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Randomized Comparison of Biodegradable Polymer Sirolimus-eluting Stents versus Durable Polymer Everolimus-eluting Stents for Percutaneous Coronary Revascularization: Rationale and Design of the BIOSCIENCE Trial

NCT01443104

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ABSTRACT

Background: Biodegradable polymers for release of antiproliferative drugs from metallic drug-eluting stents (DES) aim to improve long-term vascular healing and efficacy. We designed a large scale clinical trial to compare a novel thin strut, cobalt chromium DES with silicon carbide coating releasing sirolimus from a biodegradable polymer (Orsiro, O-SES) with the durable polymer-based Xience Prime everolimus-eluting stent (X-EES) in an all-comers patient population.

Design: The multicenter BIOSCIENCE trial (NCT01443104) randomly assigned 2,119 patients to treatment with biodegradable polymer SES or durable polymer EES at 9 sites in Switzerland. Patients with chronic stable coronary artery disease or acute coronary syndromes, including non-ST-elevation and ST-elevation myocardial infarction, were eligible for the trial if they had at least one lesion with a diameter stenosis >50% appropriate for coronary stent implantation. The primary endpoint target lesion failure (TLF) is a composite of cardiac death, target-vessel myocardial infarction, and clinically-driven target lesion revascularization within 12 months. Assuming a TLF rate of 8% at 12 months in both treatment arms and accepting 3.5% as a margin for non-inferiority, inclusion of 2,060 patients would provide 80% power to detect non-inferiority of the biodegradable polymer SES compared with the durable polymer EES at a one-sided type I error of 0.05. Clinical follow-up will be continued through five years.

Conclusion: The BIOSCIENCE trial will determine whether the biodegradable polymer SES is non-inferior to the durable polymer EES with respect to TLF.

BACKGROUND

Early generation drug-eluting stents (DES) have significantly reduced neointimal hyperplasia and the need for repeat revascularizations compared with bare metal stents (1). The reduction in restenosis came at the expense of an increased risk of very late stent thrombosis (2), motivating the development of newer generation devices. DES typically consist of three components: a metal scaffold, an antiproliferative agent, and a polymer matrix controlling the release of the drug. Modifications and technical refinements of each of the three components have contributed to an improvement in safety and efficacy of DES in recent years. New generation DES with thin strut stent platforms, biocompatible polymers and lower dosages of limus-analogues largely eliminated the risk of very late stent thrombosis while maintaining the antirestenotic efficacy of early generation DES (3, 4).

The polymer matrix of early generation DES has been shown to elicit an inflammatory response. Histopathological analysis of very late stent thrombosis specimens showed evidence of localized hypersensitivity reactions with eosinophilic infiltrates and aggregates of giant cells around polymer fragments (5). A prolonged inflammatory response to the polymer has hence been associated with delayed vascular healing with impaired stent strut endothelialization (6) and pathologic vessel remodeling resulting in coronary evaginations with secondary incomplete stent apposition (7). Moreover, early generation DES have been associated with endothelial dysfunction (8) and an increased risk of neoatherosclerosis (9) compared with bare metal stents. Delayed vascular healing after implantation of early generation DES may not only be the underlying mechanism of very late stent thrombosis, but also explain the catch-up phenomenon of delayed late loss observed during long-term angiographic follow after DES implantation (10).

DES with biodegradable polymers have been designed to reduce the inflammatory stimulus and enhance vascular healing during long-term follow-up. Several randomized controlled trials have compared DES with biodegradable polymers with early and new generation DES. In a pooled analysis of three trials comparing DES with biodegradable polymers with early generation SES, biodegradable

polymer DES have been shown to reduce the risk of target lesion revascularization and stent thrombosis throughout four years of follow-up (11). In the COMPARE II trial, biodegradable polymer biolimus-eluting stents proved non-inferior in direct comparison with durable polymer EES with respect to a composite of cardiac death, myocardial infarction and clinically-indicated target vessel revascularization at one year (12). Similarly, the NEXT trial demonstrated no significant differences between biolimus-eluting stents with a biodegradable polymer and EES with a durable polymer with regard to the primary efficacy endpoint target lesion revascularization at one year (13). Of note, all biodegradable polymer stents used in the trials mentioned above were based on stainless steel platforms with a strut thickness comparable to early generation DES and have not been combined with newer generation metallic platforms.

