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Impact of diabetes on clinical outcomes after revascularization with the dual therapy CD34 antibody-covered sirolimus-eluting Combo stent and the sirolimus-eluting Orsiro stent

Lars Jakobsen MD, PhD[1] | Evald H. Christiansen MD, PhD[1] | Phillip Freeman MD, PhD[2] | Johnny Kahlert PhD[3] | Karsten Veien MD[4] | Michael Maeng MD, PhD[1] | Bent Raungaard MD, PhD[2] | Julia Ellert MD, PhD[4] | Steen D. Kristensen MD, DMSci[1] | Martin K. Christensen MD[2] | Christian J. Terkelsen MD, DMSci[1] | Troels Thim MD, PhD[1] | Ashkan Eftekhari MD, PhD[1,2] | Rebekka V. Jensen MD, PhD[1] | Nicolaj B. Støttrup MD, PhD[1] | Anders Junker MD, PhD[4] | Henrik S. Hansen MD, DMSci[4] | Lisette O. Jensen MD, DMSci[4]

[1]Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark

[2]Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark

[3]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark

[4]Department of Cardiology, Odense University Hospital, Odense, Denmark

Correspondence

Lars Jakobsen, Department of Cardiology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, Aarhus DK-8200, Denmark.
Email: larsj@dadlnet.dk

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OrbusNeich Medical, Fort Lauderdale, Florida, USA; Biotronik, Bülach, Switzerland

Abstract

Objectives: To compare the efficacy and safety of the dual therapy CD34 antibody-covered sirolimus-eluting Combo stent (DTS) and the sirolimus-eluting Orsiro stent (SES) in patients with and without diabetes mellitus (DM) included in the Scandinavian Organization for Randomized Trials with Clinical Outcome (SORT OUT) X study.

Background: The incidence of target lesion failure (TLF) after treatment with modern drug-eluting stents has been reported to be significantly higher in patients with DM when compared to patients without DM. Thus, whether the results from the SORT OUT X study apply to patients with and without DM remains unknown.

Methods: In total 3146 patients were randomized to stent implantation with DTS (n = 1578; DM: n = 279) or SES (n = 1568; DM: n = 271). The primary end point, TLF, was a composite of cardiac death, target-lesion myocardial infarction (MI), or target lesion revascularization (TLR) within 1 year.

Results: At 1 year, the rate of TLF was increased in the DTS group compared to the SES group, both among patients with DM (9.3% vs. 4.8%; risk difference: 4.5%; incidence rate ratio: 1.99, 95% confidence interval [CI]: 1.02–3.90) and without DM (5.7% vs. 3.5%; incidence rate ratio: 1.67, 95% CI: 1.15–2.42). The differences were mainly explained by higher rates of TLR.

Conclusion: Compared to the SES, the DTS was associated with an increased risk of TLF at 12 months in patients with and without DM. The differences were mainly explained by higher rates of TLR, whereas rates of cardiac death and target lesion MI did not differ significantly between the two stent groups in patients with or without DM.

KEYWORDS
diabetes, randomized controlled trial, stent comparison, target lesion failure

1 | INTRODUCTION

The presence of diabetes mellitus (DM) is associated with a higher risk of in-stent restenosis and major cardiovascular events after percutaneous coronary intervention (PCI).[1,2] Attempts have been made to further improve early stent healing and to reduce neointima hyperplasia. The dual therapy sirolimus-eluting Combo stent (OrbusNeich Medical) (DTS) combines an abluminal, bioabsorbable polymer with a luminal CD34+ antibody designed to capture endothelial progenitor cells. The DTS appears to promote endothelialization while reducing neointima hyperplasia and inflammation[3] and was found to be noninferior to first- and second-generation drug-eluting stents (DES) in three small randomized controlled trials.[4–6] Only one study has reported outcomes after treatment with the DTS in patients with versus without DM.[7] At 1 year after DTS placement, significantly higher rates of TLF were seen in patients with DM compared to patients without DM. The Scandinavian Organization for Randomized Trials with Clinical Outcome (SORT OUT) X study was the first study to compare the DTS to a third-generation DES, the sirolimus-eluting Orsiro stent (SES) (Biotronik),[8] and showed that the DTS was inferior to the SES for target lesion failure (TLF) at 12 months mainly due to a higher incidence of target lesion revascularization (TLR) in the DTS group. The incidence of TLR after treatment with modern DES has been reported to be significantly higher in patients with DM when compared to patients without DM.[9] Thus, whether the results from the SORT OUT X study apply to patients with and without DM remains unknown. The aim of the present study (a substudy of SORT OUT X) was to compare the efficacy and safety of the DTS compared to the SES in patients with and without DM.

