



# Bioresorbable Polymer-Coated Orsiro Versus Durable Polymer-Coated Resolute Onyx Stents (BIONYX): Rationale and design of the randomized TWENTE IV multicenter trial

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**Aim** The aim was to compare in a noninferiority trial the efficacy and safety of 2 contemporary drug-eluting stents (DESs): a novel, durable polymer-coated stent versus an established bioabsorbable polymer-coated stent.

**Methods and results** The BIONYX trial ([ClinicalTrials.gov](http://ClinicalTrials.gov)-no.NCT02508714) is an investigator-initiated, prospective, randomized, patient- and assessor-blinded, international, multicenter study in all-comer patients with all types of clinical syndromes and lesions who require percutaneous coronary interventions with DES. Patients at 7 study sites in the Netherlands, Belgium, and Israel were randomly assigned (1:1, stratified for gender and diabetes mellitus) to treatment with the novel, zotarolimus-eluting, durable polymer-coated Resolute Onyx stent that has a radiopaque, thin-strut, CoreWire stent platform versus the sirolimus-eluting, bioresorbable polymer-coated Orsiro stent (reference device) that has a very thin-strut, cobalt-chromium stent backbone. The primary end point is the 1-year incidence of the composite clinical end point target vessel failure consisting of cardiac death, target vessel-related myocardial infarction, or clinically indicated target vessel revascularization. A power calculation, assuming a target vessel failure rate of 6.0% (noninferiority margin 2.5%), revealed that 2,470 study patients would give the study 80% power (α level 5%), allowing for up to 3% loss to follow-up. The first patient was enrolled on October 7, 2015; on December 23, 2016, the last patient entered the study.

**Conclusions** BIONYX is a large-scale, prospective, randomized, international, multicenter trial comparing a novel DES with durable coating versus a reference DES with biodegradable coating in all-comers. The study is the first randomized assessment of the Resolute Onyx stent, which is an often-used DES outside the United States. (*Am Heart J* 2018;198:25-32.)

## Background

Persistent concerns about the limited safety of the first-generation durable polymer coronary drug-eluting stents (DESs)<sup>1-3</sup> prompted the development of newer-generation DESs with more biocompatible durable

polymer coatings and better safety profiles.<sup>4-6</sup> These DESs showed favorable outcomes following percutaneous coronary interventions (PCIs) in broad patient populations and in all-comers of several clinical trials.<sup>7-10</sup>

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**Conflicts of interest:** C. v. B. has been an unpaid consultant to Biotronik, Boston Scientific, and Medtronic. The research department of Thoraxcentrum Twente has received research grants provided by Biotronik, Boston Scientific, and Medtronic. All other authors declared that they have no conflict of interest. RCT# NCT02508714

Submitted January 24, 2017; accepted December 14, 2017.

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0002-8703

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<https://doi.org/10.1016/j.ahj.2017.12.011>

Most recently, the Resolute Onyx stent (Medtronic Vascular, Santa Rosa, CA) has been developed, which is a newer-generation durable polymer DES that uses a novel, thin-strut metallic stent backbone with increased radiographic visibility and elutes zotarolimus from its BioLinx polymer coating. In parallel with the progress in durable polymer DES, bioresorbable polymer-coated DESs have been developed, of which recently introduced devices have very thin struts and flexible stent designs.<sup>4,10,11</sup> The Orsiro stent (Biotronik, Bülach, Switzerland), which is such a DES, elutes sirolimus from a circumferential coating that is located mainly on the abluminal side of the very thin-strut, cobalt-chromium stent platform.<sup>11,12</sup> The efficacy and safety of the Orsiro stent have previously been demonstrated in several randomized trials.<sup>10,13,14</sup> Resolute Onyx and Orsiro represent the respective summit of the engineering efforts of 2 major device-manufacturing companies to optimize the safety and efficacy of coronary DES. Both devices are clinically used in all types of patients and lesion anatomies.