A series of randomized clinical trials comparing EES with early generation DES and zotarolimus-eluting stents established EES as the current standard of care in terms of safety and efficacy (14). The biodegradable polymer SES (Orsiro, Biotronik, Bülach, Switzerland) combines a biodegradable poly-L lactic (PLLA) polymer with an ultrathin strut (60 µm) cobalt-chromium L605 platform covered with an amorphous silicon-carbide layer. The SES with biodegradable polymer has been compared with durable polymer EES in a randomized controlled trial with angiographic follow-up and was shown to be non-inferior in terms of the primary endpoint in-stent late lumen loss at nine months (0.10 ± 0.31 mm vs. 0.11 ± 0.29 mm, $p_{noninferiority}$ <0.0001). Findings from optical coherence tomography and intravascular ultrasound showed adequate stent strut coverage in both groups and documented a smaller neointimal area in patients allocated to SES with a biodegradable polymer, respectively (15). We therefore designed a randomized controlled, non-inferiority trial comparing the biodegradable polymer SES with the durable polymer EES in an all-comers population with the primary clinical endpoint target-lesion failure (TLF).

TRIAL DESIGN

Study Design and Primary Hypothesis

The BIOSCIENCE trial is a randomized, assessor blind, multicenter, non-inferiority trial comparing SES with biodegradable polymer (Orisro, O-SES) with EES with durable polymer (Xience prime/xpedition, X-EES) in an unselected patient population. The study protocol was designed by the steering committee (TP, PJ, SW), and all data were managed by the Clinical Trials Unit Bern, Switzerland. The trial is powered to investigate the study hypothesis that SES with biodegradable polymer are non-inferior to durable polymer EES stents with respect to target lesion failure (TLF), defined as a composite of cardiac death, target vessel myocardial infarction (MI), and clinically driven target lesion revascularization (TLR) within 12 months.

Statistical Analysis

The sample size calculation was based on event rates reported in the COMPARE trial (12), the RESOLUTE AC trial (16), and the LESSON registry (3), assuming a TLF rate of 8% at 12 months in both treatment arms. A non-inferiority margin of 3.5% was defined for non-inferiority of the O-SES compared with the X-EES. Enrolment of 2060 patients was calculated to provide 80% power to detect non-inferiority at a one-sided type I error of 0.05. Clinical endpoints will be analyzed according to the intention-to-treat principle. Lesion-level data will be analysed using linear and logistic mixed effects models to account for the non-independence of measurements from the same patient.

Study Population

Patients eligible for PCI with at least one lesion of >50% diameter stenosis suitable for stent implantation qualified for enrolment. The inclusion and exclusion criteria are summarized in table 1. All patients provided written informed consent.

Between March 2012 and May 2013, a total of 2,119 patients were randomly assigned to treatment with O-SES or X-EES at 9 centers in Switzerland. Random stent allocation was performed by means of an electronic web database "Cardiobase" (Copyright by Department of Cardiology, CTU Bern, Switzerland and 2mt software GmbH, Ulm, Germany) in a 1:1 ratio stratified according to center and presence or absence of ST –segment elevation myocardial infarction.

Procedure

PCI was performed according to current guidelines. Lesion preparation in terms of predilatation was left to the discretion of the operator. In case of multivessel disease, all lesions treated within the same or during a subsequent staged procedure had to be treated with the assigned study stent. There was no restriction with regards to type or number of lesions.

Study Medications

Unfractionated heparin at a dose of at least 5000 IE or 70-100 IE/kg body weight was administered during the procedure. Alternative treatment with bivalirudin and administration of GpIIb/IIIa inhibitors was left to the discretion of the operator.

Patients were loaded with acetylsalicylic acid at a dosage of at least 250 mg prior to the procedure and with clopidogrel (recommended dosage of 600 mg), prasugrel (recommended dosage of 60 mg) or ticagrelor (recommended dosage of 180 mg) immediately following stent implantation.

Combination of dual antiplatelet therapy was left to the discretion of the participating center. Dual antiplatelet therapy was continued for at least 6 months according to local practice.

Pre-specified Analyses

We will perform stratified analyses of the primary endpoint across major subgroups using the Mantel-Cox method. Subgroup analyses of the primary endpoint will be performed with respect to acute coronary syndrome status, acute ST-segment elevation myocardial infarction (also used as stratification during randomization), off- versus on-label indication, and diabetes. Rates of cerebrovascular events and bleeding complications will be analysed according to type and duration of antithrombotic and antiplatelet strategy.

Definitions

Target lesion failure (TLF) is defined as the composite of cardiac death, target vessel myocardial infarction, and clinically driven target lesion revascularization. All definitions are outlined in detail in the appendix. The clinical endpoints will be adjudicated by an independent event adjudication committee.

