT has been the best solution for this issue [58,59]. However, there has only been minor advancement in terms of shortening the duration for DAPT in the last two decades and none are based upon device-specific recommendations. Current guidelines recommend DAPT after DES for 1 year in those with ACS and for a minimum of 6 months for those with stable heart disease [60]. The evidence supporting shorter DAPT duration after implantation of DES has been increasing. In multicenter prospective clinical trial using cobalt–chromium EES, 3-months DAPT duration showed low rate of ST beyond 3 months (0.0% at 1 year) with acceptable low bleeding event rate (thrombolysis in myocardial infarction [TIMI] major/minor bleeding: 0.8% at 1 year) [3]. Additionally, in a multicenter double-blinded trial in the setting of 1 month of DAPT duration, polymer-free DES revealed significantly lower primary safety endpoint including cardiac death, MI or ST relative to BMS (9.4 vs 12.9% respectively; p = 0.005) [2]. To this end, trials such as the COBRA-PzF stenting to Reduce Duration of Triple Therapy (COBRA-REDUCE) randomized clinical trial may strongly move the bar for shortened treatments

especially in those with high risk of bleeding. As described above, endothelialization of COBRA-PzF in a porcine coronary artery model has been reported to be relatively quick with some reports stating 98% at 5 days [45]. It is the authors' opinion that although the healing speed is different between a diseased human coronary artery and a healthy animal model [61], we feel 2 weeks of DAPT may be feasible. Ultimately, it would be ideal to have a type of stent that does not need DAPT. As discussed above, patients at high risk bleeding are beginning to be studied [2,52–55]). However, there is no optimal choice for ACS patients with active bleeding. Although rare, these are the situations in which the interventionist has a difficult time determining optimal treatment.

Future perspective

Using BMS in coronary artery disease can lead to high rate of restenosis and its use is not associated with lower risk for ST. In preclinical models the COBRA-PzF stent reduced neointimal formation and thrombogenicity compared with uncoated stents and this may be due to the unique characteristics of the PzF polymer. Clinical studies have shown that COBRA-PzF achieved a performance goal for an effectiveness endpoint with an acceptable safety profile, which include low risk for MI beyond the peri-procedural period and an exceedingly low rate of ST. Further clinical studies currently underway are investigating whether a shorter duration of DAPT (i.e., 2 weeks) after COBRA-PzF stent implantation in patients at high risk for bleeding who are already taking oral anticoagulant therapy is safe. Collectively, these data suggest that our increasingly sophisticated understanding of how fluoropolymers can be used in interventional cardiology may render the BMS obsolete and reset the paradigm for DAPT in patients undergoing PCI.

Conclusion

The COBRA-PzF stent is a unique type of stent in which the polymer coating plays an important role because of its antithrombogenic anti-inflammatory nature. In preclinical models neointimal proliferation is less as compared with BMS and in clinical studies has shown low rates of restenosis with low rates of ST. Currently patients at high risk bleeding or those who need urgent surgery may be good candidates for the COBRA-PzF stent. Ongoing clinical trials will determine whether shortening the duration of DAPT to less than 1 month is feasible and these data may represent a new paradigm in terms of how patients at high risk for bleeding but requiring intervention are treated in the cath lab.

Financial & competing interests disclosure

CVPath Institute has received institutional research support from 480 Biomedical, Abbott Vascular, ART, BioSensors International, Biotronik, Boston Scientific, Celonova, Claret Medical, Cook Medical, Cordis, Edwards Lifescience, Medtronic, MicroPort, MicroVention, Celonova, OrbusNeich, ReCore, SINO Medical Technology, Spectranetics, Surmodics, Terumo Corporation, WL Gore and Xeltis. R Virmani has received honoraria from 480 Biomedical, Abbott Vascular, Boston Scientific, Cook Medical, Lutonix, Medtronic, Terumo Corporation and WL Gore; and is a consultant for 480 Biomedical, Abbott Vascular, Medtronic, and WL Gore. AV Finn has sponsored research agreements with Boston Scientific and Medtronic CardioVascular and is an advisory board member to Medtronic CardioVascular. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Company review

In addition to the peer-review process, with the author's consent, the manufacturer of the product discussed in this article was given the opportunity to review the manuscript for factual accuracy. Changes were made by the author at their discretion and based on scientific or editorial merit only. The author maintained full control over the manuscript, including content, wording and conclusions.