2 | MATERIALS AND METHODS

SORT OUT X[8] was a randomized, multicentre, single-blind, all-comer, two-arm, blinded endpoint, noninferiority trial, comparing the DTS to the SES in the treatment of coronary artery lesions. The inclusion period was from June 2017 to December 2019. A detailed study protocol has previously been provided.[10] Briefly, patients were eligible if they were ≥18 years old, had chronic stable coronary artery disease or acute coronary syndrome (ACS), 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 the number of treated lesions, the number of treated vessels, or lesion length. Exclusion criteria were life expectancy of <1 year; allergy to aspirin, clopidogrel, ticagrelor, sirolimus, or biolimus; participation in another randomized stent trial; or inability to provide written informed consent.

The investigators enrolled the patients, who were randomly allocated to treatment groups after diagnostic coronary angiography and before PCI. Block randomization by center (permuted blocks of random sizes [2/4/6]) was used to assign patients in a 1:1 ratio to receive the DTS or the SES. The allocation sequence stratified by sex and presence of DM was computer-generated by an independent organization. Patients were considered to have diabetes if they received glucose-lowering medications or reported dietary treatment for diabetes. Patients were assigned to treatment through a web-based randomization system. All individuals who were involved in the clinical event detection were blinded, whereas operators were not blinded to treatment assignment.

Stents were implanted in accordance with standard techniques. Direct stenting was allowed. Full lesion coverage was attempted by implanting one or more stents. DES other than the allocated stent and bare-metal stents were not allowed unless the allocated study stent could not be implanted. In such situations, balloon angioplasty alone or other stents were allowed. Patients were on acetylsalicylic acid (loading dose of 300 mg) before stent implantation and loaded with either ticagrelor 180 mg, clopidogrel 600 mg, or prasugrel 60 mg. Combination of dual antiplatelet therapy was left to the discretion of the participating centers. Dual antiplatelet therapy was recommended for 6 months in patients with stable angina pectoris and for 12 months in patients with unstable angina pectoris or acute myocardial infarction (MI). Unfractionated heparin dose (70–100 IU/kg) was given before the procedure. Glycoprotein IIb/IIIa inhibitors, bivalirudin or cangrelor were used at the operator's discretion.

2.1 | Outcome measures

Definitions of endpoints are provided in the main publication.[8] The primary endpoint TLF of this substudy was a composite of cardiac death, target lesion MI (not related to other than index lesion), or clinically indicated TLR within 12 months of stent implantation. Individual components of the primary endpoint comprised the

secondary endpoints: cardiac death; target lesion MI; clinically indicated TLR; all-cause death (cardiac and noncardiac), and target vessel revascularization (TVR); definite, probable, and overall stent thrombosis according to the Academic Research Consortium definition[11]; and a patient-related composite endpoint (all-cause death, all MIs, or any revascularization).

2.2 | Clinical event detection

The study was based on clinically driven event detection, and no dedicated follow-up was scheduled. At 12 months follow-up, data on mortality, hospital admission, coronary angiography, repeat PCI, and coronary artery bypass surgery (CABG) were obtained from the following national Danish administrative and healthcare registries: The Civil Registration System, the Western Denmark Heart Registry, and the Danish National Registry of Patients. The latter maintains records on all hospitalizations in Denmark. The National Health Service provides tax-funded healthcare, guaranteeing unfettered access to medical care. All acute medical conditions are exclusively treated at public hospitals in Denmark. The Danish Civil Registration System has kept electronic records on sex, birth date, residence, emigration date, and vital status changes since 1968, with daily updates. The 10-digit civil registration number assigned at birth and used in all registries allows accurate record linkage. Loss to follow-up was minimized in the study, as vital status data for our study participants was provided by the Civil Registration System. The Danish National Registry of Patients provided information on diagnoses assigned by the treating physician during hospitalizations (coded according to the International Classification of Diseases, 10th revision [ICD-10]).[12] The way Danish hospitals report data to the Danish National Registry of Patients changed on January 1, 2019. The data reported since January 2019 has not been validated. Thus, registry-based follow-up data regarding MI were not available for the entire follow-up period for 2224 patients. Instead, all discharge letters regarding these patients were evaluated to detect MI.

