Comparison of 3 biodegradable polymer and durable polymer-based drug-eluting stents in all-comers (BIO-RESORT): Rationale and study design of the randomized TWENTE III multicenter trial

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Aim To evaluate the safety and efficacy of 2 novel drug-eluting stents (DES) with biodegradable polymer-based coatings versus a durable coating DES.

Methods and Results BIO-RESORT is an investigator-initiated, prospective, patient-blinded, randomized multicenter trial in 3540 Dutch all-comers with various clinical syndromes, requiring percutaneous coronary interventions (PCI) with DES implantation. Randomization (stratified for diabetes mellitus) is being performed in a 1:1:1 ratio between ORSIRO sirolimus-eluting stent with circumferential biodegradable coating, SYNERGY everolimus-eluting stent with abluminal biodegradable coating, and RESOLUTE INTEGRITY zotarolimus-eluting stent with durable coating. The primary endpoint is the incidence of the composite endpoint target vessel failure at 1 year, consisting of cardiac death, target vessel-related myocardial infarction, or clinically driven target vessel revascularization. Power calculation assumes a target vessel failure rate of 8.5% with a 3.5% non-inferiority margin, giving the study a power of 85% (α level .025 adjusted for multiple testing). The impact of diabetes mellitus on post-PCI outcome will be evaluated. The first patient was enrolled on December 21, 2012.

Conclusions BIO-RESORT is a large, prospective, randomized, multicenter trial with three arms, comparing two DES with biodegradable coatings versus a reference DES with a durable coating in 3540 all-comers. The trial will provide novel insights into the clinical outcome of modern DES and will address the impact of known and so far undetected diabetes mellitus on post-PCI outcome. (Am Heart J 2014;167:445-51.)

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Background

More than a decade ago, the concept of drug-eluting stents (DES) was developed to minimize the risk of in-stent restenosis by the local delivery of anti-proliferative drugs from stent coatings that also helped control the release kinetics of the drugs. While effectively reducing lesion recurrence, first-generation DES with elementary durable polymer-based coatings did not improve mortality following percutaneous coronary interventions (PCI). This was to a great extent attributed to a higher incidence of late and very late stent thrombosis that was largely related to a limited biocompatibility of early DES.[1] Second-generation DES with more biocompatible durable polymer-based coatings then showed on average a more favorable clinical outcome,[2-7] while contemporary third-generation DES with more refined stent designs showed improved stent deliverability in challenging coronary anatomies.[8-12] The zotarolimus-eluting RESOLUTE INTEGRITY stent (Medtronic Vascular, Santa Rosa, CA) is such a

third-generation durable polymer DES[6,8,9] that utilizes the established combination of zotarolimus elution from a BioLinx coating, of which previous randomized controlled trials demonstrated that it is safe, highly efficacious, and non-inferior to that of fluoropolymer-coated everolimus-eluting stents.[4,5,13,14]

In parallel with the refinement of durable coating DES, concerns about durable polymers as a potential trigger of vessel wall inflammation and late adverse events prompted the development of DES with biodegradable polymer-based coatings,[15] which, after degradation, leave only a bare metal stent in the vessel wall that does not induce an excessive or prolonged inflammatory response.[15,16] Such DES recently demonstrated favorable safety and efficacy compared to first generation durable coating DES.[17]

Meanwhile, novel biodegradable coating DES have been introduced, which utilize modern, flexible, thin-strut stent platforms and drugs that are highly efficacious in preventing restenosis.[18,19] These devices employ dissimilar concepts as either the entire stent (i.e. circumferential coating) or only the abluminal stent surface (i.e., external coating) is covered by the biodegradable coating. The ORSIRO stent (Biotronik, Bülach, Switzerland) elutes sirolimus from a thin circumferential biodegradable coating,[20] and the SYNERGY stent (Boston Scientific, Natick, MA) elutes everolimus from a thin abluminal biodegradable coating.[21] While such DES are increasingly used in clinical practice, there is no data from randomized head-to-head comparisons between these stents and established third-generation durable coating DES.

