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Impact of Diabetes on Clinical Outcomes after Revascularization with Sirolimus-Eluting and Biolimus-Eluting Stents with biodegradable polymer From the SORT OUT VII Trial

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Key words: drug-eluting stent, target lesion failure, Orsiro stent, Nobori stent

Short title: sirolimus- versus biolimus-eluting stent

ABSTRACT

Objectives: In this substudy of the SORT OUT VII trial, the clinical outcomes among patient with diabetes mellitus treated with Orsiro sirolimus-eluting stent (O-SES; Biotronik, Bülach, Switzerland) or Nobori biolimus-eluting stent (N-BES; Terumo, Tokyo, Japan) were compared.

Background: Diabetes is associated with increased risk of target lesion failure (TLF) after percutaneous coronary intervention.

Methods: In total 2,525 patients were randomized to stent implantation with O-SES (n=1,261, diabetes: n=236) or N-BES (n=1,264, diabetes: n=235). The primary endpoint, TLF, was a composite of cardiac death, target-lesion myocardial infarction (MI), or target lesion revascularization (TLR) within 2 years.

Results: At 2-year, TLF did not differ between O-SES versus N-BES in diabetic (9.3% versus 9.4%; RR 0.98, 95% CI 0.54-1.78) patients. The individual components of the primary endpoint did not differ among stent type. In diabetics, cardiac death occurred in 3% of O-SES-treated and in 3.8% of N-BES-treated patients (RR 0.77, 95% CI 0.29-2.08), MI occurred in 3.0% of O-SES-treated and in 3.8% of N-BES-treated patients (RR 0.76, 95% CI 0.28-2.06) and TLR occurred in 5,5% of O-SES-treated and in 6.0% of N-BES-treated patients (RR 0.91, 95% CI 0.43-1.95).

Conclusion: TLF did not differ between O-SES and N-BES treated diabetic patients.

INTRODUCTION

The presence of diabetes mellitus has been associated with higher risk of restenosis and major cardiovascular events after percutaneous coronary intervention (PCI) [1]. New-generation drug-eluting stents (DES) are recommended for the treatment of diabetic patients undergoing PCI because of a lower risk of repeated revascularization compared with bare-metal stents and early generation DES [2]. Among available new-generation DES, the thin-strut durable polymer everolimus-eluting stent (EES) has emerged as the currently most effective and safest durable polymer stent in this high-risk group [3]. However, long-term persistence of some durable polymers may create a chronic local inflammatory response, disturb vascular healing, and be responsible for the late stent thrombosis and delayed restenosis [4]. In order to improve biocompatibility and long-term safety, the new biodegradable polymer DESs have been designed to reduce chronic local inflammation by degradation of the polymer-coating after complete elution of the anti-proliferative drug. Compared with durable polymer EES, the biodegradable polymer Nobori biolimus-eluting stent (N-BES) showed similar long-term efficacy and safety in this specific population of diabetic patients [5]. In a substudy of the “ultrathin strut biodegradable polymer sirolimus-eluting stent versus durable-polymer everolimus-eluting stent for percutaneous coronary revascularization

(BIOSCIENCE) trial", the clinical outcomes among diabetic patients treated with biodegradable polymer Orsiro sirolimus-eluting stent (O-SES) or durable polymer EES were comparable at 1 year [6]. The aim of the present study (a substudy of SORT OUT VII) was to compare long-term efficacy and safety of two biodegradable polymer stents, O-SES versus N-BES, in patients with and without diabetes mellitus.

MATERIALS AND METHODS

SORT OUT VII [7] is a randomized, multicenter, all-comer, 2-arm, noninferiority trial comparing O-SES to N-BES in treating atherosclerotic coronary artery lesions. A detailed study protocol was provided in the main publication [8].

Inclusion Criteria

Patients were eligible if they were ≥18 years old, had chronic stable coronary artery disease or acute coronary syndromes, and ≥1 coronary lesion with >50% diameter stenosis. If multiple lesions were treated, the allocated study stent was used in all lesions. There were no restrictions in number of treated lesions, number of treated vessels, or lesion length.

Exclusion Criteria

Patients were excluded from the study if life expectancy of <1year; allergy to aspirin, clopidogrel, prasugrel, ticagrelor, sirolimus, or biolimus; participation in another randomized stent trial; or inability to provide written informed consent.