Although data from a head-to-head comparison of both stents would be of interest, such data are not available yet. The aim of the present Bioresorbable Polymer Orsiro Versus Durable Polymer Resolute Onyx Stents (BIONYX) trial is to compare the safety and efficacy of the Resolute Onyx and Orsiro stents in all-comers who truly reflect routine clinical practice, addressing a noninferiority hypothesis.

## Investigational products

### Resolute Onyx stent

The Resolute Onyx stent is a Conformité Européenne-certified, newer-generation permanent polymer-coated DES. The stent is circumferentially covered with the 5.6- $\mu\text{m}$ -thin BioLinx polymer system that elutes zotarolimus as the antiproliferative agent during a period of 6 months and consists of a blend of 3 different polymers: (1) the hydrophobic C10 polymer, which aids in the control of drug release; (2) the hydrophilic C19 polymer, which supports biocompatibility; and (3) polyvinyl pyrrolidone, which increases the initial drug burst and enhances the elution rate. The stent platform of Resolute Onyx is made from a single-strand, swaged shape corewire that is manufactured into a sinusoidal waveform and automatically welded at predefined connection sites. The corewire consists of a denser core made from a platinum-iridium alloy surrounded by a cobalt-chromium alloy; the inner core increases the stent's radiopacity. The struts of Resolute Onyx (uncoated 81  $\mu\text{m}$  in 3.00-mm stents) are thinner than the struts of its predecessors Resolute and Resolute Integrity (Medtronic) (uncoated 91  $\mu\text{m}$ ). The increased radiopacity and the modified stent design of Resolute Onyx aim to improve visibility and deliverability of the stent while maintaining its longitudinal and radial strength. Stents with nominal diameters

ranging from 2.00 to 5.00 mm were available. Long-term safety and efficacy of other DESs that used the same coating as Resolute Onyx have previously been demonstrated.<sup>15-17</sup> Nevertheless, the BIONYX trial is the first randomized clinical study to assess the novel Resolute Onyx stent in a broad and unrestricted patient population.

### Orsiro stent

The Orsiro stent is a Conformité Européenne-certified DES with a circumferential, asymmetrical, bioresorbable coating that is thicker on the abluminal stent side (7.4  $\mu\text{m}$  vs 3.5  $\mu\text{m}$ ); this configuration of the coating results in a higher drug dose on the abluminal side of the stent.<sup>12</sup> The poly(L-lactide)acid coating elutes the drug sirolimus within slightly more than 3 months and is gently resorbed within 1 to 2 years, thereby attempting to minimize inflammation.<sup>12,18</sup> The active coating covers a thin passive coating of amorphous silicon carbide that encapsulates the metal stent to prevent ion leakage (hybrid coating).<sup>12,19</sup> Orsiro is based on the PRO-Kinetic double-helix stent platform, which is made from a thin-strut cobalt-chromium alloy and has 60- $\mu\text{m}$  struts (in stents with a nominal diameter < 3.50 mm) or 80- $\mu\text{m}$  struts (in stents with nominal diameters  $\geq$  3.50 mm). During study enrollment, stents with a nominal diameter ranging from 2.25 to 4.00 mm were available. The efficacy of Orsiro in preventing excessive neointimal proliferation has been assessed in the angiographic end point study BIO-FLOW II,<sup>20</sup> in which Orsiro demonstrated noninferiority versus the fluoropolymer-coated, everolimus-eluting Xience Prime stent (Abbott, Santa Clara, CA) with a low in-stent late lumen loss (0.10  $\pm$  0.32 mm vs 0.11  $\pm$  0.29 mm) and similar binary restenosis rates (4.0% vs 4.7%, respectively). The Orsiro stent was previously tested against 3 other DESs in large-sized, randomized, noninferiority studies, which ascertained the safety and efficacy of Orsiro in greatly unrestricted patient populations.<sup>10,13,14</sup>