Meanwhile, PCI with DES has become the standard of care. Current randomized comparisons of approved DES therefore address so-called all-comer populations with very limited exclusion criteria, and comprise patients with all clinical syndromes.[8] The findings of such trials are particularly valuable as they reflect the performance of DES in routine clinical practice. Therefore, in the present BIO-RESORT multicenter trial, we assess in an all-comer patient population the safety and efficacy of the ORSIRO and SYNERGY biodegradable coating DES versus the RESOLUTE INTEGRITY durable coating DES as a reference.

Investigational products

ORSIRO

ORSIRO is a Conformité Européenne (CE)–certified hybrid coating DES with a 7.5 μm thick circumferential coating that consists of a combination of an active (BIOlute) and passive coating (PROBIO). The BIOlute active coating consists of a biodegradable PLLA polymer that elutes sirolimus in which 50% of the drug is released within 30 days and 80% within 3 months (complete degradation of coating within 1–2 years),[22] resulting in promising pre-clinical data.[23] The PROBIO passive coating encapsulates the metal stent and minimizes interaction between metal and surrounding tissue at sites of contact. The configuration of the coating is asymmetrical and thicker on the abluminal side than on the luminal side (7.4 vs 3.5 μm, respectively), which results in a higher drug dose on the abluminal side of the DES.[23] The ORSIRO is based on the PRO-Kinetic cobalt-chromium stent platform with a strut thickness of 60 μm in stents with a nominal diameter ≤3.0 mm and 80 μm in stents with a nominal diameter >3.0 mm. The efficacy of this DES was assessed in the BIOFLOW studies, in which the ORSIRO showed favorable outcome and non-inferiority compared to the durable polymer based Xience Prime (Abbott Vascular, Santa Clara, CA).[20,24,25]

SYNERGY

SYNERGY is a CE-certified DES that elutes everolimus from a 4-μm-thick biodegradable PLGA (poly[lactic-co-glycolic acid]) coating that is completely resorbed within 4 months. To minimize the amount of polymer, the coating is applied on the abluminal side of the stent only. The flexible stent platform is manufactured from 74 μm struts of a platinum chromium alloy, a material that is also employed in the durable polymer-based Promus Element DES.[10] To improve stent flexibility, conformability, and longitudinal robustness, the design of SYNERGY stent platform underwent several modifications from the Element platform, including changes in connector angles and peak radius, and the presence of two additional proximal and distal end-connectors.[26] The performance of SYNERGY was assessed in the EVOLVE-I trial, in which SYNERGY achieved long-term angiographic results that were similar to Promus Element.[21]

RESOLUTE INTEGRITY

RESOLUTE INTEGRITY is a CE-certified and Food and Drug Administration–approved durable polymer DES. The 5.6-μm-thick BioLinx polymer system, which covers the entire stent platform, elutes zotarolimus as the antiproliferative agent. The polymer system consists of a blend of three 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 pyrro-lidinone, which increases the initial drug burst and enhances the elution rate. This coating is also used in Resolute, a DES that was shown to be highly effective in reducing restenosis with a favorable safety profile.[4,13] RESOLUTE INTEGRITY is based on a third-generation, cobalt-chromium stent platform (Integrity), which has a strut thickness of 91 μm and a stent design that facilitates stent delivery.[11]

Methods

Study hypothesis and design

The main objective of the current investigator-initiated, patient-blinded, randomized, multicenter BIO-RESORT trial

