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Randomized clinical comparison of the dual-therapy CD34 antibody-covered sirolimus-eluting Combo stent with the sirolimus-eluting Orsiro stent in patients treated with percutaneous coronary intervention: Rationale and study design of the Scandinavian Organization for Randomized Trials with Clinical Outcome (SORT OUT) X trial

Lars Jakobsen¹ MD, PhD; Evald H Christiansen¹ MD, PhD; Michael Maeng¹ MD, PhD; Steen D Kristensen¹ MD, DMSci; Hans E Bøtker¹ MD, DMSci, PhD; Christian J Terkelsen¹ MD, DMSci, PhD; Morten Madsen², MSc; Bent Raungaard³, MD, PhD; Svend E Jensen³, MD, PhD; Martin K Christensen³, MD; Henrik Steen Hansen⁴, MD, DMSci; Lisette O Jensen⁴ MD, DMSci, PhD

¹Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark
²Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark
³Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark
⁴Department of Cardiology, Odense University Hospital, Odense, Denmark

Corresponding author:
Lars Jakobsen,
Department of Cardiology,
Aarhus University Hospital,
Palle Juul-Jensens Boulevard 99,
DK-8200 Aarhus, Denmark.
Tel: +4522807644.
Mail: larsj@dadlnet.dk

Short title: SORT OUT X: Combo stent versus Orsiro stent
Abstract

Background: The Combo stent (OrbusNeich, Hoevelaken, The Netherlands) combining an abluminal, bioabsorbable polymer eluting sirolimus with a luminal CD34+ antibody to capture endothelial progenitor cells has been developed to further improve safety and efficacy of coronary interventions. We have designed a large scale registry-based randomized clinical trial to compare the Combo stent to the Orsiro stent (Orsiro; Biotronik, Bülach, Switzerland) in patients undergoing percutaneous coronary intervention.

Methods: The SORT OUT X study will randomly assign 3,140 patients to treatment with Combo or Orsiro stents at 3 sites in Western Denmark. Patients are eligible, if they are ≥18 years old; have chronic stable coronary artery disease or acute coronary syndromes; and ≥1 coronary lesion with >50% diameter stenosis, requiring treatment with a drug eluting stent. The primary endpoint target lesion failure is a composite of cardiac death, myocardial infarction (not related to other than index lesion), or target lesion revascularization within 12 months. Clinically driven event detection will be derived from validated Danish registries. An event rate of 4.2% is assumed in each stent group. With a sample size of 1,570 patients in each treatment arm, a 2-group large-sample normal approximation test of proportions with a 1-sided 5% significance level will have 90% power to detect non-inferiority of the Combo stent compared with the Orsiro stent with a predetermined non-inferiority margin of 2.1%.

Conclusion: The SORT OUT X trial will determine whether the dual-therapy Combo stent is non-inferior to the Orsiro stent with respect to clinically driven events. (ClinicalTrials.gov NCT03216733)
Introduction

Biodegradable polymer drug eluting stents (DES) like the Biomatrix Flex stent, the Nobori stent, and the Orsiro stent are all using a similar biodegradable polymer that disappears after 8-24 months(1, 2). At this time, the implanted DES is identical to a bare metal stent, as the drug is eluted, and the polymer degraded. The Biomatrix Flex stent and the Nobori stent have the same biodegradable polymer, they release the same medicine (biolimus A9) and have shown favourable long-term results in terms of low risk of late stent thrombosis(3, 4). The sirolimus eluting Orsiro stent (Orsiro; Biotronik, Bülach, Switzerland) was non-inferior to the Nobori stent at one and two years follow-up in the SORT OUT VII study (5, 6). Nevertheless, stent thrombosis, restenosis and in-stent neo-atherosclerosis remain an issue with contemporary DES. Therefore, attempts have been made to further improve early healing with neointimal stent strut coverage.