An independent event committee reviewed all endpoints and source documents to adjudicate causes of death, reasons for hospital admission, and diagnosis of MI. Two dedicated operators at each participating center reviewed cine films for the event committee to

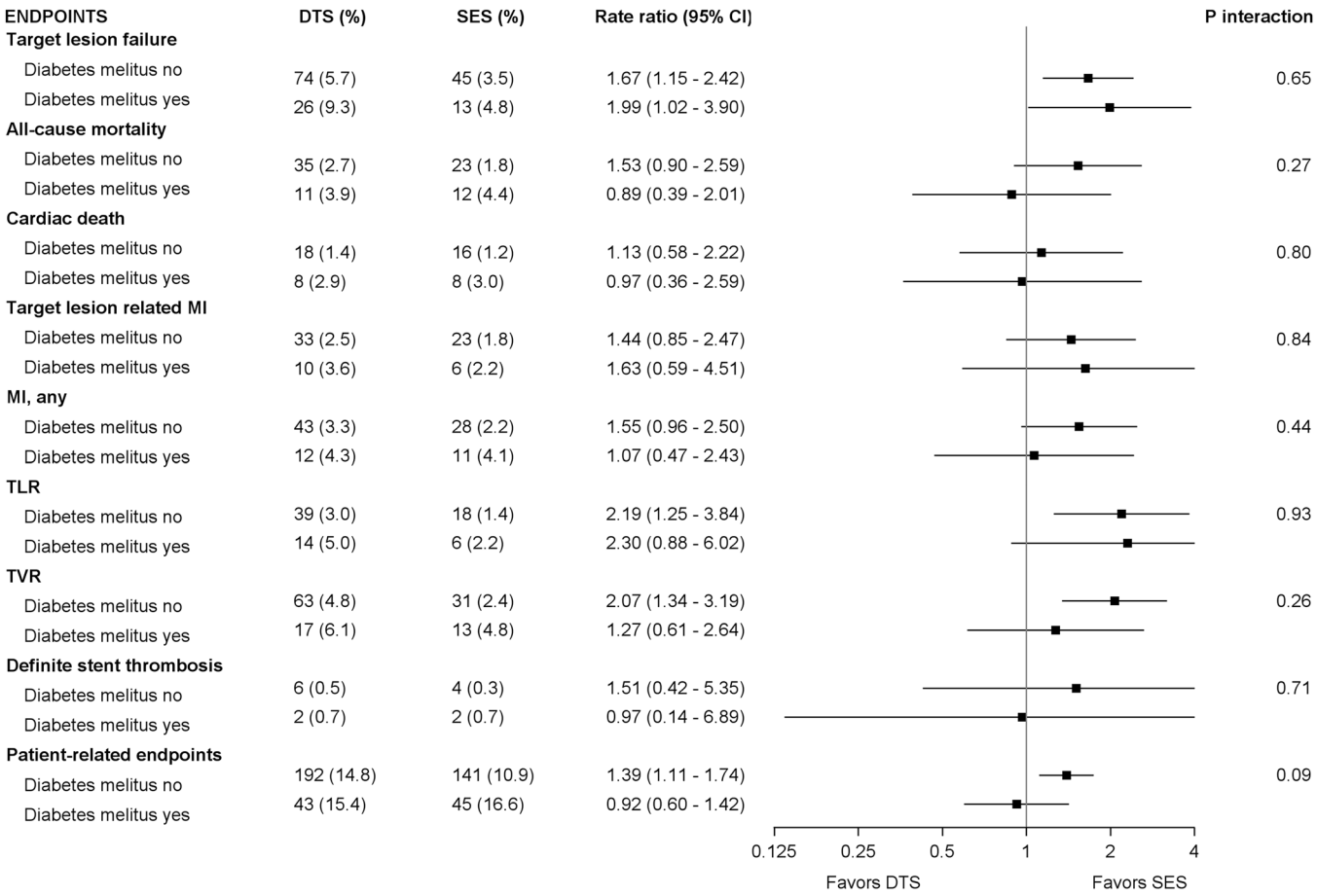

FIGURE 1 One-year clinical outcomes in randomized patients with and without diabetes mellitus treated with a DTS or an SES. Values are presented as number of patients (%). CI, confidence interval; DTS, dual therapy CD34 antibody-covered sirolimus-eluting Combo stent; MI, myocardial infarction; SES, sirolimus-eluting Orsiro stent; TLR, target lesion revascularization; TVR, target vessel revascularization

classify stent thrombosis, TLR, and TVR (with either PCI or CABG). The independent event committee was blinded to study stent type assignment during the adjudication process. This methodology has been used in the previous SORT OUT studies.[13–16]

2.3 | Statistical analysis

Distributions of continuous variables were compared between study groups using two-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 χ^2 test. In analyses of every endpoint, follow-up continued until the date of an endpoint event, death, emigration, or 12 months after stent implantation, whichever came first. Survival curves were constructed based on cumulated incidences, accounting for death as a competing risk.[17] Incidence rate ratios were calculated using patients who received the SES as the reference group. The intention-to-treat principle was used in all analyses. A two-sided *p* value of less than 0.05 indicated statistical significance. Analyses were conducted using SAS 9.4 (SAS Institute). This trial is registered with ClinicalTrials.gov, number NCT03216733.