Figure

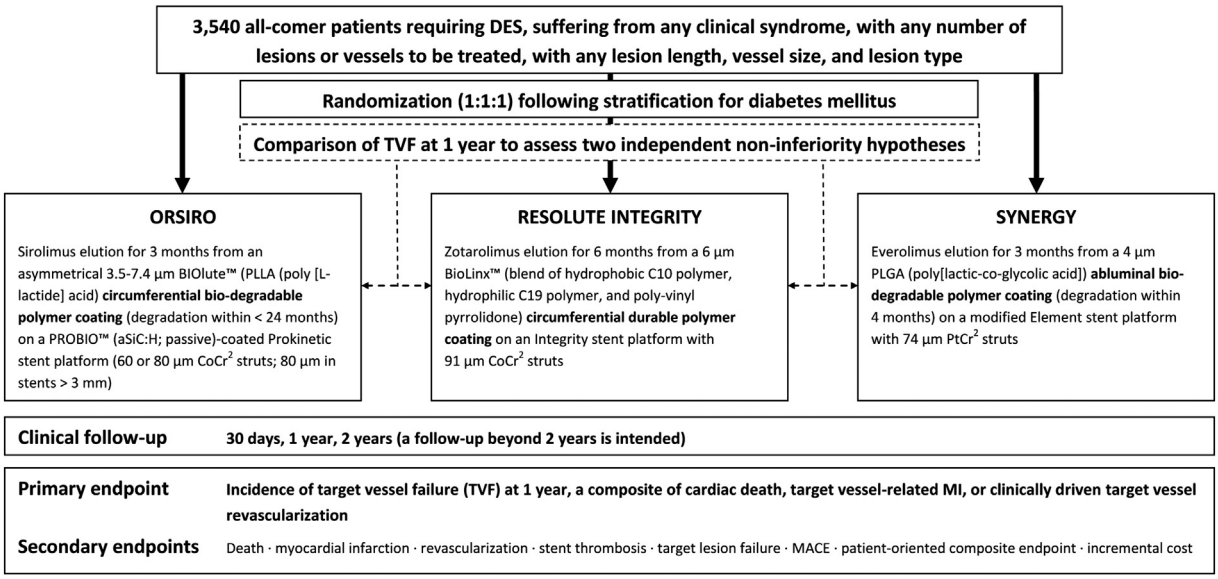

Table. BIO-RESORT inclusion and exclusion criteria

Inclusion criteria

1. Patient ≥18 years, capable of providing informed consent and willing and able to cooperate with study procedures and follow-up
2. Coronary artery or bypass graft lesion(s) requiring PCI with DES implantation according to clinical guidelines and/or the operator's judgment

Exclusion criteria

1. Participation in another randomized drug or device trial before reaching its primary endpoint
2. Known pregnancy
3. Known intolerance to components of an investigational product, or to antithrombotic or anticoagulant medication, preventing adherence to dual antiplatelet therapy
4. Planned elective surgical procedure during the first 6 months after randomization, necessitating the interruption of dual antiplatelet therapy
5. Adherence to scheduled follow-up is uncertain and/or life expectancy assumed to be <1 year

(ClinicalTrial.gov no. NCT01674803) is to compare the safety and efficacy of two novel biodegradable coating DES with that of the established RESOLUTE INTEGRITY durable coating DES (the reference device) in an all-comer population with many complex lesions and patients (Figure). The study will independently assess whether the safety and efficacy of (1) the ORSIRO stent and (2) the SYNERGY stent is non-inferior to that of RESOLUTE INTEGRITY. Randomization for DES type is performed in a 1:1:1 ratio after stratification for the prevalence of diabetes mellitus. The investigator-initiated trial was planned and is performed by cardiologists of the participating PCI centers. Biotronik, Boston Scientific, and Medtronic provided equal financial support.

Study population

A total of 3540 all-comer patients (age ≥18 years) with various clinical syndromes, requiring PCI with DES implantation, are studied. All-comers are studied to assess patients and lesions that reflect routine clinical practice. This implies the application of only few exclusion criteria (Table).

The study complies with the Declaration of Helsinki and was approved by the Ethical Review Board Twente. All patients provide written informed consent. Enrollment is currently performed at four study sites in The Netherlands (Thoraxcentrum Twente at Medisch Spectrum Twente, Enschede; Rijnstate Hospital, Arnhem; Albert Schweitzer Hospital, Dordrecht; and Haga Hospital, The Hague). The first patient was enrolled on December 21, 2012. The expected completion of enrollment is in spring 2015.

Study protocol, patient demographics, and medical data

Patient demographics and clinical data at inclusion are collected online in an electronic database (CRO Diagram, Zwolle, The Netherlands). Cardiac marker assessment is scheduled prior to PCI and 6 to 18 hours after PCI, with

subsequent serial measurements in case of relevant biomarker elevation or complaints until the peak elevation has been determined.