The sirolimus eluting Combo stent (OrbusNeich, Hoevelaken, The Netherlands) combines an abluminal, bioabsorbable polymer with a luminal CD34+ antibody designed to capture endothelial progenitor cells (EPCs). Bone marrow–derived EPCs circulate in the peripheral blood and migrate to areas of vascular injury. It is hypothesized that the EPCs differentiate into mature endothelial cells, contributing to the vascular repair and formation of a functional endothelium(7, 8), thus preventing excess neointima formation and restenosis. In a preclinical study using a porcine model, the Combo stent showed promising results with less neointimal thickness and a higher degree of platelet and endothelial cell adhesion molecule expression compared to a sirolimus eluting stent and an everolimus-eluting stent. Thus, the Combo stent appeared to promote endothelialisation while reducing neointimal formation and inflammation(9). In the REMEDEE trial, the Combo stent was compared to the second-generation paclitaxel-eluting Taxus Liberté stent in the treatment of single de novo native coronary artery lesions in 183 patients(10). The Combo stent was found to be non-inferior to the Taxus Liberté stent when comparing angiographic in-stent late lumen loss after 9 months and major adverse cardiac events after 12 months. A recent registry study has shown excellent results with the Combo stent in 1000 all-comers patients(11). However, the Combo stent has not been compared head to head to a contemporary third generation DES. In the SORT OUT X trial, we have designed a
randomized controlled non-inferiority trial in all-comers patients comparing the Combo stent with a third-generation Orsiro stent in a population-based setting, using registry detection of clinically driven events.

Materials and Methods

Patients and study design
SORT OUT X study (ClinicalTrials.gov NCT03216733) is a randomized, multi-centre, single blinded, all-comer, 2-arm, non-inferiority trial comparing the Combo stent with the Orsiro stent in treating atherosclerotic coronary artery lesions, vein graft disease and in-stent restenosis. Patients are eligible, if they are ≥18 years old; have chronic stable coronary artery disease or acute coronary syndromes (ACS); and ≥1 coronary lesion with >50% diameter stenosis, requiring treatment with a DES (Angiographic diameter stenosis>90%; FFR<0.80 or iFR<0.90 for angiographic diameter stenosis 50-90%; proven large area of ischemia (>10%) by non-invasive test). If multiple lesions are treated, the allocated study stent should be used in all lesions. No restrictions are placed on number of treated lesions, number of treated vessels, or lesion length. Exclusion criteria are life expectancy of <1 year; an allergy to aspirin, clopidogrel, ticagrelor, prasugrel or sirolimus; participation in another randomized stent trial; or inability to provide written informed consent.

Study devices
The Combo stent consists of a 316L stainless-steel alloy platform with an abluminal coating of urethane-linked lactide-glycolide multiblock copolymers (SynBiosys; Surmodics Inc, Eden Prairie, MN). This biocompatible, biodegradable polymer is loaded with sirolimus. Covalently attached to this matrix is a layer of murine, monoclonal, antihuman CD34 antibody. The immobilized antibody surface specifically targets CD34+ cells from the circulating blood, of which EPCs are CD34+. The base platform for the Combo stent is the OrbusNeich Medical R stent, which has a proprietary dual-helix stent design with a strut thickness of 100 μm. The 316L stainless-steel base platform (R stent) is coated sequentially with the drug/polymer matrix on the abluminal surface, then treated to immobilize antibody on the coated stent surface, and then finally
treated with a stabilization treatment to preserve the antibody activity in the dried immobilized state on the stent. The biodegradable polymer is completely absorbed within 90 days. The dose of sirolimus is 5.0 μg/mm and the drug is released within 30 days(9). The Combo stent is available in 2 different diameters mounted on 5 different balloon sizes (1: 2.50 and 2.75 mm balloons, 2: 3.00, 3.50, and 4.00 mm balloons) and 8 lengths (9, 13, 15, 18, 23, 28, 33 and 38 mm).

The Orsiro stent platform is composed of Cobalt chromium. The thickness of the stent struts is 60 μm for stents with a nominal diameter of ≤3.0 mm and 80 μm for the 2 larger sizes. The Orsiro stent surface is fully coated with a layer of amorphous hydrogen-rich silicon carbide acting as a diffusion barrier (PROBIO), sealing the bare metal surface and reducing ion release. The PROBIO silicon carbide coating consists of silicon carbide, a ceramic material, a chemical compound of the element silicium, and the element carbon. The polymer compound used as a carrier material for the supply and release of sirolimus is a high molecular poly-L-lactic acid (PLLA). The stent body surface is completely coated by a matrix consisting of the carrier PLLA and the active substance sirolimus. The matrix coating has an abluminal thickness of 7.5 μm and a luminal coating of 3.5 μm. The polymer is completely degraded in 12 to 24 months. The drug load is 1.4 μg/mm and the drug is released within 12-14 weeks(2). The Orsiro stent is available in 2 different diameters mounted on 6 different balloon sizes (1: 2.25, 2.50, 2.75, and 3.00 mm balloons. 2: 3.50, and 4.00 mm balloons) and 7 lengths (9, 13, 15, 18, 22, 26, and 30 mm).