## Methods

### Main study hypothesis and study design

The BIONYX trial ([ClinicalTrials.gov](https://clinicaltrials.gov) no. NCT02508714) is an international, multicenter, assessor- and patient-blinded, randomized clinical trial in an all-comer population. The main objective is to compare the 1-year safety and efficacy of the novel Resolute Onyx durable-polymer stent with that of the established Orsiro bioresorbable-polymer stent (the reference device) in all-comer patients who undergo PCI with DES implantation. The study assesses whether the safety and efficacy of the novel Resolute Onyx stent are non-inferior to those of Orsiro. The randomization for DES type was performed in a 1:1 ratio after stratification for gender and presence of diabetes mellitus. The investigator-initiated trial was

**Table.** BIONYX inclusion and exclusion criteria

Inclusion criteria

1. Patients  $\geq 18$  y, capable of providing informed consent
2. Patients requiring PCI for the treatment of significant coronary artery of bypass graft lesions that are suitable for treatment with both DES types, according to clinical guidelines and/or the operator's judgment

Exclusion criteria

1. Participation in another randomized trial of cardiovascular devices or antithrombotic or anticoagulant therapy before reaching the primary end point
2. Known intolerance to components of 1 of the study DESs or known intolerance to antithrombotic and/or anticoagulant therapy that prevents adherence to any DAPT
3. Planned elective surgical procedure necessitating interruption of DAPT during the first 3 m after randomization
4. Known pregnancy
5. Adherence to scheduled follow-up is unlikely or assumed life expectancy is  $< 1$  y

DAPT, dual antiplatelet therapy.

planned by cardiologists of Thoraxcentrum Twente and is performed in close cooperation with cardiologists of all study sites.

### Study population and study sites

The study examines 2,488 all-comer patients. Patients with a minimum age of 18 years who required PCI with DES implantation were eligible for enrollment. Patients with all clinical syndromes were allowed, irrespective of number, type, location, vessel size, or length of lesions to be treated, as long as operators considered them suitable for treatment with both stents. To assess patients and lesions that reflect routine clinical practice, only few exclusion criteria were applied (Table). The study complies with the Declaration of Helsinki and was approved by the Ethical Review Board Twente and by the study centers' institutional review boards. All patients provided written informed consent.

Patient enrollment was performed in the Netherlands, in Belgium, and in Israel at 7 study sites (in the Netherlands: Thoraxcentrum Twente, Medisch Spectrum Twente, Enschede; Haga Hospital, The Hague; Treat Zorggroep, Emmen; Rijnstate Hospital, Arnhem; in Belgium: Virga Jessa Hospital, Hasselt; University Hospital Charleroi, Charleroi; in Israel: Rambam Hospital, Haifa). The first patient was enrolled in BIONYX on October 7, 2015; study enrollment was finished on December 23, 2016. (See study flow chart Figure).

### Study protocol, patient demographics, and medical data

At baseline, patient demographics and clinical data were collected online in an electronic database of the clinical research organization Diagram (Zwolle, the Netherlands). Laboratory tests were performed in the local laboratories of the participating centers as part of the routine clinical practice. Cardiac biomarker measurements were scheduled prior to PCI and 4-18 hours after

PCI or before discharge, with subsequent serial measurements in case of relevant biomarker elevation or complaints until the peak elevation has been measured. Analysts, blinded for the stent type used, will perform angiographic analyses and offline quantitative coronary angiographic measurements according to present standards (QangioXA, version 7.3).