PCI will be performed according to routine clinical practice. In accordance with current guidelines, the use of Fractional Flow Reserve for the assessment of angiographically intermediate stenoses is recommended. If clinically indicated, intravascular ultrasound or optical coherence tomography may be used for guidance of the PCI procedure at the operator's discretion. Operators were requested to report any evident (or suspected) longitudinal stent deformation, which is defined as distortion or shortening of an implanted stent in the longitudinal axis following initially successful deployment.[27] In case of stent thrombosis, the use of optical coherence tomography or intravascular ultrasound is encouraged to identify the mechanism of stent thrombosis. If an operator is unable to insert the randomized study stent despite various measures, crossover to a stent of choice is allowed.

Treatment of all target lesions within a single PCI procedure is encouraged, if reasonable and safe; however, staged procedures (defined as procedures planned at the time of the index procedure or shortly thereafter and being performed within 6 weeks with the allocated type DES) are permitted. During follow-up, in patients with potential restenosis and visually determined lumen narrowing ≤80%, the use of Fractional Flow Reserve is encouraged to evaluate its hemodynamic significance and indication for reintervention. In case of unplanned revascularization procedures, the use of the allocated type DES is recommended, except for the treatment of a restenosis in a study stent.

Medical therapy during the PCI procedure conforms to routine medical treatment. Dual antiplatelet therapy is recommended for 6 to 12 months according to current medical guidelines. In patients on oral anticoagulation (eg, for atrial fibrillation), triple therapy is recommended for at least 1 to 3 month(s), after which oral anticoagulation in combination with clopidogrel, ticagrelor, or prasugrel is prescribed for 6 to 12 months.

Follow-up data collection

After 1 month, 12 (±1) months, and 24 (±1) months, follow-up data will be collected at visits at outpatient clinics or, if not feasible, by telephone follow-up and/or a medical questionnaire, carried out by staff that is blinded to the allocated treatment. Follow-up beyond 2 years is intended. During visits and telephone calls, patients will be interviewed regarding repeat hospitalizations, revascularization procedures, and myocardial infarctions (MIs) during follow-up. Survival is checked from the municipal population register; in case of death, information will be obtained from the patient's medical chart, general practitioner, and/or cardiologist.

Clinical endpoints and definitions

The primary endpoint is the incidence of target vessel failure (TVF) at 1-year follow-up, a composite endpoint to assess device efficacy as well as patient safety. Components of TVF are in hierarchical order: cardiac death, target vessel MI, and clinically driven target vessel revascularization. *Cardiac death* is defined as any death caused by proximate cardiac cause (eg, MI, low-output failure, or fatal arrhythmia), unwitnessed death, death of unknown cause, and all procedure-related deaths, including those related to concomitant therapy. As in our previous trials,[4,5] *target vessel MI* is defined by any creatine kinase concentration of more than double the upper limit of normal with elevated values of a confirmatory cardiac biomarker,[28] and can be related to a target vessel or cannot be related to another vessel. *Clinically indicated repeated revascularization* includes revascularization procedures by PCI and coronary artery bypass graft surgery.

Secondary endpoints include device and patient-oriented efficacy and safety parameters such as target lesion failure, major adverse cardiac events, patient-oriented composite endpoint as previously described,[8] and stent thrombosis according to the Academic Research Consortium definitions.[29] Among the secondary endpoints, the impact of diabetes mellitus on post-PCI outcome will be evaluated. In addition, a sub-study will investigate the prevalence of so far undetected diabetes and its potential relevance for clinical outcome. At 24-month follow-up, we will assess TVF as a major secondary endpoint. Moreover, one of the elements of the BIO-RESORT is the health economic evaluation comprising a Markov decision model constructed to model all three treatment arms. Information on resource use will be collected during the trial. The EQ-5D, a standardized measure of health status, will be used to estimate quality-adjusted life years in all treatment groups. The incremental cost-effectiveness ratio (ICER) will be calculated for the three stents, and probabilistic sensitivity analysis will be applied to analyze decision uncertainty.