3 | RESULTS

Between June 2017 and December 2019, 3146 patients were randomly assigned to receive either the DTS (1578 patients [2008 lesions]) or the SES (1568 patients[1982 lesions]; Figure 1). In total, 550 patients had DM of whom 279 were treated with the DTS and 271 were treated with the SES. Six patients emigrated and were censored at the time of emigration (total follow-up: 99.8%).

Baseline patient characteristics (Table 1) and procedural characteristics (Table 2) were well balanced in both DM and non-DM patients treated with DTS versus SES. The only exception was a higher frequency of patients with ACS in the DM patients treated with an SES when compared to DM patients treated with a DTS. Compared to patients without DM, those with DM were more frequently treated for hypertension or hypercholesterolemia and they had a higher rate of previous CABG, previous MI, previous PCI, a

TABLE 1 Baseline patient characteristics

	Patients with diabetes			Patients without diabetes			*p* value diabetes
Variable	DTS (*n* = 279)	SES (*n* = 271)	*p* value	DTS (*n* = 1299)	SES (*n* = 1297)	*p* value	versus nondiabetes
Age (years)	67.6 (±10.2)	67.3 (±10.2)	0.72	67.0 (±10.8)	66.6 (±11.1)	0.35	0.18
Male gender	211 (75.6%)	207 (76.4%)	0.84	1002 (77.1%)	1001 (77.2%)	0.98	0.56
Arterial hypertension	208 (75.9%)	209 (79.2%)	0.37	627 (49.0%)	662 (51.9%)	0.14	<0.00001
Hypercholesterolemia	216 (79.4%)	198 (74.7%)	0.20	567 (44.1%)	585 (45.7%)	0.41	<0.00001
Current smoker	54 (21.4%)	71 (30.0%)	0.031	356 (30.8%)	358 (30.6%)	0.93	0.02
Body mass index, kg/m^2	30.0 (±4.9)	30.4 (±5.3)	0.45	27.6 (±4.6)	27.4 (±4.4)	0.24	0.0001
Previous myocardial infarction	54 (19.6%)	61 (23.7%)	0.25	186 (14.5%)	160 (12.6%)	0.17	<0.00001
Previous PCI	74 (26.9%)	78 (29.5%)	0.50	221 (17.2%)	225 (17.7%)	0.76	<0.00001
Previous CABG	39 (14.1%)	26 (9.8%)	0.13	72 (5.6%)	63 (4.9%)	0.45	<0.00001
Indication for PCI			0.02			0.14	<0.00001
STEMI	34 (12.2%)	51 (18.8%)		355 (27.3%)	304 (23.4%)		
NSTEMI or UAP	77 (27.6%)	89 (32.8%)		390 (30.0%)	410 (31.6%)		
Stable angina	148 (53.0%)	120 (44.3%)		503 (38.7%)	534 (41.2%)		
Other	20 (7.2%)	11 (4.1%)		51 (3.9%)	49 (3.8%)		
Comorbidity index score			0.23			0.83	<0.00001
0	69 (24.7%)	72 (26.6%)		775 (59.7%)	777 (59.9%)		
1–2	137 (49.1%)	114 (42.1%)		418 (32.2%)	407 (31.4%)		
3+	73 (26.2%)	85 (31.4%)		106 (8.2%)	113 (8.7%)		

Note: Data are presented as mean ± SD, median (interquartile range), or number of patients (%).

Abbreviations: CABG, coronary artery bypass graft surgery; DTS, dual-therapy CD34 antibody-covered sirolimus-eluting stent; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; SES, sirolimus-eluting stent; STEMI, ST-segment elevation myocardial infarction; UAP, unstable angina pectoris.

