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Design and Rationale of a Randomized Trial of COBRA PzF Stenting to REDUCE Duration of Triple Therapy (COBRA-REDUCE)

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ABSTRACT

Background/purpose: A coronary stent with thromboresistant and pro-healing properties such as the polymer polyzene F-coated (COBRA PzF) stent might safely allow for a very short duration of triple therapy in patients taking oral anticoagulation (OAC) who undergo coronary stenting.

Methods: The COBRA-REDUCE trial is a prospective, multinational, randomized, open-label, assessor-blinded trial. A total of 996 patients at high bleeding risk because of requirement for OAC (with a vitamin K antagonist or non-vitamin K antagonist for any indication) will be randomized at sites in the United States and Europe to treatment with the COBRA-PzF stent followed by very short duration (14 days) DAPT or a Food and Drug Administration (FDA)-approved new generation drug-eluting stent followed by guideline-recommended DAPT duration (3 or 6 months). Two co-primary endpoints will be tested at 6 months: a bleeding co-primary endpoint (bleeding academic research consortium [BARC] ≥2 bleeding beyond 14 days or after hospital discharge, whichever is later [superiority hypothesis]) and a thrombo-embolic co-primary endpoint (the composite of all-cause death, myocardial infarction, definite/probable stent thrombosis or ischaemic stroke [non-inferiority hypothesis]). The trial is registered at clinicaltrials.gov (NCT02594501).

Conclusion: The COBRA-REDUCE trial will determine whether coronary stenting with the COBRA PzF stent followed by 14 days of clopidogrel will reduce bleeding without increasing thrombo-embolic events compared with FDA-approved DES followed by 3–6 months clopidogrel in patients taking OAC and aspirin.

1. Introduction

In patients undergoing coronary stenting, drug-eluting stents (DES) markedly reduced rates of restenosis and repeat revascularisation compared with bare metal stents (BMS) [1–4]. However, the efficacy advantage afforded by elution of anti-proliferative drug is at the expense of delayed vascular healing. This manifested as an increased risk of late and very late stent thrombosis with early generation DES compared with BMS. However, contemporary DES are associated with lower

Abbreviations: ACS, acute coronary syndrome; BARC, bleeding academic research consortium; BMS, bare metal stent; CAD, coronary artery disease; COR, class of recommendation; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; eCRF, electronic case report form; FDA, Food and Drug Administration; HBR, high bleeding risk; ITT, intention-to-treat; LOE, level of evidence; NOAC, non-vitamin K oral anticoagulant; OAC, oral anticoagulation; PCI, percutaneous coronary intervention; PzF, polyzene F; VKA, vitamin K antagonist.

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rates of stent thrombosis compared with early generation DES [5–8] and BMS [9–11]. Accordingly, in patients with stable coronary artery disease (CAD), current European guidelines recommend 6 months of DAPT after stenting, irrespective of stent type [12]. In contrast, US guidelines continue to recommend DAPT for at least 6 months after DES implantation and for 1 month after BMS-implantation [13].

Up to 10% of patients undergoing coronary stenting have an indication for oral anticoagulation (OAC) and are deemed to be at high bleeding risk (HBR) [14,15]. Indeed, addition of an antiplatelet agent to OAC in patients with coronary artery disease ("dual antithrombotic therapy") increases bleeding risk [16]. Furthermore, concomitant treatment with OAC plus DAPT ("triple antithrombotic therapy") compared with dual therapy (with aspirin omission) significantly increased the rate of bleeding in a number of randomized trials of patients with atrial fibrillation after coronary stenting or acute coronary syndrome (ACS) [17–20]. Nonetheless, meta-analysis of these trials showed an increased risk of thrombotic events with aspirin omission [21]. Only one trial to date has investigated different durations of triple therapy in such patients. The ISAR TRIPLE trial showed no significant improvement with respect to net clinical benefit but no safety concerns with 6 weeks versus 6 months of triple therapy (followed by clopidogrel discontinuation) in patients taking OAC after DES-implantation [22].

Both US and European guidelines recommend that the duration of triple therapy should be kept as short as possible in HBR patients, such as those taking OAC [12,23]. Both guidelines recommend consideration of 3 months of triple therapy in patients with stable CAD (class of recommendation [COR] IIb, level of evidence [LOE] C-LD in US guidelines; COR IIa, LOE A in European guidelines), and 6 months of triple therapy in patients with ACS (COR IIB, LOE C-LD in US guidelines; COR IIa, LOE B in European guidelines) [12,23]. In addition, European Guidelines make recommendations specific to patients treated with OAC for 1 to 6 months of triple therapy, depending on clinical presentation (COR IIa, LOE B) [12]. Both guidelines also recommend that dual therapy may be considered as an alternative to triple therapy in selected patients (e.g. if bleeding risk outweighs ischaemic risk).