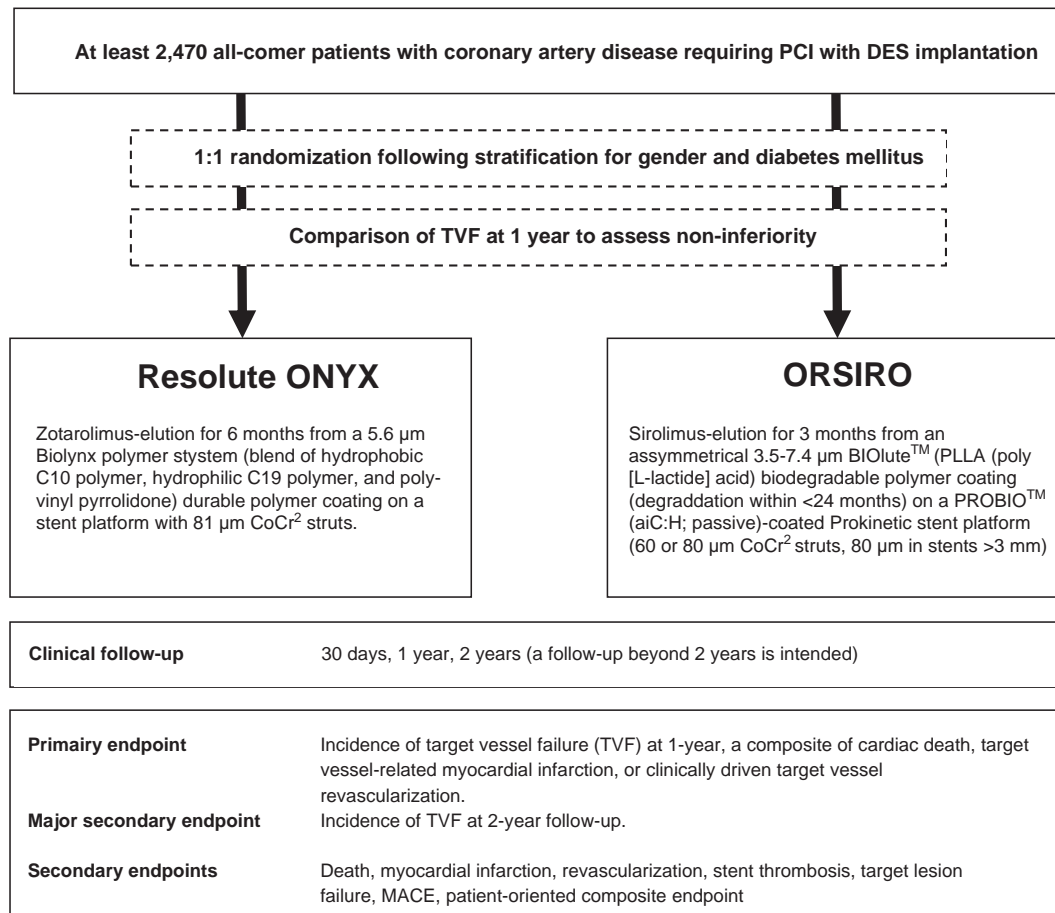
PCI was performed according to routine medical practice and current guidelines. Fractional flow reserve assessment of angiographically intermediate stenosis was recommended in accordance with current guidelines. If clinically indicated, use of intravascular ultrasound or optical coherence tomography was permitted for guidance of the PCI procedure at the operator's discretion. If the operator was unable to insert the randomized study stent, crossover to a stent of choice was allowed. Mixture of stents was generally avoided but was permitted if the operator was unable to insert the randomized stent. Outside the setting of primary PCI, we generally encouraged the treatment of all target lesions in 1 session if this was reasonable and safe. However, *staged PCI procedures* (defined as procedures planned at the time of the index procedure or shortly thereafter and performed within 6 weeks with the same type of study stent) were permitted. During follow-up, in patients with potential restenosis and visually determined lumen narrowing  $\leq 80\%$ , the use of fractional flow reserve is encouraged to evaluate its hemodynamic significance and the potential indication for reintervention. In case of additional unplanned revascularization procedures, the use of the allocated DES type was recommended except for the treatment of an in-stent restenosis of one of the study stents.

Medical therapy during the PCI procedure was performed according to local routine medical treatment. The use of glycoprotein IIb/IIIa inhibitors was left at the operators' discretion. Dual antiplatelet therapy was recommended for 6 to 12 months according to current medical guidelines. In patients on oral anticoagulation, triple therapy was recommended for at least 1 month, after which oral anticoagulation in combination with a P2Y<sub>12</sub> receptor antagonist, generally clopidogrel, was prescribed for 6 to 12 months. Moreover, in patients on oral anticoagulation, gastric protection with a proton pump inhibitor was generally suggested.