TABLE 2 Baseline lesion and procedure characteristics

Variable	Patients with diabetes			Patients without diabetes			*p* value diabetes versus nondiabetes
	DTS (*n* = 279)	SES (*n* = 271)	*p* value	DTS (*n* = 1299 patients 1638 lesions)	SES (*n* = 1297 patients 1620 lesions)	*p* value	
Target vessel location			0.46			0.19	0.13
Left main artery	16 (14.3%)	10 (2.8%)		38 (2.3%)	40 (2.5%)		
Left anterior descending artery	146 (39.5%)	156 (43.1%)		713 (43.6%)	749 (46.3%)		
Left circumflex artery	93 (25.1%)	80 (22.1%)		346 (21.1%)	360 (22.2%)		
Right artery	112 (30.3%)	110 (30.4%)		527 (32.2%)	457 (28.2%)		
Saphenous vein graft	3 (0.8)	6 (1.7%)		13 (0.8%)	13 (0.8%)		
Lesion type			0.75			0.32	0.010
• A	25 (6.8%)	32 (8.8%)		159 (9.7%)	178 (11.0%)		
• B1	170 (45.9%)	160 (44.2%)		655 (40.0%)	623 (38.5%)		
• B2	98 (26.5%)	93 (25.7%)		469 (28.6%)	492 (30.4%)		
• C	77 (20.8%)	77 (21.3%)		354 (21.6%)	326 (20.1%)		
Chronic total occlusion lesions	19 (5.1%)	16 (4.4%)	0.64	70 (4.3%)	87 (5.4%)	0.14	0.97
Bifurcation lesions	88 (23.8%)	80 (22.1%)	0.59	393 (24.0%)	371 (22.9%)	0.46	0.77
Lesion length > 18 mm	189 (51.1%)	189 (52.2%)	0.76	810 (49.5%)	801 (49.5%)	1.00	0.29
Lesion length (mm)	20.0 (12–30)	20.0 (12–28)	0.89	18.0 (13.0–28.0)	18.0 (12.0–28.0)	0.74	0.47
Reference vessel size (mm)	3.4 (±0.6)	3.4 (±0.6)	0.61	3.4 (±0.6)	3.5 (±0.6)	0.49	0.62
No. of stents per lesion	1.3 (±0.6)	1.3 (±0.6)	0.49	1.3 (±0.6)	1.3 (±0.7)	0.40	0.46
No. of stents per patient	1.8 (±1.0)	1.8 (±1.0)	0.89	1.7 (±1.0)	1.7 (±1.1)	0.72	0.05
Total stent length per lesion (mm)	28.7 (±19.0)	28.1 (±17.5)	0.63	22.7 (±15.4)	22.7 (±15.9)	0.92	0.74
Total stent length per patient (mm)	38.4 (±28.0)	38.4 (±26.3)	0.98	29.4 (± 22.4)	29.3 (±24.9)	0.88	0.02
Direct stenting	40 (10.8%)	32 (8.9%)	0.38	196 (12%)	195 (12.1%)	0.98	0.09
Stent delivery failure	6 (1.6%)	13 (3.6)	0.094	42 (2.6%)	48 (3.0)	0.49	0.80
Maximum pressure (atm)	19.0 (±3.7)	18.9 (±4.4)	0.53	18.5 (±3.8)	18.3 (±4.0)	0.15	0.0005
Length of procedure (minutes)	38.0 (±36.7)	34.4 (±32.5)	0.23	29.6 (±24.3)	29.2 (±23.6)	0.65	0.0001
Flouro time (minutes)	13.9 (±16.5)	13.2 (±16.8)	0.58	10.1 (±11.1)	9.9 (±10.8)	0.62	0.0001
Contrast (ml)	107.9 (±69.0)	104.1 (±75.7)	0.54	91.0 (±59.0)	95.1 (±66.1)	0.09	0.0001

(Continues)

TABLE 2 (Continued)

Variable	Patients with diabetes			Patients without diabetes			p value diabetes versus nondiabetes
	DTS (n = 279)	SES (n = 271)	p value	DTS (n = 1299 patients 1638 lesions)	SES (n = 1297 patients 1620 lesions)	p value	
Use of glycoprotein IIb/IIIa inhibitor	2 (0.7%)	3 (1.1%)	0.63	19 (1.5%)	33 (2.5%)	0.05	0.08
Use of bivalirudin	3 (1.1%)	3 (1.1%)	0.96	28 (2.2%)	21 (1.6%)	0.31	0.20

Note: Data are presented as mean ± SD, median (interquartile range), or number of patients (%).

Abbreviations: DTS, dual-therapy CD34 antibody-covered sirolimus-eluting stent; SES, sirolimus-eluting stent.

higher body mass index, and more comorbidity. Compared to patients without DM, the patients with DM were more often treated with PCI because of stable coronary artery disease and less often because of ST-elevation MI and fewer were current smokers. The patients with DM had a longer total stent length, higher maximum pressure, longer procedure times, longer flouro times, and a higher contrast volume when compared to patients without DM.