Executive summary

Device description

- The COBRA-PzF™ is composed of thin strut cobalt chromium platform (71 μm) and a Polyzene-F (PzF) nanothin polymer (≤50-nm thickness) coating.

Impact of strut thickness

- Strut thickness is important to prevent thick neointima and restenosis and jailed side branches resulting in peri-procedural myocardial infarction. Furthermore, it reduces thrombogenicity, which can decrease stent thrombosis.

PzF coating

- PzF is a fluorinated polymer, which combines the benefits of inorganic polyphosphazene within a fluoropolymer.
- PzF polymer consists of poly [bis(trifluoroethoxy)phosphazene], a soft pliable inorganic polymer with a -[p = N] n-backbone and trifluoroethoxy side groups.
- This polymeric coating itself appears to have some mild antirestenotic effect perhaps due to its thromboresistance.

Blood–material interaction

- Bare surface stent directly contact with blood element including plasma proteins, leads to the initiation of the coagulation cascade and activates platelet secondary to accumulation fibrin networks and thrombus.
- The polymer prevents the metal surface of the stents from directly contacting blood elements and reduces the activated platelets and thrombus from attaching to the stent surface.

COBRA-PzF stent in preclinical studies

- The porcine arteriovenous shunt experiments showed significantly less thrombogenicity in COBRA-PzF than COBRA-BMS and Vision BMS.

Clinical studies of COBRA-PzF

- There are several clinical studies evaluating COBRA-PzF which show safety such as low stent thrombosis events and myocardial infarction rates.

Polymer-free drug-coated stent

- Polymer-free drug-coated stent is another possibility for patients at high risk for bleeding or the patients requiring noncardiac surgery.

Toward shorter duration for dual antiplatelet therapy – authors' opinion

- Clinical data supporting shortened dual antiplatelet therapy (DAPT) after implantation of drug-eluting stent are increasing.
- COBRA-REDUCE randomized clinical trial is being conducted to evaluate the safety of short duration (i.e., 14 days) of DAPT in patients requiring oral anticoagulation treated with COBRA-PzF.

Future perspective

- Further clinical studies currently underway have the possibility of showing safety and effectiveness of the COBRA-PzF stent with shorter duration of DAPT such as 2 weeks, in patients at high risk for bleeding who are already taking oral anticoagulant therapy. This stent may be a reasonable option for these patients because of the limited DAPT needed after stent placement.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. WHO. The top 10 causes of death: Fact sheet. World Health Organisation. www.who.int/mediacentre/factsheets/fs310/en/
2. Urban P, Meredith IT, Abizaid A *et al.* Polymer-free drug-coated coronary stents in patients at high bleeding risk. *N. Engl. J. Med.* 373(21), 2038–2047 2015).

•• **Polymer-free stent is a new concept.**

3. Natsuaki M, Morimoto T, Yamamoto E *et al. Cardiovasc. Interv. Ther.* 31(3), 196–209 (2016).
4. Faxon DP, Eikelboom JW, Berger PB *et al.* Antithrombotic therapy in patients with atrial fibrillation undergoing coronary stenting: a North American perspective: executive summary. *Circ. Cardiovasc. Interv.* 4(5), 522–534 (2011).
5. Wang TY, Robinson LA, Ou FS *et al.* Discharge antithrombotic strategies among patients with acute coronary syndrome previously on warfarin anticoagulation: physician practice in the CRUSADE registry. *Am. Heart J.* 155(2), 361–368 (2008).
6. Kastrati A, Mehilli J, Dirschinger J *et al.* Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STEREO) trial. *Circulation* 103(23), 2816–2821 (2001).
7. Pache J, Kastrati A, Mehilli J *et al.* Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STEREO-2) trial. *J. Am. Coll. Cardiol.* 41(8), 1283–1288 (2003).
8. Applegate R, Hermiller J, Williams J *et al.* Evaluation of the effects of everolimus-eluting and paclitaxel-eluting stents on target lesions with jailed side branches: 2-year results from the SPIRIT III randomized trial. *Catheter. Cardiovasc. Interv.* 76(5), 644–651 (2010).