Randomization and Management

Patients were enrolled by the investigators and randomly allocated to treatment groups after diagnostic coronary angiography and before PCI. Block randomization by center (permuted blocks of random sizes (7/9/11)) was used to assign patients in a 1:1 ratio to receive the biodegradable polymer O-SES (Orsiro; Biotronik, Bülach, Switzerland) or the biodegradable polymer N-BES (Nobori, Terumo, Tokyo, Japan). Randomization was stratified by presence/absence of diabetes. An independent organization computer generated the allocation sequence, stratified by gender and presence of diabetes. Patients were assigned to treatment through a web-based randomization and electronic case record form software (TrialPartner). Stents were implanted according to standard techniques. Direct stenting without previous balloon dilatation was allowed. Full lesion coverage was attempted by implanting ≥1 stents. Before implantation, patients were treated with acetylsalicylic acid (loading dose of 300mg) and loaded with either clopidogrel, 600mg; ticagrelor, 180mg; or prasugrel, 60mg. Combination of dual antiplatelet therapy was left to the discretion of the participating center, whereas the duration of dual antiplatelet therapy was recommended for 12 months. Unfractionated heparin dose (5,000 IE or 70-100IU/kg) was administered before the procedure. Glycoprotein IIb/IIIa inhibitors or bivalirudin were used at the operator's discretion.

Endpoints

Definitions of endpoints were provided in the main publication [8]. The primary endpoint "target lesion failure" (TLF) of this substudy was a composite of cardiac death, myocardial infarction (MI) (not related to other than index lesion) or clinically indicated target lesion revascularization (TLR) within 24 months of stent implantation. Individual components of the primary endpoint comprised the secondary endpoints: cardiac death; MI; clinically indicated TLR; all death (cardiac and noncardiac) and target vessel revascularization (TVR); definite, probable, and overall stent thrombosis according to the Academic Research Consortium definition [9]; and a patient-related composite endpoint (all death, all MI, or any revascularization).

Data Collection

Clinically driven event detection was used to avoid study-induced re-interventions. Data on mortality, hospital admission, coronary angiography, repeated PCI, and coronary bypass surgery were obtained for all randomly selected patients from the following national registries: Civil Registration System; Western Denmark Heart Registry [10]; Danish National Registry of Patients [11], which maintains records on all hospitalizations in Denmark; and Danish Registry of Causes of Death [12]. An independent event committee, which was blinded to treatment group assignment during the adjudication process, reviewed all endpoints and source documents to adjudicate causes of death, reasons for hospitalization, and diagnosis of MI. In addition, the cine films were reviewed independently by two experienced PCI-operators to classify stent thrombosis and TVR (with PCI or coronary artery bypass grafting). The Danish National Health Service provides universal tax-supported health care, guaranteeing residents free access to general practitioners and hospitals. The Danish Civil Registration System has kept electronic records on gender, birthdate, residence,

emigration date, and vital status changes since 1968 [13] with daily updates. A unique 10-digit civil registration number is assigned to all residents at birth and upon immigration and is used in all registries, which allows accurate record linkage between registries. The Civil Registration System provided vital status data for our study participants, which reduced the probability of loss to follow-up. To capture co-morbidity, we used the Danish National Registry of Patients to obtain data on all hospital diagnoses in study patients from 1977 until the implantation date [11]. We then computed Charlson Comorbidity Index scores, which cover 19 major disease categories including heart failure, cerebrovascular diseases, and cancer [14].

Statistical Analysis

Distributions of continuous variables were compared between study groups using 2-sample *t* test (or Cochran test for cases of unequal variance) or Mann-Whitney *U* Test depending on whether the data followed a normal distribution. Distributions of categorical variables were compared using chi-square test. In analyses of every endpoint, follow-up continued until the date of an endpoint event, death, emigration, 24 months after stent implantation, or study end - whichever came first. Survival curves were constructed based on cumulated incidences, accounting for death as a competing risk [15]. Patients who received the N-BES were used as the reference group for overall and subgroup analyses. We calculated rate ratios (RR) for TLF at 24-month follow-up for prespecified patient subgroups (based on baseline demographic and clinical characteristics). To improve the precision of risk estimates, we used the change-in-estimate method, which entailed retaining variables that changed relative risk estimates for an outcome by >10% [16]. Number of variables included in the final regression models varied from 0 to 1. The intention-to-treat principle was used in all analyses.