Although a number of randomized trials have evaluated comparative efficacy and safety of newer generation DES on a background of very short DAPT durations (1 month) in patients at HBR [24–27], there are no randomized trial data to support the safety of such short DAPT durations compared with guideline-recommended durations. A stent that would safely allow a reduced DAPT duration without significantly compromising efficacy would be ideal for HBR patients.

With this in mind, a coronary stent with thromboresistant and pro-healing properties might safely allow for a very short duration of triple therapy in patients taking OAC who undergo PCI. The COBRA Polyzene-F (COBRA PzF, *CeloNova BioSciences Inc. San Antonio, TX*) stent is a thin strut cobalt-chromium alloy stent coated with a nano-thin layer (≤0.05 μm) of Polyzene-F – a durable inorganic polymer – with no elution of anti-restenotic drug (Fig. 1). PzF is a high-molecular-weight polymer with a backbone of alternating nitrogen and phosphorus atoms and trifluoroethanol side groups with high biocompatibility and mechanical characteristics that allow use as an implant coating at a nanoscale thickness [28]. The Cobra PzF stent is designed to optimize the interface with blood proteins by preferentially binding serum albumin over fibrinogen, thus preventing activation of inflammatory cells and platelets [28]. In addition, bound albumin on the stent surface avoids becoming denatured, a process that would trigger adhesion of inflammatory cells [28].

Preclinical evaluation has shown that the Cobra PzF stent is associated with reduced thrombus formation as well as reduced neointimal hyperplasia and reduced inflammation compared with BMS [29]. Preclinical studies have also shown increased thromboresistance and accelerated healing compared with contemporary high performance DES, including a durable polymer everolimus-eluting stent (Xience), a biodegradable polymer EES (Synergy), and a polymer-free biolimus A9-eluting stent (BioFreedom) [30].

Against this background, the Randomized Trial of COBRA PzF Stenting to REDUCE Duration of Triple Therapy (COBRA-REDUCE) trial was designed to compare, in patients taking an oral anticoagulant and aspirin, the clinical safety and efficacy of the COBRA PzF stent in combination with 14 days of clopidogrel therapy with United States Food and Drug Administration (FDA)-approved DES in combination with 3–6 months of clopidogrel therapy.