### Follow-up data collection

After 1 month, 12 ( $\pm 1$ ) months, and 24 ( $\pm 1$ ) months, follow-up data will be collected during routine visits to the outpatient clinic or, if not feasible, by a medical questionnaire and/or a telephone follow-up carried out by staff that is blinded to the allocated treatment. Patients will be interviewed regarding repeat hospitalization, revascularization procedures, and myocardial infarction (MI) during follow-up. Findings will be confirmed by review of medical records. Survival is checked from the

Figure



Study FLOWCHART.

municipal population register. In case of death, information will be obtained from the patients' medical record, general practitioner, or the referring cardiologist. In case of loss to follow-up or consent withdrawal, outcome data will be used until time of loss to follow-up or withdrawal. Pending approval of additional financial support, the investigators are willing to extend the open-label follow-up beyond 24 months until 5 years.

#### Clinical end points and definitions

The primary composite end point is the incidence of target vessel failure (TVF) at 1-year follow-up, which evaluates both device efficacy and patient safety. Components of TVF are in hierarchical order: cardiac death, target vessel MI, or clinically indicated target vessel revascularization. *Cardiac death* is defined as any death caused by proximate cardiac cause, unwitnessed death, death of unknown cause, and all procedure-related deaths, including those related to concomitant therapy. As in our previous trials,<sup>8-10,21</sup> *target vessel MI* is defined

as any creatine kinase (CK) concentration of more than double the upper limit of normal with elevated values of a confirmatory cardio biomarker, and can be related to a target vessel or cannot be related to another vessel. In case no repeat angiography was performed, MI was assumed to be related to the target vessel. If CK from index MI has not yet reached its maximum level, *periprocedural MI* is, according to the definitions of the Academic Research Consortium, defined as recurrent thoracic chest pain or ischemia >20 minutes or new ECG changes consistent with MI and appropriate cardiac enzyme data (rise in CK within 24 hours of the index event of more than double the upper limit of normal and ≥50% above previous level). In the absence of CK, or of both CK and CK-MB, CK-MB and troponin were used, respectively.<sup>22</sup> Clinically indicated target vessel revascularization includes revascularization procedures by PCI and coronary artery bypass grafting. TVF at 2-year follow-up is a major secondary end point. Other secondary end points include device and patient-

oriented efficacy and safety parameters such as target lesion failure, major adverse cardiac events, patient-oriented composite end point, and stent thrombosis according to the definitions of the Academic Research Consortium, as well as periprocedural MI according to the Academic Research Consortium and other established definitions.<sup>22</sup>

### Sample size calculation

The main outcome parameter is the difference in TVF between the 2 treatment arms after 12 months. At least 2,470 patients had to be enrolled based on a power calculation that assumed TVF rates of 6.0% at 1-year follow-up, based on available outcome data of the Durable Polymer-Based Stent Challenge of Promus Element Versus Resolute Integrity (DUTCH PEERS) trial<sup>9</sup> at the time of designing the current study, with a 2.5% noninferiority margin, giving the study a power of 80% with an  $\alpha$  level of .05 and allowing for at least 3% loss to follow-up. If the upper limit of the 1-sided 95% CI for the between-DES difference is <2.5%, noninferiority will be declared. Sample size calculation was performed with PASS software (NCSS, Kaysville, UT). After noninferiority has been established, superiority will be performed as well as a calculation of the 2-sided 95% CIs.

Although the assumed TVF rate of 6.0% in de BIONYX trial may be quite realistic, an adaptive sample size based on the results of interim analyses at 33% and 66% recruitment would have been a valuable alternative.

### Randomization

Randomization was performed by a computer program, and the randomization was done in blocks of 8 and 4 in random order. Moreover, patients were stratified according to the presence of diabetes mellitus and gender before randomization.

### Statistical considerations

The primary end point TVF at 1 year will be analyzed by the log-rank test by comparing the time to the primary end point using Kaplan-Meier method. Noninferiority will be achieved if the upper limit of the 1-sided 97.5% CI of the absolute risk difference is less than the noninferiority margin. The primary analyses will be performed based on intention-to-treat. Prespecified subgroup analyses will be performed in analogy to previous clinical trials of our group.<sup>8-10</sup> Subgroup analyses will be performed to assess consistency of treatment effect across different subsets.  $P < .05$  will be considered statistically significant, except for the primary analyses, as outlined.