Sample size calculation

The BIO-RESORT trial will assess two non-inferiority hypotheses independently of each other, using RESOLUTE INTEGRITY as the reference to compare the novel biodegradable coating DES ORSIRO and SYNERGY. The main outcome parameter is the difference in TVF between two treatment arms after 12 months, analyzed by χ^2 test. A total of 3540 patients is enrolled based on a power calculation that assumes a TVF rate of 8.5% at 1-year follow-up, based on data of the TWENTE and Resolute All Comers trials,[4,13] with a 3.5% non-inferiority margin, giving the study a power of at least 85% with a one-sided α level of .025 (from .05 adjusted for multiple testing to .025) and allowing for up to 3% loss to follow-up. The sample size calculation was performed with PASS software (NCSS, Kaysville, UT).

Randomization

Patients are randomized by custom-designed computer software (Diagram, Zwolle, The Netherlands) when stent implantation is intended. Randomization is performed in random blocks of 6 and 3 in random order and stratified on the prevalence of medically treated diabetes mellitus.

Statistical considerations

Between-group differences in TVF rate at 12 months will be analyzed for the two primary comparisons (SYNERGY versus RESOLUTE INTEGRITY and ORSIRO versus RESOLUTE INTEGRITY). The primary endpoint will be analyzed by the log-rank test by comparing the time to the primary endpoint using the Kaplan-Meier method. Non-inferiority will be achieved if the upper limit of the 1-sided 97.5% confidence interval of the absolute risk difference is less than the non-inferiority margin.

After non-inferiority has been established, superiority testing will be performed as well as calculation of 2-sided 95% CIs. The primary analyses will be performed based on intention-to-treat. In addition, we will perform a more conservative per-protocol analysis (i.e., based on the actual stents implanted) of the primary endpoint. Pre-specified subgroup analyses will be performed for, but will not be limited to, diabetes mellitus, age, gender, recent MI, in-stent restenosis, known renal insufficiency, bifurcation lesion, left main stenting, bypass graft lesion treated, multivessel stenting, number of implanted stents, lesion length, small vessels, and number of treated lesions, in which the primary and secondary endpoints will be analyzed. The 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 coordination 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 clinical events committee will adjudicate all potential clinical endpoints. Moreover, an independent data safety monitoring board will evaluate safety interim analyses of all-cause mortality in the three stent arms performed after inclusion of 33% and 66% of the patient population.

The authors are solely responsible for the design and conduct of the study, all study analyses, the drafting and editing of the manuscript, and its final contents. Device-manufacturing companies will have no access to the study database and are not involved in the interpretation of data or manuscript preparation.

Discussion

The prospective BIO-RESORT multicenter trial performs a 1:1:1-randomized head-to-head comparison of two contemporary, flexible biodegradable coating DES (ORSIRO and SYNERGY) versus a third-generation, highly deliverable durable coating DES (RESOLUTE INTEGRITY) in all-comer patients. The trial examines two independent hypotheses, namely that the efficacy and safety of both ORSIRO and SYNERGY is non-inferior to that of RESOLUTE INTEGRITY. In addition, the three-arm study design offers the unique opportunity to compare the clinical performance of two modern biodegradable coating DES as a major secondary research question. The trial does not only compare three devices, but also three different "philosophies" as both biodegradable coating DES differ significantly in the distribution of coating and in the speed by which coatings are resorbed.

The development of DES with biodegradable coatings was prompted by a debate on the role of durable polymers as potential triggers of vascular inflammation and late adverse clinical events.[15,16] While the first biodegradable coating DES had more rigid stent designs with thicker struts, they had a clinical outcome that was generally similar and sometimes even superior to first and some second-generation durable coating DES. For instance, in the LEADERS trial, the BioMatrix stent showed non-inferiority at 5-year follow-up compared to Cypher (Cordis, NJ) for a composite primary endpoint that included cardiac death, MI, or clinically-indicated TVR (22.3% vs. 26.1%, respectively; P non-inferiority <.0001).[17] Similar to LEADERS, in COMPARE II, non-inferiority was shown for the same composite endpoint, comparing the biolimus-eluting, biodegradable coating Nobori stent (Terumo, Tokyo, Japan) with Xience (5.2% vs. 4.8%, respectively; $P = .69$).[30] The SORT OUT V study, which compared Nobori and Cypher stents, however, did not find non-inferiority of the biodegradable stent[31]; this may partly be related to the particularly low event rate in SORT OUT V that was at one year in the biodegradable stent arm lower than that of the BioMatrix stent in LEADERS (5.4% vs. 11%, respectively).[17,31]