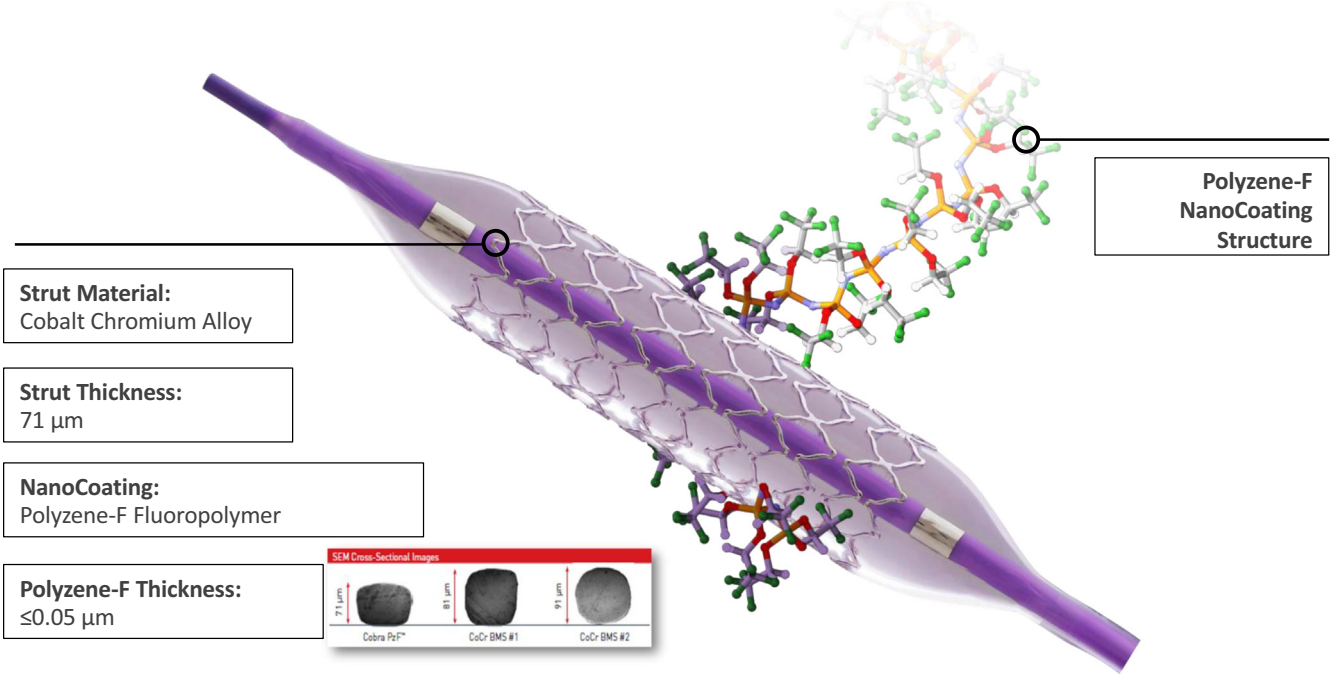

Fig. 1. Properties of the COBRA PzF stent.

2. Methods and analysis

2.1. Study design

The Randomized Trial of COBRA PzF Stenting to REDUCE Duration of Triple Therapy (COBRA-REDUCE) is a multicentre, prospective, randomized, parallel-group, open-label, assessor-blinded clinical trial conducted at 62 sites in the United States and Europe. The event adjudication committee is blinded to treatment allocation. The planned enrolment of 996 patients is complete: the first patient was enrolled in February 2016 and the last patient was enrolled in May 2020. The trial is sponsored and financed by CeloNova BioSciences Inc. San Antonio, TX, USA. The co-ordinating centre (ISAResearch Center, Deutsches Herzzentrum München, Munich, Germany) is responsible for project management, management of safety events, data management, and the angiographic core lab. The trial protocol was written by the principal and co-principal investigators (AK and RAB), in association with the steering committee. Details of the study organisation and participating sites are shown in the Appendix. The trial is registered at www.clinicaltrials.gov (NCT02594501). The current report is based on protocol version 8 dated 11 July 2020.

2.2. Study objectives and endpoints

The study hypothesis is that in patients undergoing coronary stenting who are taking oral anticoagulation, treatment with the Cobra PzF stent plus 14 days of DAPT is superior to standard FDA-approved DES plus 3–6 months of DAPT with respect to bleeding events at 6 months and non-inferior with respect to thrombo-embolic events at 6 months. The trial has two co-primary endpoints. The bleeding co-primary endpoint is bleeding academic research consortium (BARC) class ≥2 bleeding beyond 14 days (or after hospital discharge, whichever is later) until 6 months post-randomization. The thrombo-embolic co-primary endpoint is the composite of all-cause death, myocardial infarction, definite or probable stent thrombosis, and ischaemic stroke from the time of the procedure until 6 months post-randomization. Bleeding events within 14 days of the procedure are not considered in the co-primary endpoint because the antithrombotic therapy is identical in both groups during this time. Thrombotic events are considered from the time of the procedure because rates may also be influenced by the stent used, which differed between the treatment groups. Primary and secondary endpoints are shown in Table 1. The definitions of the components of the co-primary endpoints are shown in Table 2.

Table 1
Trial endpoints.

Co-primary endpoints
1. BARC class ≥2 bleeding beyond 14 days (or after hospital discharge, whichever is later) until 6 months post-randomization
2. Composite endpoint of all-cause death, myocardial infarction, definite or probable stent thrombosis, or ischaemic stroke from the procedure until 6 months post-randomization
Secondary endpoints
▪ Composite of all cause death, myocardial infarction, definite and probable stent thrombosis, ischaemia-driven target lesion revascularisation or ischaemic stroke at 12 months post-randomization
▪ Composite of cardiac death and myocardial infarction at 12 months
▪ Ischaemia driven target lesion revascularisation at 12 months
▪ Definite and probable stent thrombosis at 12 months
▪ Ischaemic stroke at 12 months
▪ BARC class 3–5 bleeding at 6 months
▪ TIMI major bleeding; TIMI major and minor bleeding at 6 months
▪ Health economic utilities (total cardiovascular and bleeding related costs with cost effectiveness based on events avoidEd.)[a]

[a] This data will only be collected from participating sites in the US, France and Switzerland.