Data Collection

Patient data are collected in a web-based data entry system hosted at the Clinical Trials Unit, University of Bern, Switzerland. Data entry is performed by the study personnel on site. Central and on-site data monitoring is organized by the Clinical Trials Unit according to a pre-specified monitoring plan. All electronic case report forms underwent central data monitoring. On-site monitoring was performed of the complete case report forms of first 10 patients included at each participating site,

followed by a random sample of 20% at each site. Written informed consent for participation in the study was verified in all study subjects. All serious adverse events are submitted to the Clinical Trials Unit at the University of Bern, Switzerland, in a blinded fashion. Any death, myocardial infarction, revascularization procedure, stent thrombosis, cerebrovascular accident, and bleeding event will be independently adjudicated by a blinded clinical event committee.

CONCLUSION

The BIOSCIENCE trial is a randomized multicenter study enrolling a total of 2,119 patients, which will determine whether O-SES are non-inferior to X-EES in terms of the primary endpoint TLF at 12 months.

FUNDING

The study is investigator-initiated and supported by an unrestricted grant from Biotronik, Bülach. Switzerland. The funding source was not involved in the design of the study or data collection and management. It has and will have no role in the analyses or interpretation of the data.

CONFLICT OF INTEREST STATEMENT

TP has received travel expenses and payment for lectures from Biotronik. MR has received grants from Boston Scientific, Abbott Vascular, Medtronic, and Biosensors; and payment for lectures from Lilly-Daiichy Sankyo. DT has received travel expenses from Biotronik, Biosensors, Terumo, and Medtronic. PJ is an unpaid steering committee or statistical executive committee member of trials funded by Abbott Vascular, Biosensors, Medtronic and Johnson & Johnson. CTU Bern, which is part of the University of Bern, has a staff policy of not accepting honoraria or consultancy fees. However,

CTU Bern is involved in design, conduct, or analysis of clinical studies funded by Abbott Vascular, Ablynx, Amgen, AstraZeneca, Biosensors, Biotronik, Boehringer Ingelheim, Eisai, Eli Lilly, Exelixis, Geron, Gilead Sciences, Nestlé, Novartis, Novo Nordisc, Padma, Roche, Schering-Plough, St. Jude Medical, and Swiss Cardio Technologies. SW has received research contracts to the institution from Biotronik and St Jude. All other authors have reported that they have no relationships to disclose.

APPENDIX

Study Organisation

Sponsor: Clinical Trials Unit Bern, Bern, Switzerland and Department of Cardiologiy, Bern University Hospital, Bern, Switzerland.

Funding: Unrestricted grant from Biotronik, Bülach, Switzerland

Steering committee: Thomas Pilgrim, Peter Jüni, Stephan Windecker

Clinical adjudication committee: Pascal Vranckx, Hasselt, Belgium (Chair); Gerrit Hellige, Solothurn, Switzerland; Daniel Mattle, Münsterlingen, Switzerland.

Data coordination and analysis: Clinical Trials Unit Bern, Bern University Hospital, Switzerland (Dik Heg, Sven Trelle, Peter Jüni).

Site management and on-site data monitoring: Clinical Trials Unit Bern, Bern University Hospital, Bern, Switzerland (Brigitte Wanner, Lucia Kacina, Stefanie Hossmann).

Central data monitoring: Clinical Trials Unit Bern, Bern University Hospital, Bern, Switzerland (Timon Spörri).

Data safety and monitoring board: none

SECONDARY ENDPOINTS

Clinically indicated and not clinically indicated target lesion revascularization (TLR); clinically indicated and not clinically indicated target vessel revascularization (TVR); target vessel failure (TVF); cardiac death; all death (cardiac and non-cardiac); myocardial infarction; definite stent thrombosis; definite and probable stent thrombosis; device success defined as achievement of a final residual diameter stenosis of <30% (by visual estimation), using the assigned device only; lesion success defined as achievement of <30% residual stenosis (by visual estimation), using any PCI method;

procedural success defined as achievement of a final diameter stenosis of <30% (by visual estimation) using any PCI method, without the occurrence of death, MI, or repeat target vessel revascularization during hospital stay.

ENDPOINT DEFINITIONS

1. Death

All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established. Cardiac death: Any death due to immediate cardiac cause (e.g. MI, low-output failure, fatal arrhythmia). Unwitnessed death and death of unknown cause will be classified as cardiac death.

Vascular death: Death due to cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular cause.

Non-cardiovascular death: Any death not covered by the above definitions, including death due to infection, sepsis, pulmonary causes, accident, suicide or trauma.