**Informed consent and randomization**

Between June 2017 and approximately January 2019, a total of 3140 patients will be randomly assigned to treatment with a Combo stent or an Orsiro stent at 3 sites in Western Denmark (Odense University Hospital, Aalborg University Hospital, and Aarhus University Hospital). All patients will sign the informed consent before randomization. Patients will be enrolled by the investigators and randomly allocated to treatment the groups after diagnostic coronary angiography and before percutaneous coronary intervention (PCI). 24/7 web-based computer randomization was used to allocate patients to the treatment groups at a 1:1 ratio stratified by gender, and diabetes (Yes/No) using: stratified, permuted block randomization with random varying block sizes of 4,6 and 8. Proper concealment of randomization was obtained using external
randomization services (Clinical Trial Unit, Department of Clinical Medicine, Aarhus University). Although operators will not be blinded, all individuals analysing data will be blinded to treatment assignment. By January 8th 2018, 1419 patients have been included in the study.

**Study procedures and antithrombotic therapy**

Stents will be implanted according to standard techniques. Direct stenting without prior balloon dilation is allowed. Full lesion coverage will be attempted by implanting \(\geq 1\) stents. DES not specified by the random allocation scheme will be prohibited, unless the study stent cannot be implanted. In such cases, other stents or balloon angioplasty alone will be allowed. Before implantation or immediately after, patients will be treated with acetylsalicylic acid and loaded with either clopidogrel, ticagrelor, or prasugrel. The combination of dual antiplatelet therapy will be left to the discretion of the participating centres, whereas the duration of dual antiplatelet therapy will be recommended for 12 months for ACS patients and 6 months for stable patients. Unfractionated heparin dose will be administered before the procedure. Glycoprotein IIb/IIIa inhibitors, bivalirudin, or cangrelor will be used at discretion of the operator.

**Outcome measures**

The primary endpoint “target lesion failure” (TLF) is a composite of cardiac death, myocardial infarction (MI) (not related to other than index lesion), or clinically indicated target lesion revascularization (TLR) within 12 months. Individual components of the primary endpoint comprise the secondary endpoints: cardiac death, MI and clinically indicated TLR. Further predefined secondary endpoints are all death (cardiac and non-cardiac) and target vessel revascularization (TVR); definite, probable, possible, and overall stent thrombosis (ST) according to the Academic Research Consortium definition(12); and a patient-related composite endpoint (all death, all MI, or any revascularization). Clinical follow-up will be continued through 5 years.

**Definitions**
Cardiac death: any death due to an evident cardiac cause, any death related to PCI, an unwitnessed death, or death from unknown causes.

MI: the universal definition used by the European Society of Cardiology, the American College of Cardiology, the American Heart Association, and the World Heart Federation(13). Biomarkers will not be assessed at the time of the index PCI procedure.

MI not related to other than index lesion: any MI that is not clearly attributable to a non-target vessel.

ST: definite, probable, or possible ST, according to the Academic Research Consortium definition(12).

TVR: any repeat PCI or surgical bypass of any segment within the entire major coronary vessel that is proximal or distal to a target lesion, including upstream and downstream branches and the target lesion itself.

TLR: repeat revascularization caused by a significant stenosis (eyeballing > 50%, positive FFR (<0.80) or iFR (<0.90) within the stent or within a 5-mm border proximal or distal to the stent. TVR and TLR will be clinically driven (angina, CCS > 1).

Comorbidity: For all patients, we will obtain data on all hospital diagnoses from the Danish National Registry of Patients covering all Danish hospitals from 1977 until the implantation date(14). Using this information, we will compute the Charlson Comorbidity Index score, which covers 19 major disease categories including diabetes mellitus, heart failure, cerebrovascular diseases, and cancer(15) and has adapted for use with hospital discharge registry data(16).