2.3. Participants

Patients >18 years of age with symptoms (stable or unstable angina or ACS without thrombosis of the target lesion on coronary angiography) or objective evidence of myocardial ischaemia and ≥50% de novo stenosis in a native coronary vessel (maximum of 2 lesions in a maximum of 2 vessels) with an indication for long-term oral anticoagulation with a coumadin-derivative or a non-vitamin K oral anticoagulant (NOAC) were eligible for inclusion. Inclusion and exclusion criteria are shown in Table 3.

2.4. Randomization

Consecutive patients who met the eligibility criteria were randomly allocated in a 1:1 treatment ratio to COBRA PzF plus 14 days of clopidogrel or a FDA-approved DES plus 3–6 months of clopidogrel in the order in which they qualified. Treatment allocation was stratified according to participating centre and treatment with coumadin derivatives or non-vitamin K oral anticoagulants (NOAC) and was done by means of a computer-generated list pre-generated in permuted blocks for each site and therapy stratification, provided by the electronic case report form (eCRF). Randomization was done by study personnel at each participating site immediately after the lesion was crossed with a guidewire. Time zero is defined as the time of randomization.

2.5. Procedure

All patients underwent coronary angiography and, left ventriculography or echocardiogram according to standard practices if not performed within the previous 6 months. PCI was done according to institutional guidelines and standards. The decision to use single or multiple coronary stents and to perform single or two-vessel interventions was left to the operator's discretion. The same randomly assigned stent had to be implanted in all lesions. Implantation of more than one stent per lesion was permitted. Balloon and stent sizing and applied inflation pressure was at the operator's discretion.

Blood samples were drawn 12–24 h after the procedure for the determination of cardiac markers (CK, CK-MB, and troponin) and blood cell counts (haemoglobin, haematocrit, platelet count, white blood cell count). An ECG was performed directly following the index procedure and 12–24 h after the procedure.

2.6. Devices

The investigational device is the COBRA Polyzene-F (COBRA PzF, *CeloNova BioSciences Inc. San Antonio, TX*) stent. The device is CE-marked for use in Europe and received FDA approval for use in February 2017.

The stent in the control group had to be a FDA-approved new generation DES (e.g. Xience/Promus, Resolute or Synergy), the choice of which was at the discretion of the operator. This could include DES from the same family used under a different name in Europe (e.g. Xience PRO).

2.7. Antithrombotic therapy

All patients received a loading dose of 600 mg of clopidogrel before catheterisation or immediately after the index procedure. For patients who were already on daily maintenance clopidogrel or an alternative P2Y12-inhibitor during the week prior to randomization, the loading dose of clopidogrel was given at the discretion of the treating physician. After the decision to stent, patients were given aspirin (if they had not received it within the previous 12 h); and intra-arterial or intravenous unfractionated heparin (70−100 U/kg body weight) or bivalirudin (intravenous bolus of 0.75 mg/kg prior to the start of the intervention,

Table 2
Definitions of the components of the co-primary endpoints.