A two-sided p value of less than 0.05 indicated statistical significance. We calculated RR by modified Poisson regression analysis with a sandwich error estimation [17] to assess whether difference detected at baseline had any effect on the result. Analyses were conducted using SAS 9.4 (SAS Institute, Cary, North Carolina). This trial is registered with ClinicalTrials.gov NCT01879358.

RESULTS

Study Characteristics

Between November 2012 and February 2014, 2,525 patients were randomly assigned to receive either the biodegradable polymer O-SES (1261 patients (1590 lesions)) or the biodegradable polymer N-BES (1264 patients (1588 lesions)). In total, 471 patients had diabetes, of whom 236 patients received O-SES and 235 patients received N-BES. Three patients were lost to follow-up (on day 6, 81 and 610) because of emigration. Complete follow-up data were available for 2,522 patients (99.9%) for all type of events.

Patient Characteristics

Baseline patient characteristics for diabetics are summarized in Table I and did not differ significantly between the patient groups except for age, which was significantly higher in diabetic patients, who received the biodegradable polymer O-SES compared to the N-BES (67.3 ± 10.6 years vs. 65.0 ± 10.0 years, p=0.02).

Lesion and procedure characteristics

Lesion and procedure characteristics did not differ significantly between the patients treated with O-SES and N-BES in the diabetic subgroup (Table II).

Outcome

Composite endpoint TLF and individual components of the primary endpoint are presented in Table III. At 24-month follow-up, in patients with diabetes, the occurrence of TLF did not differ significantly in patients treated with O-SESs compared to patients treated with N-BESs (n=22, 9.3%, vs. n=22, 9.4%, RR 0.98, 95% CI 0.54 to 1.78, p=0.94) (Figure 1 and Table III). There were also no differences in the individual components of the primary endpoint in diabetics treated with O-SESs versus N-BESs (Table III, Figure 2-4). Differences by type of stent were driven mainly by numerically lower rates of definite and definite/probable stent thrombosis in the O-SES group (Table III and Figure 5).

Of the 471 patients with diabetes mellitus, 137 (29.1%) were treated with insulin. There was no difference in TLF in insulin-treated diabetic patients treated with O-SESs versus N-BESs (n=5, 10.4%, vs. n=7, 10.4%, RR 0.63, 95% CI 0.20 to 2.04, p=0.44) or in noninsulin treated diabetic patients treated with O-SESs versus N-BESs (n=17, 10.2%, vs. n=15, 8.9%, RR 1.15, 95% CI 0.57 to 2.38, p=0.69).

DISCUSSION

The present SORT OUT VII subgroup analyses provide the first clinical head-to-head comparison of two third-generation DES with biodegradable polymers, the O-SES versus the N-BES, in patients with and without diabetes mellitus. Our trial showed no significant difference between stent type for diabetic patients overall.

Patients with diabetes have a higher risk of restenosis after stenting, making DESs preferable to bare-metal stents in this patient population. First-generation DESs decreased restenosis rates significantly compared to bare-metal stents, especially in patients with diabetes [18-22]. Randomized studies comparing the first two DESs found that the sirolimus-eluting stent compared to the paclitaxel-eluting stent was associated with less TLR in patients with diabetes [18-20, 22]. Efficacy and safety of second-generation EES and zotarolimus-eluting stents versus first-generation DESs in patients with diabetes were evaluated in a meta-analysis of randomized trials [23]. A total of 18 trials comprising of 8095 patients were included. Compared to first-generation DES, EES significantly decreased major adverse cardiac events by 18%, MI by 43%, and stent thrombosis by 46% in patients with diabetes. Moreover, EES showed a trend towards a reduction in rates of TLR and TVR ($p=0.05$). Zotarolimus-eluting stent was associated with an 89% increased risk of TLR compared to first-generation DES [23].

Current evidence supports the use of durable polymer EES in patients with diabetes mellitus undergoing PCI. However, diabetes mellitus attenuates the antirestenotic effects of DES and the risk of adverse events after PCI is higher for diabetics compared with patients without diabetes mellitus.