9. Lansky AJ, Yaqub M, Hermiller JB *et al.* Side branch occlusion with everolimus-eluting and paclitaxel-eluting stents: three-year results from the SPIRIT III randomised trial. *Eurointervention Suppl. J.* 6, 44–52 (2010).
10. Otsuka F, Cheng Q, Yahagi K *et al.* Acute thrombogenicity of a durable polymer everolimus-eluting stent relative to contemporary drug-eluting stents with biodegradable polymer coatings assessed *ex vivo* in a swine shunt model. *JACC Cardiovasc. Interv.* 8(9), 1248–1260 (2015).

• **First report about arteriovenous shunt model study.**

11. Koppara T, Cheng Q, Yahagi K *et al.* Thrombogenicity and early vascular healing response in metallic biodegradable polymer-based and fully bioabsorbable drug-eluting stents. *Circ. Cardiovasc. Interv.* 8(6), e002427–e002427 (2015).
12. Virmani R, Guagliumi G, Farb A *et al.* Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? *Circulation* 109(6), 701–705 (2004).
13. Carter AJ, Aggarwal M, Kopia GA *et al.* Long-term effects of polymer-based, slow-release, sirolimus-eluting stents in a porcine coronary model. *Cardiovasc. Res.* 63(4), 617–624 (2004).
14. Finn AV, Nakazawa G, Kolodgie FD *et al.* Temporal course of neointimal formation after drug-eluting stent placement: is our understanding of restenosis changing? *JACC Cardiovasc. Interv.* 2(4), 300–302 (2009).
15. Thyssen JP, Menné T. Metal allergy – a review on exposures, penetration, genetics, prevalence, and clinical implications. *Chem. Res. Toxicol.* 23(2), 309–318 (2010).
16. Köster R, Vieluf D, Kiehn M *et al.* Nickel and molybdenum contact allergies in patients with coronary in-stent restenosis. *Lancet (London, England)* 356(9245), 1895–1897 (2000).
17. Iijima R, Ikari Y, Amiya E *et al.* The impact of metallic allergy on stent implantation: metal allergy and recurrence of in-stent restenosis. *Int. J. Cardiol.* 104(3), 319–325 (2005).
18. Saito T, Hokimoto S, Oshima S, Noda K, Kojyo Y, Matsunaga K. Metal allergic reaction in chronic refractory in-stent restenosis. *Cardiovasc. Revasc. Med.* 10(1), 17–22 (2009).
19. Halwani DO, Anderson PG, Lemons JE, Jordan WD, Anayiotos AS, Brott BC. *In vivo* corrosion and local release of metallic ions from vascular stents into surrounding tissue. *J. Invasive Cardiol.* 22(11), 528–535 (2010).
20. Hsu HC, Yen SK. Evaluation of metal ion release and corrosion resistance of ZrO2 thin coatings on the dental Co-Cr alloys. *Dent. Mater.* 14(5), 339–346 (1998).
21. Shimokado A, Kubo T, Utsunomiya H *et al.* Scanning electron microscopic analysis of polymer damage in drug-eluting stents during multiple stenting. *Int. J. Cardiovasc. Imaging* 29(8), 1909–1913 (2013).
22. Yazdani SK, Sheehy A, Pacetti S, Rittlemeyer B, Kolodgie FD, Virmani R. Stent coating integrity of durable and biodegradable coated drug eluting stents. *J. Interv. Cardiol.* 29(5), 483–490 (2016).
23. Otsuka F, Vorpahl M, Nakano M *et al.* Pathology of second-generation everolimus-eluting stents versus first-generation sirolimus- and paclitaxel-eluting stents in humans. *Circulation* 129(2), 211–223(2014).