BARC ≥ 2 bleeding	BARC Type 2 Any overt, actionable sign of haemorrhage (e.g. more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation. BARC Type 3 Type 3a - Overt bleeding plus haemoglobin drop of 3 to <5 g/dL* (provided haemoglobin drop is related to bleed) - Any transfusion with overt bleeding Type 3b - Overt bleeding plus haemoglobin drop ≥5 g/dL* (provided haemoglobin drop is related to bleed) - Cardiac tamponade - Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/haemorrhoid) - Bleeding requiring intravenous vasoactive agents Type 3c - Intracranial haemorrhage (not including micro--bleeds or haemorrhagic transformation, including intraspinal) - Subcategories confirmed by autopsy or imaging or lumbar puncture - Intraocular bleed compromising vision BARC Type 4: CABG-related bleeding - Perioperative intracranial bleeding within 48 h - Reoperation after closure of sternotomy for the purpose of controlling bleeding - Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period - Chest tube output ≥2 L within a 24-h period BARC Type 5: fatal bleeding Type 5a - Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious Type 5b - Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation
All-cause death	The primary endpoint includes all-cause death. Deaths will also be classified as cardiac or non-cardiac.
Myocardial infarction	Cardiac death: Cardiac death is defined as death due to any of the following: Acute myocardial infarction; Cardiac perforation/pericardial tamponade; Arrhythmia or conduction abnormality; Stroke within 30 days of the procedure or stroke suspected of being related to the procedure; Death due to complication of the procedure, including bleeding, vascular repair, transfusion reaction, or bypass surgery; Any death in which a cardiac cause cannot be excluded. Acute myocardial infarction: Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn) or CKMB, if cTn is not available. For peri-procedural MI, CKMB will be used] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following: - Symptoms of ischaemia. - New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB). - Development of pathological Q waves in the ECG. - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. - Identification of an intracoronary thrombus by angiography or autopsy. - Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased. Myocardial infarction related to percutaneous coronary intervention (PCI): Myocardial infarction associated with PCI is defined by elevation of CKMB >3 × URL (cTn values >5 × 99th percentile URL, if CKMB is not available) in patients with normal baseline values (99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischaemia, or (ii) new ischaemic ECG changes or new LBBB, or (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow- or no-flow or embolization, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required. Myocardial infarction related to coronary artery bypass grafting (CABG): Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker CKMB >5 × URL (or cTn values>10 × 99th percentile URL, if CKMB is not available) in patients with normal baseline CKMB or cTn values (<99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
Definite or probable stent thrombosis	Definite or probable stent thrombosis will be classified by the Academic Research Consortium definition. Definite: presence of an acute coronary syndrome with angiographic or autopsy evidence of thrombus or occlusion. Probable: Any unexplained deaths within 30 days after the procedure or acute myocardial infarction involving the target-vessel territory without angiographic confirmation.
Ischaemic stroke	Acute neurological event of ischaemic aetiology of at least 24 h duration, with focal signs and symptoms and without evidence supporting an alternative explanation.

BARC = bleeding academic research consortium.

followed by infusion of 1.75 mg/kg per hour for the duration of the procedure), with activated clotting time guidance at the operator's discretion.

After the intervention, recommencement of oral anticoagulation within 24 h is recommended. All patients continue oral anticoagulation and aspirin (75–200 mg/day) for the trial duration. In addition, patients receive clopidogrel 75 mg/day for a total of 14 days after COBRA PzF implantation or for 3–6 months after FDA-approved DES implantation. In patients taking coumadin derivatives, the recommended target INR for the duration of triple therapy is 2.0 for atrial fibrillation and 2.5 for mechanical heart valves. After clopidogrel discontinuation, the recommended INR is according to standard guidelines. Treatment with NOAC is recommended according to current guidelines. NOAC dosing is at the discretion of the treating physician.

2.8. Concomitant medication

Other cardiac medications (e.g. β-blockers, ACE-inhibitors, statins) are given according to the judgment of the patient's physician. Proton pump inhibitor therapy is recommended for all patients [31,32].

Table 3
Eligibility criteria for the COBRA-REDUCE trial.

Inclusion criteria
1. Patients older than 18 years of age with ischaemic symptoms (stable or unstable angina or ACS without thrombosis of the target lesion on coronary angiography) or evidence of myocardial ischaemia in the presence of ≥50% de novo stenosis located in a native coronary vessel (a maximum of 2 lesions in a maximum of 2 vessels)
2. Patient receiving or with an indication for new treatment with long-term oral anticoagulation with a coumadin-derivative or a NOAC
3. Written, informed consent by the patient for participation in the study
Exclusion criteria
1. Cardiogenic shock
2. Target lesion located in the left main trunk
3. Bifurcation intervention with a planned 2-stent strategy
4. Vessel size too small for implantation of a 2.5 mm stent by visual estimation
5. Requirement for staged PCI procedure within 6 months after the index procedure
6. Requirement for DAPT for >2 weeks after the index procedure
7. Contraindication or allergy to cobalt, chromium, platinum, Polyzene-F, Everolimus, Zotarolimus or inability to take triple therapy for at least 6 months
8. Relevant haematologic deviations: platelet count $<100 \times 10^9$ cells/L or $>600 \times 10^9$ cells/L
9. Active bleeding; bleeding diathesis; recent trauma or major surgery in the last month; history of intracranial bleeding or structural abnormalities; suspected aortic dissection
10. Malignancies or other co-morbid conditions with life expectancy <12 months or that may result in protocol non-compliance
11. Pregnancy, current (positive pregnancy test), suspected or planned; breast feeding
12. Known allergy or intolerance to the study medications: aspirin, clopidogrel, Coumadin and its derivatives
13. Inability to fully cooperate with the study protocol

ACS = acute coronary syndrome; DAPT = dual antiplatelet therapy; NOAC = non-vitamin K oral anticoagulant; PCI = percutaneous coronary intervention.