### Trial organization

Trial organization and data management will be performed by Cardio Research Enschede, Enschede, the Netherlands. Study monitoring will be carried out by an

independent external contract research organization (Diagram, Zwolle, the Netherlands). An independent external clinical event committee will adjudicate all potential adverse clinical events. Moreover, an independent Data Safety Monitoring Board will evaluate safety interim analyses of all-cause mortality in both stent arms, performed after the inclusion of 33% and 66% of the patient population. Termination of the trial or one of the study arms may be considered if a sufficient amount of events has occurred and mortality exceeds the all-cause mortality of comparable all-comers studies by more than 50% in one of the study arms, and in case such difference cannot be explained by other factors (eg, noncardiac causes) and a relation with a study DES is likely. The DSMB will not supervise the incidence of the primary study end point, and all-cause mortality is not a component of the primary end point of this trial. Therefore, no correction of the power analysis is required based on the evaluations of the DSMB.

### Funding

Biotronik and Medtronic provided equal financial support. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents. Sponsors will have no access to the study database and are not involved in the interpretation of data or manuscript preparation.

### Discussion

The prospective, international, multicenter BIONYX trial performs in all-comer patients who undergo PCI a randomized head-to-head comparison of the safety and efficacy of implanting the novel, zotarolimus-eluting Resolute Onyx stent with a durable polymer coating versus the established, sirolimus-eluting Orsiro stent with a bioresorbable polymer coating (reference device). The study will evaluate clinical outcome in a noninferiority setting by comparing the composite primary end point TVF at 1-year follow-up. In addition, the study will assess established device- and patient-oriented composite clinical end points (eg, target-lesion failure, major adverse cardiac events, and patient-oriented composite end point), acute angiographic results, as well as the rate of stent thrombosis. All-comer studies are particularly valuable, as their results best reflect the device performance in routine clinical practice and the study findings may be generalized to a great extent.<sup>6-10,13-17,23-25</sup> Based on the findings of previous clinical studies that examined BioLinx-coated zotarolimus-eluting stents other than Resolute Onyx<sup>10,15,16,17</sup> and on the results of randomized trials that compared durable polymer DES with early or newer bioresorbable polymer DES,<sup>10,13,14,23-26</sup> noninferiority of Resolute Onyx versus Orsiro may be expected. Nevertheless, so far, this hypothesis has never been

tested, and Resolute Onyx and Orsiro stents have never been compared in clinical practice.

The novel stent platform that is used in the Resolute Onyx stent uses cobalt-chromium struts with a platinum-iridium core. Because of the denser strut core, radiographic visibility of the novel stent is increased. This might decrease the risk of geometrical miss, for instance, when treating ostial disease and short or severely calcified target lesions. Moreover, it may facilitate the identification of stents with suboptimal expansion that may benefit from vigorous postdilation. Similar to Resolute Onyx, platinum-chromium-based everolimus-eluting stents have a superior angiographic visibility.<sup>9,10,27</sup> In the DUTCH PEERS trial, lesions that had been treated with the more radiopaque Promus Element stent (Boston Scientific, Natick, MA) were significantly more often postdilated than lesions in which an angiographically less visible cobalt-chromium stent had been implanted (79% vs 74%,  $P = .002$ ).<sup>9</sup> It has been argued that the excellent radiographic visibility of the platinum-chromium stents might have contributed to that higher frequency of stent postdilation.<sup>9</sup> On the other hand, if stents have a high radiographic visibility, longitudinal stent deformation, which sporadically occurs in most contemporary DESs,<sup>28,29</sup> can be more easily identified and corrected. The latter may explain to some extent why in the DUTCH PEERS trial longitudinal deformation of the Promus Element stent turned out to be rather benign—even after cessation of dual antiplatelet therapy and during 5-year follow-up.<sup>9,30,31</sup>