Novel biodegradable coating DES, such as ORSIRO and SYNERGY, provide improved stent flexibility due to thin-strut stent designs and more flexible stent materials.[10,21,23] The SYNERGY stent uses a modified Element stent platform, made from a highly radiopaque platinum-chromium alloy with favorable strength and durability[12,32,33]; and the ORSIRO stent is based on a PRO-Kinetic Energy stent platform made from cobalt chromium.[23] While ORSIRO utilizes an asymmetric encompassing coating (abluminal coating > luminal coating) that is degraded within 1–2 years,[23] SYNERGY uses an abluminal coating only[21] that is degraded within 4 months; these dissimilarities in coating might result in differences of vascular inflammatory response to both DES. Differences in strut thickness could be of interest, as flexible thin-strut stent designs have previously been shown to be particularly efficacious in preventing restenosis.[18,19] Data provided by the BIO-RESORT trial may serve as reference to compare the results of upcoming studies with polymer-free DES[34,35] such as the novel BioFreedom stent[36] or the Cre8 stent (CID, Salugia, Italy), which has shown a lower 6-month late lumen loss than the Taxus Liberté stent (Boston Scientific Corporation, Natick, MA).[37]

In parallel with this innovative approach, novel durable coating DES with improved biocompatibility, such as the second-generation RESOLUTE stent, were developed and demonstrated a favorable clinical performance in the randomized Resolute All Comers and TWENTE trials.[5,38] Meanwhile, third-generation durable coating DES, such as RESOLUTE INTEGRITY, combine the proven efficacy and safety profiles of coatings and drugs of second-generation DES with more flexible stent designs. The cobalt chromium Integrity stent design is formed by a continuous sinusoidal technology that has shown to be highly deliverable.[11] The DUTCH PEERS (TWENTE II) trial is the first randomized study that reported safety and efficacy of RESOLUTE INTEGRITY in all-comers.[6]

The comparison of stents in all-comer patient populations is particularly useful, as the results of such studies

reflect device performance in routine clinical practice and may be generalized.[2,6,13,17,30,31] A recent analysis of data of the TWENTE trial demonstrated an increased incidence of peri-procedural MI in patients with previously undetected diabetes.[39] Because of the increasing clinical and economic burden of diabetes in aging populations with a western lifestyle, BIO-RESORT pays particular attention to the outcome of diabetic patients. In brief, prior to randomization, all patients are stratified for medically treated diabetes mellitus. In addition, the levels of glycated hemoglobin (HbA1C) and fasting serum glucose are collected to identify previously undetected diabetics and assess the true impact of diabetes on clinical outcome, and to study in diabetic patients the impact of glycemic control on clinical outcome. The collected data will allow evaluation of the added value of testing for undetected diabetes regarding resource utilization.

Thus, BIO-RESORT is a large, prospective, randomized, controlled, multicenter trial with three arms, comparing in 3540 all-comers two contemporary biodegradable coating DES versus a third-generation durable polymer coating DES as the reference. The trial will provide novel insights into the clinical outcome of modern DES and will address the impact of known and so far undetected diabetes mellitus on post-PCI outcome.

Disclosures

Conflict of Interest: Clemens von Birgelen is consultant to and has received lecture fees or travel expenses from Abbott Vascular, Boston Scientific, and Medtronic; he received travel expenses from Biotronik and lecture fees from MSD. The institution has received research grants from Abbott Vascular, Biotronik, Boston Scientific, and Medtronic. The BIO-RESORT trial is equally funded by Medtronic, Biotronik, and Boston Scientific.

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