TLF and the secondary endpoints are presented in Table 3, Figures 1 and 2. At 12 months, TLF occurred in 26 (9.3%) in the DTS group and 13 (4.8%) in the SES group in patients with DM (incidence rate ratio 1.99 [1.02–3.90]). This difference was mainly explained by a higher rate of TLR in the DTS group compared to the SES group. Furthermore, in-stent restenosis was more frequent in the DTS group (12 [4.3%] vs. 3 [1.1%]; incidence rate ratio 3.95 [1.12–14.0]) when compared to the SES group. The point estimate suggested a potential higher frequency of target lesion MI and TLR in the DTS group compared to the SES group, but confidence intervals were wide.

In patients without DM, TLF occurred in 74 (5.7%) in the DTS group and in 45 (3.5%) patients in the SES group (incidence rate ratio 1.67 [1.15–2.42]). Again, this difference was mainly explained by a higher rate of TLR in the DTS group when compared to the SES group. Furthermore, when compared to the SES group, the rate of TVR and in-stent restenosis was higher in the DTS group.

Of the 550 patients with DM, 186 (33.8%) were treated with insulin. The incidence of TLF did not differ significantly in the insulin-treated DM patients and noninsulin-treated DM patients (16 [8.6%] vs. 23 [6.3%], incidence rate ratio 1.41, 95% confidence interval 0.74–2.69). Differences in TLF rates after treatment with the DTS versus SES in the insulin-treated DM patients did not reach statistical significance (9 [9.5%] vs. 7 [7.7%], incidence rate ratio 1.25, 95% confidence interval 0.46–3.40). However, in the noninsulin-treated DM patients, the rate of TLF was higher after treatment with the DTS compared to the SES (17 [9.2%] vs. 6 [3.3%], incidence rate ratio 2.86, 95% confidence interval 1.12–7.29).

4 | DISCUSSION

This SORT OUT X substudy provides a 12-month head-to-head comparison of the DTS and the SES in patients with and without DM. The study showed that in patients with and without DM, the DTS group had a significantly worse outcome at 12-months follow-up when compared to the SES group.

The SORT OUT X trial was the first randomized trial comparing the DTS to a contemporary third-generation DES and the largest randomized trial comparing the DTS to another DES. In the main SORT OUT X study, we concluded that the DTS was not noninferior to the SES for TLF at 12 months. The SES was superior to the DTS mainly because the DTS was associated with an increased risk of TLR. However, rates of death, cardiac death, and target lesion MI did not differ significantly between the two stent groups.[8]

Patients with DM undergoing PCI have a higher risk of cardiovascular events including repeat revascularization, compared

TABLE 3 Clinical outcomes at 12 months according to diabetes status

Variable	Patients with diabetes				Patients without diabetes				*p* value interaction
	DTS (*n* = 279)	SES (*n* = 271)	IRR (95% CI)	*p* value	DTS (*n* = 1299)	SES (*n* = 1297)	IRR (95% CI)	*p* value	
Target lesion failure	26 (9.3%)	13 (4.8%)	1.99 (1.02–3.90)	0.045	74 (5.7%)	45 (3.5%)	1.67 (1.15–2.42)	0.0074	0.65
Death									
All-cause mortality	11 (3.9%)	12 (4.4%)	0.89 (0.39– 2.01)	0.77	35 (2.7%)	23 (1.8%)	1.53 (0.90–2.59)	0.11	0.27
Cardiac	8 (2.9%)	8 (3.0%)	0.97 (0.36–2.59)	0.95	18 (1.4%)	16 (1.2%)	1.13 (0.58–2.22)	0.72	0.80
Noncardiac	3 (1.1%)	4 (1.5%)	0.73 (0.16–3.23)	0.67	17 (1.3%)	7 (0.5%)	2.44 (1.01–5.88)	0.047	0.17
Target lesion Myocardial infarction	10 (3.6%)	6 (2.2%)	1.63 (0.59–4.51)	0.35	33 (2.5%)	23 (1.8%)	1.44 (0.85–2.47)	0.18	0.84
Myocardial infarction	12 (4.3%)	11 (4.1%)	1.07 (0.47–2.43)	0.88	43 (3.3%)	28 (2.2%)	1.55 (0.96–2.50)	0.074	0.44
Stent thrombosis (all)	5 (1.8%)	6 (2.2%)	0.81 (0.25– 2.65)	0.72	11 (0.8%)	8 (0.6%)	1.38 (0.56–3.44)	0.49	0.48
Definite	2 (0.7%)	2 (0.7%)	0.97 (0.14 - 6.89)	0.97	6 (0.5%)	4 (0.3%)	1.51 (0.42–5.35)	0.53	0.71
Possible	2 (0.7%)	3 (1.1%)	0.64 (0.11– 3.85)	0.63	4 (0.3%)	4 (0.3%)	1.00 (0.25–4.01)	0.99	0.70
Probable	1 (0.4%)	1 (0.4%)	0.97 (0.06– 15.5)	0.98	1 (0.1%)	0			
Definite or probable	3 (1.1%)	3 (1.1%)	0.97 (0.19– 4.82)	0.97	7 (0.5%)	4 (0.3%)	1.76 (0.51–6.02)	0.37	0.56
Target vessel revascularization	17 (6.1%)	13 (4.8%)	1.27 (0.61– 2.64)	0.52	63 (4.8%)	31 (2.4%)	2.07 (1.34–3.19	0.00099	0.26
Target lesion revascularization	14 (5.0%)	6 (2.2%)	2.30 (0.88– 6.02)	0.088	39 (3.0%)	18 (1.4%)	2.19 (1.25–3.84)	0.0060	0.93
In-stent restenosis	12 (4.3%)	3 (1.1%)	3.95 (1.12– 14.0)	0.033	33 (2.5%)	11 (0.8%)	3.03 (1.53–6.00)	0.0014	0.72