Biodegradable polymer DES was conceived to overcome the safety issues of early generation durable polymer DES. Polymer remnants within the arterial wall may impair vascular healing and

be responsible for long term adverse events, such as late stent thrombosis and delayed restenosis [24]. The pooled analysis of 3 randomized clinical trials (ISAR-TEST 3, ISAR-TEST 4 and LEADERS), which included 1094 patients with diabetes in the analysis, compared the first-generation biodegradable polymer DES with durable polymer DES. In patients with diabetes, biodegradable polymer DES showed comparable clinical outcomes compared with first generation durable polymer DES and a favorable safety profile with significantly lower rates of stent thrombosis at 4 years of follow-up [24].

However, a non-randomized study comparing the 20-month efficacy and safety of the biodegradable polymer N-BES and the reference durable polymer EES in diabetic patients showed no significant differences [5]. Compared to our results, the mortality rate in the N-BES group for diabetic patients was lower. This is probably related to differences in the indications for PCI (more patients with ST-segment elevation myocardial infarction and Non-ST-segment elevation myocardial infarction in our study: 48.5% vs. 23%), comorbidity or patient selection [5].

The geometry of newer biodegradable polymer DES has been improved with a significant reduction of strut thickness. As compared to N-BES, which was the first DES with a biodegradable polymer, the newer O-SES has significantly thinner stent struts (60-80 μm compared to the 120 μm for the N-BES). Thin stent struts have been associated with less wall shear and thrombogenicity [25], which may be an explanation for the numerically lower rates of definite and definite/probable stent thrombosis in diabetic and nondiabetic patients treated with the O-SES.

The first subgroup analysis of the randomized “ultrathin strut biodegradable polymer sirolimus-eluting stent versus durable polymer everolimus-eluting stent for percutaneous coronary revascularization (BIOSCIENCE) trial” looked at the clinical outcome according to diabetic status

in patients treated with O-SES versus the durable polymer EES [6]. Among 2119 patients enrolled, 486 (22.9%) had diabetes mellitus. Overall, diabetic patients experienced a significantly higher risk of TLF compared with nondiabetic patients (10.1% vs. 5.7%, p=0.001). No significant differences were found for TLF and stent thrombosis among patients with diabetes mellitus allocated to the biodegradable polymer O-SES or the durable polymer EES group at 1 year. The TLF and the risk of definite or probable stent thrombosis for the O-SES was lower in the SORT OUT VII diabetes substudy compared to the BIOSCIENCE trial diabetes substudy at 1 year (TLF 4.7% vs. 10.9%; definite/probable stent thrombosis 1.3% vs. 4.0%). This difference can be explained partly by procedure-related MI, which was not part of the primary endpoint in the SORT OUT VII trial, and by the higher clinically-indicated TLR rate in the BIOSCIENCE trial (TLR: 6.6% vs. 3.0%) at 1 year.

Study Limitations

The present analysis has some limitations. First, current findings are limited to 2-year follow-up whereas potential differences between the compared stents could emerge later. Second, SORT OUT VII was not powered for detection of differences among subgroups and subgroup analysis should consequently be considered as hypothesis-generating. Third, it should be noted that N-BES is not commercially available in a broad majority of countries anymore. However, our study provides important information for patients with a previously implanted N-BES.

CONCLUSION

The SORT OUT VII diabetes substudy showed that there was no difference between the biodegradable polymer O-SES and the biodegradable polymer N-BES in diabetic subgroup.

DISCLOSURES

LOJ has received research grants from St Jude Medical, Biosensors and Biotronik to her institution. MM has received unrestricted research grants from Volcano (now Philips), Biosensors and Boston Scientific to his institution. JE, EHC, BR, SEJ, SDK, KTV, ABJ, LJ, JA, CJT, JK, ABV, HEB declare that they have no conflicts of interest.

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FIGURE LEGENDS

Figure 1. Time-to-event curve for the composite endpoint target lesion failure (TLF) at 24 months of follow up in diabetic patients.

Figure 2. Time-to-event curve for cardiac death at 24 months of follow-up in diabetic patients.

Figure 3. Time-to-event curve for myocardial infarction (MI) at 24 months of follow-up in diabetic patients.

Figure 4. Time-to-event curve for target lesion revascularization (TLR) at 24 months of follow-up in diabetic patients.

Figure 5. Time-to-event curve for the incidence of definite stent thrombosis at 24 months of follow-up in diabetic patients.