Adding platinum to stent strut material is known to provide solid solution strengthening that permits a significant reduction in strut thickness.<sup>32</sup> In the Resolute Onyx stent, the novel corewire strut material and subtle changes in stent design allowed to reduce the thickness of the (uncoated) strut from 91  $\mu\text{m}$  in the stent's predecessor (Resolute Integrity)<sup>9</sup> to now 81  $\mu\text{m}$ . Previously, thin struts were shown to reduce strut malapposition, flow disturbance, thrombogenicity, and restenosis.<sup>33-35</sup> In the Orsiro stents with a nominal diameter of 3.5 mm or larger, the thickness of the uncoated stent strut is 80  $\mu\text{m}$  and thus similar to Resolute Onyx, whereas Orsiro stents <3.5 mm have even thinner struts.<sup>10</sup>

Most DESs only use 2 basic stent designs to cover their entire range of stent diameters provided.<sup>36</sup> This is not the case for Resolute Onyx that has 4 basic stent designs to cover its range of stent diameters (2.0-5.0 mm), which currently is wider than for any other DES type, including the predecessor Resolute Integrity.<sup>36,37</sup> In large-sized vessels, such as the left main stem and some saphenous vein graft, the availability of an extra-large stent may avoid incomplete stent apposition, which is an important risk factor of stent thrombosis in DES.<sup>38</sup> In very small target vessels—typically side branches or very distal vessels—stents with a nominal diameter of 2.0 mm may be useful

to avoid incomplete stent expansion which is related to a higher risk of restenosis and stent thrombosis.<sup>39</sup> Moreover, in Resolute Onyx, the risk of thrombus formation may be expected to be low because in previous clinical studies of other BioLinx-coated (Resolute-type) zotarolimus-eluting stents, the risk of definite stent thrombosis was found to be low.<sup>16,40</sup>

In the BIONYX trial, the role of the Orsiro stent as reference device is more than justified. As a matter of fact, 3 randomized all-comer studies demonstrated noninferiority of Orsiro versus the respective comparator DES and showed excellent clinical outcomes for Orsiro.<sup>10,13,14</sup> In the BIOSCIENCE trial, Orsiro was compared with the everolimus-eluting Xience stent (Abbott Vascular); both DES showed at 12-month follow-up similar rates of the primary composite end point target lesion failure (6.5% vs 6.6%,  $P = .95$ ).<sup>13</sup> The BIO-RESORT trial, which so far is the only randomized trial that compared Orsiro with the Resolute Integrity stent, the predecessor of Resolute Onyx, revealed after 12 months similar rates of the primary end point TVF for both stents (4.7% vs 5.4%,  $P = .46$ ).<sup>10</sup> Although BIO-RESORT has 3 treatment arms, it was formally not designed to compare the Orsiro stent with the Synergy stent (Boston Scientific),<sup>27</sup> which is another modern, very thin-strut, bioresorbable polymer DES. Nevertheless, it is undeniably of interest that the TVF rates were low and similar for these 2 DESs (4.7% for Orsiro as well as Synergy).<sup>10</sup> Moreover, in the SORT OUT VII trial, Orsiro was noninferior to the early-generation, bioresorbable polymer, biolimus-eluting Nobori stent (Terumo, Japan) for target lesion failure at 12 months (3.8% vs 4.6%,  $P = .34$ ); however, the definite stent thrombosis rate was lower in the Orsiro stent group (0.4% vs 1.2%,  $P = .03$ ).<sup>14</sup> The results of all 3 aforementioned trials represent strong evidence for the safety and clinical efficacy of the Orsiro stent and support the choice of Orsiro as the reference device in the BIONYX trial.

Thus, BIONYX is a large-scale, prospective, randomized (1:1), controlled, international, multicenter trial with 2 arms comparing in all-comer patients 2 dissimilar contemporary DESs. The study will provide new insights into the clinical outcome of PCI with modern bioresorbable polymer versus permanent polymer DES in patients who reflect routine clinical practice. In addition, the study is the first randomized assessment of the Resolute Onyx stent, which is an often-used DES outside the United States.

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