Note: Data are presented as the number of patients (%).

Abbreviations: CI, confidence interval; DTS, dual-therapy CD34 antibody-covered sirolimus-eluting stent; IRR, incidence rate ratio; SES, Sirolimus-eluting stent.

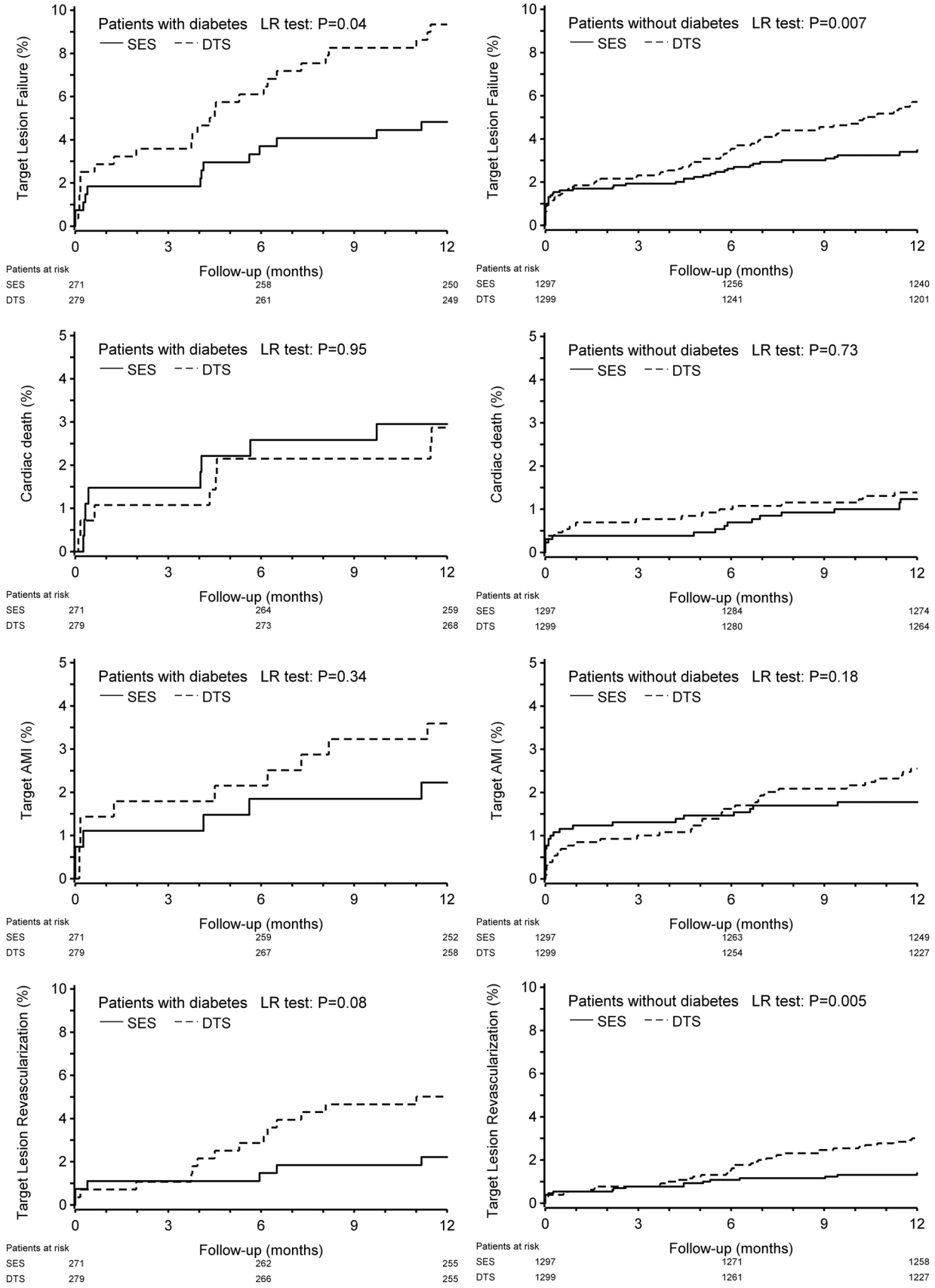

FIGURE 2 Event rates of target lesion failure and the individual components (cardiac death, target lesion myocardial infarction, and target lesion revascularization) in patients with and without diabetes after implantation with a DTS (dotted line) or SES (solid line) during 12-month follow-up. AMI indicates acute myocardial infarction; DTS, dual therapy CD34 antibody-covered sirolimus-eluting Combo stent; SES, sirolimus-eluting Orsiro stent.

with patients without DM even after the development of modern DES.[1,9,18,19] Angiographic and intravascular ultrasound studies suggest a higher risk of late lumen loss and increased neointima hyperplasia in patients with DM compared with patients without DM.[20–22] Also, patients with DM tend to have a higher frequency of negative remodeling compared with patients without DM.[23] The DTS was designed to promote endothelialization while reducing neointima hyperplasia and inflammation. Studies have shown that the dose of the drug released and the drug release time are important stent features.[24] The biodegradable polymer attached to the DTS is completely absorbed within 90 days (compared with 12–24 months for the SES) and the drug release is faster (1 vs. 3 months). These differences might be a part of the explanation of why the DTS is inferior to the SES. Only one study has compared outcomes after treatment with the DTS in patients with and without DM and it showed similar results with worse clinical outcomes after DTS implantation in patients with DM compared to patients without DM.[7]

Several previous SORT OUT studies have compared outcomes after treatment with different DES in patients with DM. The DM substudy of the SORT OUT III study showed a significant difference in the clinical outcome at 18 months after treatment with the endeavor zotarolimus-eluting stent and the cypher sirolimus-eluting stent in patients with DM (18.3% vs. 4.8%; hazard ratio 4.05 [1.86–8.82]) in favor of the Cypher stent.