**Clinical event detection**

Clinically driven event detection will be used to avoid study-induced re-interventions (Figure 1). Data on mortality, hospital admission, coronary angiography, repeat PCI, and coronary artery bypass surgery will be obtained for all randomly allocated patients from the national Danish administrative and health care registries. The National Health Service provides tax-supported healthcare, guaranteeing unfettered access to medical care. All invasive cardiac procedures are performed at public hospitals in Denmark. The Danish Civil Registration System keeps records of sex, date of birth, and vital status(17). The records carry a 10-digit civil registration number assigned to every Danish citizen and used in all Danish registers, enabling unambiguous record linkage between them. All risk factors, baseline information, and procedure data are
typed in to the Western Denmark Heart Registry(18), which contains detailed patient- and procedure-specific information on all coronary angiographies, coronary interventions, and coronary bypass surgery performed at the 4 interventional and 8 non-interventional cardiac centres in Western Denmark. Reporting to the registries is mandatory and data quality is ensured by systematic validation procedures and random spot-checks of data after entry. For each hospital admission, the Danish National Registry of Patients(14) provides dates of admission and discharge, surgical procedures performed, and up to 20 diagnoses classified according to the International Classification of Diseases, Eighth Revision, until the end of 1993, and 10th revision thereafter. Clinically driven event detection has been used in previous SORT OUT III to VII publications(5, 19, 20). An independent event committee, masked to treatment group assignment during the adjudication process, reviewed all endpoints and source documents to adjudicate causes of death, reasons for hospital admission, and diagnosis of MI. Two dedicated PCI operators at each participating centre reviewed independently cine films for the event committee to classify stent thrombosis, TLR, and TVR (either with PCI or coronary artery bypass grafting). In case of disagreement between the two reviewers, consensus will be reached.

**Statistical analysis**

In analyses of every endpoint, follow-up will continue until the date of an endpoint event, death, emigration, or 12 months after stent implantation, whichever comes first. Survival curves will be constructed based on time to events, accounting for the competing risk of death. Hazard ratios will be computed using Cox proportional hazards regression analysis. Patients treated with the Orsiro stent will be used as the reference group for overall and subgroup analyses. Hazard ratios will be calculated for TLF at 12-month follow-up for pre-specified patient subgroups (based on baseline demographic and clinical characteristics). The intention-to-treat principle will be used in all analyses.

The trial is powered for assessing non-inferiority of the Combo stent to the Orsiro stent with respect to the primary endpoint at 12 months. An event rate of 4.2% is assumed in each stent group base on the results from SORT OUT VII(5). With a sample size of 1,564 patients in each treatment arm, a 2-group large-sample normal approximation test of proportions with a 1-sided 5% significance level will have 90% power to detect non-inferiority with a predetermined non-inferiority margin of 2.1%. Given the use of the Danish
Civil Registration System, a 0% lost-to-follow-up rate is expected. However, we have decided to include 1570 patients in each treatment arm.

Data monitoring, data management and data analysis is done by the Department of Clinical Epidemiology, Aarhus University Hospital.

**Funding:**
The study is supported with equal unrestricted grants from Biotronik, Bülach, Switzerland, and OrbusNeich, Hoevelaken, The Netherlands. 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 combination of an abluminal biodegradable coating eluting sirolimus and a luminal anti-CD34(+) antibody layer attracting EPCs used in the Combo stent is a novel technique to promote vessel healing; and thus, preventing excess neointima formation and restenosis. In a small randomised pilot study including a total of 183 patients, the Combo stent has shown promising results when compared to a Taxus Liberté stent (10). The Combo stent was found to be non-inferior to the Taxus Liberté stent in 9-month angiographic in-stent late lumen loss with 0.39 ± 0.45 mm versus 0.44 ± 0.56 mm. At 12 months, the occurrence of major adverse cardiac events was 8.9% in the Combo group and 10.2% in the Taxus Liberté stent group with no difference in mortality, occurrence of myocardial infarction, or target lesion revascularization. No ST was reported in either group. In a study using serial optical coherence tomography to continuously document early healing profile and late neointimal transformation, the Combo stent was found to exhibit a unique late neointimal regression (from 9 to 24 months) that has not been previously reported for any DES, translating into good 36-month clinical results with minimal restenosis and no late ST(21). Also, registry based studies on Combo stents have shown promising results in ACS(22), in diabetic patients(23) and when compared to other second-generation DES(24). However, no large scale randomised controlled trials comparing the
Combo stent to a contemporary third-generation DES using a biodegradable polymer has so far been done. The SORT OUT X trial will provide a head-to-head randomized comparison of the Combo stent using an abluminal biodegradable coating eluting sirolimus and a luminal anti-CD34(+) antibody layer to a contemporary third-generation DES with biodegradable polymers: the Combo stent versus the Orsiro stent.

The long-term safety and efficacy of coronary stents in everyday clinical practice need continuous assessment. The current third generation DES have demonstrated excellent safety even regarding late ST(3-5). However, the role of stents combining an abluminal biodegradable coating eluting sirolimus and a luminal anti-CD34(+) antibody layer is presently unknown. Furthermore, the two SORT OUT X study stents have different stent strut thickness and polymer degradation times.