2.9. Follow-up

After hospital discharge, clinical follow-up is scheduled at 14 days, 30 days, 6 months, and 12 months by office visit, telephone, or letter. A study flow chart is shown in Fig. 2.

2.10. Discontinuation of study participation

Individual trial participants have the right to discontinue study participation at any time. Reasons may include an active patient decision (drop-out), investigator-initiated factors, or loss to follow-up. In case of drop-out, no further data will be collected. Data available at the time of discontinuation will be used for final analysis. If a patient misses a follow-up visit and data cannot be obtained for the scheduled follow-up, it will be considered a "missed visit". All efforts will be made to contact the patient at the next scheduled follow-up. At least 3 attempts, per scheduled visit, should be made to contact the patient through all available routes. A patient will be considered "lost to follow-up" only after their last scheduled follow-up visit.

2.11. Data collection and management

Data are collected at each clinical site and stored in the eCRF. Research coordinators will perform primary data collection on source-documented hospital chart reviews. Angiographic images are sent to the angiographic core lab.

Data management activities are conducted by the ISAResearch Center and the Institut für Herzinfarktforschung (IHF), Ludwigshafen, Germany. IHF is responsible for creating and maintaining the study-specific database, the data management, validation and export plans, and annotated CRFs. All IHF data is protected by firewalls, backups, virus protection software and user access management. All data will be transferred with SSL encryption standard and stored on an IHF server.

2.12. Statistical analysis

2.12.1. Sample size calculation

To calculate the sample size for the bleeding co-primary endpoint, we assumed an incidence of 5.6% in patients assigned to DES plus 3–-6 months DAPT [33] and an incidence of 2.1% in patients assigned to the COBRA PzF plus 14 days DAPT. The null hypothesis states that the COBRA PzF-based strategy will be associated with a BARC class ≥2 bleeding rate equal to the DES-based strategy. An evaluable sample size of

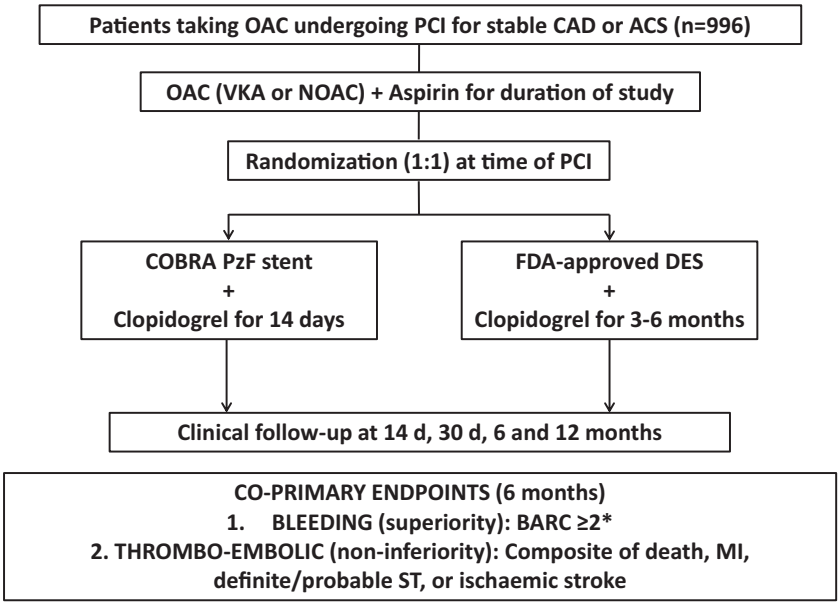

Fig. 2. COBRA-REDUCE study flow. Legend. * beyond 14 days (or after hospital discharge, whichever is later). ACS = acute coronary syndrome; BARC = bleeding academic research consortium; CAD = coronary artery disease; FDA = Food and Drug Administration; MI = myocardial infarction; NOAC = non vitamin K oral anticoagulant; OAC = oral anticoagulation; ST = stent thrombosis; VKA = vitamin K antagonist.

948 (474 patients in each treatment arm) provides 80% power to reject the null hypothesis at a two-sided α-error level of 0.05, signifying that the treatment strategy utilizing COBRA PzF is *superior* to the use of a FDA-approved DES-based strategy with respect to BARC ≥2 bleeding. A total of 996 subjects will be enrolled to account for loss to follow-up, which is not expected to exceed 5%.