•• **Shows problems of second-generation drug-eluting stent.**

24. Okazoe T. Overview on the history of organofluorine chemistry from the viewpoint of material industry. *Proc. Jpn. Acad. Ser. B Phys. Biol. Sci.* 85(8), 276–289 (2009).
25. Garfinkle AM, Hoffman AS, Ratner BD, Reynolds LO, Hanson SR. Effects of a tetrafluoroethylene glow discharge on patency of small diameter dacron vascular grafts. *Trans. Am. Soc. Artif. Intern. Organs* 30, 432–439 (1984).
26. Guidoin R, Marois Y, Zhang Z *et al.* The benefits of fluoropassivation of polyester arterial prostheses as observed in a canine model. *ASAIO J.* 40(3), M870–M879 (1994).
27. Chinn JA, Sauter JA, Phillips RE *et al.* Blood and tissue compatibility of modified polyester: thrombosis, inflammation, and healing. *J. Biomed. Mater. Res.* 39(1), 130–140(1998).
28. Lin JC, Tiong SL, Chen CY. Surface characterization and platelet adhesion studies on fluorocarbons prepared by plasma-induced graft polymerization. *J. Biomater. Sci. Polym. Ed.* 11(7), 701–714 (2000).
29. Hasebe T, Shimada A, Suzuki T *et al.* Fluorinated diamond-like carbon as antithrombogenic coating for blood-contacting devices. *J. Biomed. Mater. Res. A* 76(1), 86–94 (2006).
30. Hasebe T, Yohena S, Kamijo A *et al.* Fluorine doping into diamond-like carbon coatings inhibits protein adsorption and platelet activation. *J. Biomed. Mater. Res. A* 83(4), 1192–1199 (2007).
31. Massa TM, Yang ML, Ho JYC, Brash JL, Santerre JP. Fibrinogen surface distribution correlates to platelet adhesion pattern on fluorinated surface-modified polyetherurethane. *Biomaterials* 26(35), 7367–7376 (2005).
32. Massa TM, McClung WG, Yang ML, Ho JYC, Brash JL, Santerre JP. Fibrinogen adsorption and platelet lysis characterization of fluorinated surface-modified polyetherurethanes. *J. Biomed. Mater. Res. A* 81(1), 178–185 (2007).
33. Mori H, Atmakuri DR, Torii S *et al.* Very late pathological responses to cobalt-chromium everolimus-eluting, stainless steel sirolimus-eluting, and cobalt-chromium bare metal stents in humans. *J. Am. Heart Assoc.* 6(11), pii:e007244 (2017) (Epub ahead of print).

•• **Reveals that fluorinated polymer is more useful as compared with bare metal stent.**

34. Sunny MC, Sharma CP. Titanium-protein interaction: changes with oxide layer thickness. *J. Biomater. Appl.* 6(1), 89–98 (1991).
35. Courtney JM, Lamba NM, Sundaram S, Forbes CD. Biomaterials for blood-contacting applications. *Biomaterials* 15(10), 737–744 (1994).
36. Sheppard JI, McClung WG, Feuerstein IA. Adherent platelet morphology on adsorbed fibrinogen: effects of protein incubation time and albumin addition. *J. Biomed. Mater. Res.* 28(10), 1175–1186 (1994).
37. Gorbet MB, Sefton MV. Biomaterial-associated thrombosis: roles of coagulation factors, complement, platelets and leukocytes. *Biomaterials* 25(26), 5681–5703 (2004).
38. Whicher SJ, Brash JL. Platelet-foreign surface interactions: release of granule constituents from adherent platelets. *J. Biomed. Mater. Res.* 12(2), 181–201 (1978).
39. Lyman DJ, Metcalf LC, Albo D, Richards KF, Lamb J. The effect of chemical structure and surface properties of synthetic polymers on the coagulation of blood. III. *In vivo* adsorption of proteins on polymer surfaces. *Trans. Am. Soc. Artif. Intern. Organs* 20, 474–478 (1974).
40. Szott LM, Irvin CA, Trollsas M, Hossainy S, Ratner BD. Blood compatibility assessment of polymers used in drug eluting stent coatings. *Biointerphases* 11(2), 029806 (2016).
41. Richter GM, Stampfl U, Stampfl S *et al.* A new polymer concept for coating of vascular stents using PTFEP (poly(bis(trifluoroethoxy)phosphazene) to reduce thrombogenicity and late in-stent stenosis. *Invest. Radiol.* 40(4), 210–218 (2005).
42. Satzl S, Henn C, Christoph P *et al.* The efficacy of nanoscale poly[bis(trifluoroethoxy) phosphazene] (PTFEP) coatings in reducing thrombogenicity and late in-stent stenosis in a porcine coronary artery model. *Invest. Radiol.* 42(5), 303–311 (2007).
43. Henn C, Satzl S, Christoph P *et al.* Efficacy of a polyphosphazene nanocoat in reducing thrombogenicity, in-stent stenosis, and inflammatory response in porcine renal and iliac artery stents. *J. Vasc. Interv. Radiol.* 19(3), 427–437 (2008).
44. Radeleff B, Thierjung H, Stampfl U *et al.* Restenosis of the CYPHER-Select, TAXUS-Express, and Polyzene-F nanocoated cobalt-chromium stents in the minipig coronary artery model. *Cardiovasc. Intervent. Radiol.* 31(5), 971–980 (2008).
45. Koppara T, Sakakura K, Pacheco E *et al.* Preclinical evaluation of a novel polyphosphazene surface modified stent. *Int. J. Cardiol.* 222, 217–225 (2016).