The Combo stent has been found to be non-inferior to the Taxus Liberté stent in 9-month angiographic in-stent late lumen loss. The efficacy of Orsiro in preventing excessive neointimal proliferation has been assessed in the angiographic end point study BIO-FLOW II in which Orsiro demonstrated noninferiority versus Xience Prime stent with a low in-stent late lumen loss (0.10 ± 0.32 mm vs 0.11 ± 0.29 mm) (25). As a surrogate endpoint, late lumen loss can provide useful information on the range of long-term luminal dimensions that mechanistically correlate with clinical outcome. However, direct comparisons between stent platforms may yield statistically significant P values whose clinical relevance is unclear, especially at the lower ranges of late lumen loss. Thus, to access the efficacy of coronary stents large scale randomized trials with clinical end points like Sort Out X are needed.

Our study uses patient-driven event detection based on Danish registries. This registry-based randomized clinical trial design has been used in all SORT OUT trials (26-28) and also in the TASTE and VALIDATE trials (29, 30), and has received substantial interest as a way of undertaking large-scale, independent clinical trials. Advantages of this approach include a substantial reduction in the expense associated with a randomized trial because we are able to use the established registry infrastructure. Moreover, the study design provides data that are more comparable with real-life situations because of the absence of study-related intervention, and participants will be exposed to the same clinical monitoring as non-study patients. Data on mortality (cardiac and non-cardiac) are obtained from the Danish Civil Registration System (17); hospital admission for MI from the Danish National Registry of Patients (14); and
basic descriptive data, coronary angiography, repeat PCI, and coronary bypass surgery from the Western Denmark Heart Registry(18). An important advantage of this study approach is the ability to describe baseline demographics and clinical outcomes in all patients treated with coronary stents during the study period and not only those included in the RCT. Thus, important information is available regarding the general applicability, that is, the external validity of the study results. In a population-based health care database like the Western Denmark Heart Registry, data are collected for quality control and administrative purposes. This may reduce certain forms of bias, such as nonresponse bias, recall bias, and bias from loss to follow-up, which may influence prognostic estimates(31).

Like any conventional RCT, the SORT OUT X trial uses independent endpoint committee adjudication. Although the Danish health care databases capture events of sufficient severity for patients to seek medical attention, these records might underestimate event rates compared with follow-up by dedicated trial staff(32). However, this situation should not bias differences detected between treatment groups, and the negligible loss to follow-up probably compensated for this potential limitation.

Limitations
The primary endpoint is assessed after 1 year, and the TLF at 1 year may not predict the long-term outcome with safety and efficacy after 5 years. The clinical outcomes after implantation of DES have improved in recent years. Therefore, we expect that the event rate in our study is representative of the real event rate among this patient population. Both study stents are available on the market, and even if the one of the study stent will be replaced by a newer third-generation DES, both stent types have still been implanted in many patients, so the results within 1 year as well as long-term follow-up will be relevant.

SORT OUT X study group
Principal investigators: Lars Jakobsen, Aarhus University Hospital, Skejby

Steering committee: Evald Høj Christiansen and Lisette Okkels Jensen (chairmen), Hans Erik Bøtker, Henrik Steen Hansen, Phillip Freeman and Leif Thuesen.
The primary investigator and the members of the steering committee will be given full access to the database and will take part in the interpretation of data.

The study office is located at the Department of Cardiology, Aarhus University Hospital, Skejby. Randomization will be done via a closed website exclusively for this study.

The endpoint committee is situated at Department of Clinical Epidemiology, Aarhus University Hospital.

Protocol and written publications are prepared by the physicians at the Department of Cardiology, Aarhus University Hospital in collaboration with the steering committee.

**Declarations of interest**

This study is investigator initiated and supported with equal unrestricted grants from Biotronik, Büllach, Switzerland, and OrbusNeich, Hoevelaken, The Netherlands. These companies did not have a role in study design and will not have a role in the data collection, data analysis, or interpretation of the results. They will neither have access to the clinical trial database nor an opportunity to review the manuscript.
References


Figure legends

Figure 1: Event detection using population-based health care databases. The Danish Civil Registration System allows linkage of individual-level information across registries (17). It is updated daily, and maintains records on date of birth, death, and current residence of all Danish citizens. The National Registry of Patients contains information on all admissions and outpatient visits (14). The Western Denmark Heart Registry provides detailed patient-and procedure-specific information on all coronary angiographies, coronary interventions, and coronary bypass surgery procedures performed in Western Denmark (18).

CABG, coronary artery bypass grafting; ISR, in-stent restenosis; MI, myocardial infarction; PCI, percutaneous coronary intervention; SAP, stable angina pectoris; ST, stent thrombosis; TLR, target lesion revascularization; UAP, unstable angina pectoris
Figures:

Figure 1