For the thrombo-embolic co-primary endpoint, we assumed a rate of 8.0% at 6 months [33]. We selected a non-inferiority margin of 5.0% based on clinically important differences and study feasibility [34]. Therefore, the null hypothesis states that the rate of the thrombo-embolic co-primary endpoint in the COBRA PzF group will exceed that in the DES group by ≥5.0%. Assuming the true rate of the thrombo-embolic co-primary endpoint is 8.0% in both treatment groups, an evaluable sample size of 948 (474:474) provides 88% power to reject the null hypothesis at a one-sided α-error level of 0.05, accounting for loss to follow-up of 5%. The minimum detectable margin with a sample size of 948 (474:474) patients, providing 80% power and a one-sided α-error level of 0.05, is 4.4%.

2.12.2. Analysis population

Analysis of the co-primary endpoints, the individual components of the co-primary endpoints and the secondary endpoints will be done according to the intention-to-treat (ITT) principle: all subjects who signed the written informed consent and are randomized will be included according to the treatment to which they were allocated, irrespective of protocol violations or continued participation in the study. A patient is considered to have adequate follow-up if he/she has an event or has follow-up of ≥166 days, allowing for a visit window of 6 months± 14 days. Analysis will also be performed on the per-protocol population, defined as subjects with procedural success and no major protocol violations.

2.12.3. Pre-specified subgroups

Pre-specified subgroup analysis will be done according to age, gender, diabetes status, history of stroke, history of bleeding, clinical presentation, indication for OAC, ejection fraction, proton pump inhibitor treatment, access site, renal function, treatment with coumadin derivatives or NOAC and number of major bleeding risk criteria as defined by the Academic Research Consortium for High Bleeding Risk. A post-hoc sensitivity analysis is planned according to the actual duration of DAPT received in the control group.

2.12.4. Statistical analysis plan

For demographics, baseline characteristics and secondary endpoints, categorical variables will be presented as counts and percentages and differences between groups will be compared using chi-square or Fisher's exact test, as appropriate. Continuous variables will be presented as mean ± standard deviation or median (interquartile range) and differences between groups will be compared using asymptotic or non-parametric methods, depending on the distribution of the analysed variable.

For the bleeding co-primary endpoint, an assessment of the null and alternative hypotheses will be carried out using the z-test for two binomial proportions at the 0.025 level of significance (one-sided) on the ITT subjects. The null hypothesis will be rejected once the significance level of the z-test with pooled variance and no continuity correction is ≤0.025 and bleeding rate in the COBRA-PzF arm is lower than in the DES arm. For the thrombo-embolic co-primary endpoint, an assessment of the null and alternative hypotheses will be carried out using the Farrington and Manning test of non-inferiority for two binomial proportions with an additive non-inferiority margin of 5.0% at the 0.05 level of significance on the ITT subjects. The null hypothesis will be rejected once the *p*-value of the Farrington and Manning one-sided test of non-inferiority is ≤0.05 and composite endpoint rate in the COBRA-PzF arm is non-inferior to that in the DES arm. Trial success will be declared in the case that the null hypotheses for both co-primary endpoints will be rejected. The analysis of co-primary endpoints described above will be repeated in the per-protocol population. The assessment of the two hypotheses will also be carried out on all ITT patients by comparing time to each of the co-primary endpoints in the two study groups using the Kaplan-Meier method and significance level of a log-rank test.

2.13. Ethical considerations

The sponsor will ensure that the study fully adheres to the principles outlined in the "Declaration of Helsinki" [35], the "Guideline for Good Clinical Practice" International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Tripartite Guideline (January 1997) and ISO 14155:2011(E). The trial is being conducted in compliance with FDA regulations 21 CFR 50, 54, 56 and 812, 45 CFR part 46. Prior to study enrolment, approval for the protocol and informed consent form was obtained from the Ethics Committee (EC)/Institutional Review Board (IRB) at each clinical site. At the institution of the co-ordinating centre, approval was obtained from the ethics committee of the Technical University of Munich, Germany (ID number 271/15S). All patients provided informed written consent prior to enrolment.

2.14. Protocol amendments

The mandated DAPT duration in the control arm specified in the protocol was amended during the trial. The original protocol mandated 6 months of DAPT in the control arm on the recommendation of the US FDA, who were consulted regarding the trial design and protocol amendments. However, because of slow recruitment in response to the availability of new data and changes in clinical practice guideline recommendations while the trial was ongoing, a protocol amendment was made on May 22nd 2017, in consultation with the FDA, to allow for reduced DAPT durations, as short as 3 months, in the control arm, consistent with current clinical practice guidelines.