2. Myocardial infarction

Spontaneous MI is documented in case of a typical rise and gradual fall of biochemical markers in combination with either one of the following characteristics: ischemic symptoms, development of new pathologic (defined by Minnesota Code) Q-waves on the ECG, ECG changes indicative of ischemia (ST segment elevation or depression), pathologic findings of an acute MI, development of new pathologic Q-waves on follow-up ECG in the absence of cardiac biomarker assessment during the acute event.

According to the electrocardiographic definition we distinguish between Q-wave MI and Non Q-wave MI. Q-wave MI is determined by the presence of new pathological Q's in 2 or more contiguous leads (according to the Minnesota code as assessed by the ECG core laboratory) with or without post-procedure CK or CK-MB levels elevated above normal. All other MIs are classified as Non Q-wave MI's.

MI's occurring within 48 hours after PCI or within 7 days after CABG are categorized as peri-procedural MI's. In patients presenting with stable angina peri-procedural MI is defined as elevation of total CK >2 times the upper limit of normal (ULN) in the presence of a confirming cardiac specific biomarker obtained after the procedure. Alternatively, CKMB >3 times ULN and Troponin elevation >5 times the 99th percentile is considered as a periprocedural MI in the absence of total CK

measurement or CKMB measurement, respectively. MI following CABG is defined as development of new Q-waves not present on the patient's baseline ECG and a peak CKMB/peak total CK ratio >10% on 3 consecutive samples within 7 days post intervention, or CKMB >5x ULN.

Peri-procedural MI in the setting of evolving MI is documented for recurrent chest pain lasting >20 minutes (or new ECG changes consistent with MI) in combination with a >50% elevation of peak CK (or CKMB in the absence of CK) level above the previous level measured within 24 hours after the event. If the elevated CK (or CK-MB) levels from the index infarction are falling or have returned to normal within 24 hours post index PCI, a new elevation of CK >2 x ULN within 24 hours post index PCI if the CK level has returned to <ULN, or a rise by >50% above the previous nadir level if the CK level has not returned to <ULN are defined as periprocedural MI.

3. Target-vessel myocardial infarction

Target-vessel myocardial infarction is defined as any myocardial infarction that is not clearly attributable to a non-target-vessel.

4. Target-vessel

The target vessel is the index coronary artery which was in physical contact with any component (guiding catheter, guide wire, balloon catheter, etc.) of the angioplasty hardware during the initial procedure.

5. Target lesion

The target lesion is the treated lesion starting 5 mm proximal of the stented lesion and to end 5 mm distal of the stented lesion.

6. Target lesion revascularization

Target lesion revascularization (TLR) is defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel. TLRs are documented as clinically-indicated if repeat

angiography shows a percent diameter stenosis ≥50% and the patients has a history of recurrent angina, objective signs of ischemia, or abnormal results of any invasive functional diagnostic tests. TLRs for percent diameter stenosis ≥70% are considered clinically significant even in the absence of the above-mentioned criteria.

7. Device success

Device success is defined as the attainment of <30% residual stenosis by QCA (or <20% by visual assessment), using the assigned device only.

8. Lesion success

Lesion success is define as the attainment of <30% residual stenosis by QCA (or <20% by visual assessment), using any percutaneous method.

9. Procedural success

Procedural success is defined as the attainment of <30% residual stenosis by QCA (or <20% by visual assessment) in all lesions using any percutaneous method , without the occurrence of death, MI, or repeat revascularization of the target vessel during the hospital stay.

10. Stent thrombosis

Stent thrombosis is categorized into definite, probable and possible according to the definition provided by the Academic Research Consortium (17).

11. Bleeding

Bleeding complications will be defined in accordance with the BARC criteria (18).

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Table 1

Inclusion Criteria:
1. Age ≥ 18 years;
2. Symptomatic coronary artery disease including patients with chronic stable angina, silent ischemia, and acute coronary syndromes including NSTE-ACS and STE-ACS;
3. Presence of one or more coronary artery stenosis >50% in a native coronary artery or a saphenous bypass graft in a vessel which can be treated with a stent ranging in diameter from 2.25 to 4.0 mm and can be covered with one or multiple stents;
4. No limitation to the number of treated lesions, number of vessels or lesion length according to the randomization group.
Exclusion Criteria:
1. Pregnancy;
2. Known intolerance to aspirin, clopidogrel, heparin, stainless steel, sirolimus, everolimus, contrast material;
3. Inability to provide informed consent;
4. Currently participating in another trial before reaching the primary endpoint;
5. Planned surgery within 6 months of PCI unless dual antiplatelet therapy is maintained throughout the peri-surgical period.