• **Evaluates thrombogenicity comparing COBRA™ stent and two different bare metal stent.**

46. Tamburino C, La Manna A, Di Salvo ME *et al.* First-in-man 1-year clinical outcomes of the catania coronary stent system with nanothin Polyzene-f in *de novo* native coronary artery lesions. *JACC Cardiovasc. Interv.* 2(3), 197–204 (2009).

• **First clinical outcome study.**

47. Capodanno D, La Manna A, Di Salvo ME, Sanfilippo A, Corcos T, Tamburino C. Early and mid-term clinical outcomes with the CATANIA coronary stent system vs. bare metal stents in patients with coronary artery disease. *Cardiovasc. Revasc. Med.* 10(4), 216–220 (2009).
48. La Manna A, Capodanno D, Cera M *et al.* Optical coherence tomographic results at six-month follow-up evaluation of the CATANIA coronary stent system with nanothin Polyzene-F surface modification (from the Assessment of The LAtest Non-Thrombogenic Angioplasty Stent [ATLANTA] Trial). *Am. J. Cardiol.* 103(11), 1551–1555 (2009).
49. Tamburino C, Capodanno D, Di Salvo ME *et al.* Safety and effectiveness of the Catania Polyzene-F coated stent in real world clinical practice: 12-month results from the ATLANTA 2 registry. *EuroIntervention* 7(9), 1062–1068 (2012).
50. Cutlip DE, Garratt KN, Novack V *et al.* 9-Month clinical and angiographic outcomes of the COBRA Polyzene-F NanoCoated coronary stent system. *JACC Cardiovasc. Interv.* 10(2), 160–167 (2017).
51. Maillard L presented in EuroPCR 2017. Evaluation of the safety and efficacy of the Cobra-PzF™ NanoCoated Coronary Stent (NCS) in 1 000 all-comers, consecutive, prospective, high risk patients: The e-Cobra Registry (30-Day analysis). https://abstractbook.pcronline.com/export/pdf/id/988
52. Costa RA, Abizaid A, Mehran R *et al.* Polymer-free biolimus A9-coated stents in the treatment of de novo coronary lesions. *JACC Cardiovasc. Interv.* 9(1), 51–64 (2016).
53. Naber CK, Urban P, Ong PJ *et al.* Biolimus-A9 polymer-free coated stent in high bleeding risk patients with acute coronary syndrome: a Leaders Free ACS sub-study. *Eur. Heart J.* 38(13), 961–969 (2016).
54. Garot P, Morice M-C, Tresukosol D *et al.* 2-year outcomes of high bleeding risk patients after polymer-free drug-coated stents. *J. Am. Coll. Cardiol.* 69(2), 162–171(2017).
55. Morice M-C, Talwar S, Gaemperli O *et al.* Drug-coated versus bare-metal stents for elderly patients: a predefined sub-study of the LEADERS FREE trial. *Int. J. Cardiol.* 243(15), 110–115 (2017).
56. Sigwart U, Puel J, Mirkovitch V, Joffre F, Kappenberger L. Intravascular stents to prevent occlusion and re-stenosis after transluminal angioplasty. *N. Engl. J. Med.* 316(12), 701–706 (1987).
57. Serruys PW, de Jaegere P, Kiemeneij F *et al.* A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. *N. Engl. J. Med.* 331(8), 489–495 (1994).

58. Schömig ALS, Eumann FRON, Astrati ADK *et al.* A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. *N. Engl. J. Med.* 334(17), 1084–1089 (1996).

59. Colombo A, Hall P, Nakamura S *et al.* Intracoronary stenting without anticoagulation accomplished with intravascular ultrasound guidance. *Circulation* 91(6), 1676–1688 (1995).

60. Bittl JA, Baber U, Bradley SM *et al.* Duration of dual antiplatelet therapy: a systematic review for the 2016 ACC/AHA Guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J. Am. Coll. Cardiol.* 68(10), 1116–1139 (2016).

61. Virmani R, Kolodgie FD, Farb A, Lafont A. Drug eluting stents: are human and animal studies comparable? *Heart* 89(2), 133–138 (2003).