Any amendments to the protocol and consent form must be submitted to the EC/IRB and written approval obtained prior to implementation. Protocol amendments must be communicated in writing to investigators at participating sites and to the US FDA and shown on clinicaltrials.gov. All amendments will be shown as tracked changes in the final version of the protocol, which will be published with the trial report.

2.15. Informed consent

Informed consent will be obtained by investigators at participating sites. The investigator will inform the patient orally and in writing about the scope and purpose, rights, duties and possible risks/benefits of the study in lay language. The patient must authorise the release of his medical data by signing the "Research subject information and consent form". A template is shown in the supplementary appendix.

3. Summary

The COBRA-REDUCE trial is the first trial to investigate a novel polymer-coated stent without elution of antiproliferative drug in combination with 14 days of DAPT compared with guideline-recommended therapy in patients with an indication for long-term OAC who undergo coronary stenting.

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CRediT authorship contribution statement

Róisín Colleran: Investigation, Writing – original draft. **Michael Joner:** Funding acquisition, Investigation, Writing – review & editing. **Donald Cutlip:** Investigation, Writing – review & editing. **Philip Urban:** Writing – review & editing. **Michael Maeng:** Investigation, Writing – review & editing. **Jonathan M. Michel:** Writing – review & editing. **Roxana Mehran:** Writing – review & editing. **Ajay J. Kirtane:** Writing – review & editing. **Luc Maillard:** Investigation, Writing – review & editing. **Adnan Kastrati:** Conceptualization, Supervision, Investigation, Writing – review & editing. **Robert A. Byrne:** Conceptualization, Supervision, Investigation, Writing – review & editing.

Declaration of competing interest

Dr Colleran reports speakers fees from Medtronic. Dr Joner reports personal fees from Biotronik, personal fees from Orbus Neich, grants and personal fees from Boston Scientific, grants and personal fees from Edwards, personal fees from Astra Zeneca, personal fees from Recor, grants from Amgen outside the submitted work. Dr Urban reports honoraria for CEC and DSMB activities from Edwards Lifesciences and Cardialysis, is a consultant for Biosensors and is a shareholder of CERC (Massy, France) and of MedAlliance (Morges, Switzerland). Dr Maeng has received lecture or advisory board fees from Astra-Zeneca, Bayer, Boehringer-Ingelheim, Boston Scientific, Bristol-Myers Squibb, and Novo Nordisk; and has received a research grant from Bayer. Dr Barakat is an employee of Celonova Biosciences Inc. Dr Mehran reports consultant fees to the institution from Abbott Laboratories and Spectranetics/Philips/Valcano Corp; consulting fees from Boston Scientific, Cardiovascular Systems Inc., Medscape, Siemens Medical Solutions, Regeneron Pharmaceuticals Inc., Roivant Sciences Inc., and Sanofi; being the spouse of a consultant for Abiomed and The Medicines Company; research funding to the institution from AstraZeneca, Bayer, Beth Israel Deaconess Hospital, BMS, CSL Behring, Eli Lilly and DSI, Medtronic, Novartis Pharmaceuticals, and Orbus Neich; scientific advisory board fees from PLx Opco Inc., dba PLx Pharma Inc.; scientific advisory board fees to the institution from Bristol-Myers Squibb; executive committee fees from Janssen Pharmaceuticals and Osprey Medical; speaker engagements for Abbott Laboratories; equity from Claret Medical and Elixir Medical; and Data Safety Monitoring Board fees to the institution from Atermark Research Partners. Dr. Kirtane reports institutional funding to Columbia University and/or Cardiovascular Research Foundation from Medtronic, Boston Scientific, Abbott Vascular, Abiomed, CSI, CathWorks, Siemens, Philips, ReCor Medical. In addition to research grants, institutional funding includes fees paid to Columbia University and/or Cardiovascular Research Foundation for speaking engagements and/or consulting; no speaking/consulting fees were personally received; personal fees received consist of travel expenses/meals from Medtronic, Boston Scientific, Abbott Vascular, Abiomed, CSI, CathWorks, Siemens, Philips, ReCor Medical, Chiesi, OpSens, Zoll, and Regeneron. Dr. Byrne reports research funding to the institution of prior employment from Celonova Biosciences and research or educational funding to the institution of current employment from Abbott Vascular, Biosensors, Biotronik and Boston Scientific. The other authors report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.carrev.2021.01.022.

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