[25] Since then, the newer DES have narrowed the gap between different DES, also in patients with DM, and the following SORT OUT DM substudies have not been able to show statistically significant differences between the study stents. In the SORT OUT IV DM substudy, the Xience V Everolimus-eluting stent had a statistically nonsignificant 5.5% lower risk of major adverse cardiac events compared to the Cypher Select + sirolimus-eluting stent (10.3% vs. 15.8%) at 18-month follow-up. In SORT OUT VII, the 2-year TLF rate was similar in DM patients treated with two new-generation DES (SES 9.3% vs. Nobori Biolimus-eluting stent 9.4%).[26] Finally, the SORT OUT VIII DM substudy compared the Everolimus-eluting Synergy stent and the Biolimus-eluting BioMatrix stent in patients with DM. There was an absolute difference of 2.1% in favor of the Synergy stent (3.6% vs. 5.7%) although the difference was statistically nonsignificant.[27]

The present SORT OUT X DM substudy found TLF rates of 9.3% and 4.8% among patients with DM in the DTS group and the SES group, respectively. Thus, the TLF rate was almost twice as high in the DTS group compared to the SES group, and the difference reached statistical significance in spite of the relatively low number of patients in each group. The difference in the TLF rates was mainly explained by a difference in the TLR rate. These findings are in line with the findings of the main SORT OUT X study.[8]

Besides the different drug-eluting kinetics mentioned above, there are important differences in the DES technologies between the two study stents that may have contributed to the higher TLF rate observed in the DTS group in the present study. These include the murine, monoclonal, antihuman CD34 antibody attached to the polymer of the DTS; different stent struts thickness; and other stent-related factors. These differences are discussed in detail in the main SORT OUT X study.[8]

5 | LIMITATIONS

The SORT OUT X trial, in line with the previous SORT OUT trials,[13–16] relied on registry-based outcome ascertainment without study-related angiographic or clinical follow-up. However, new data showed a high degree of concordance between investigator-reported and adjudicated endpoints in a randomized trial.[28] Patient care complied with standard clinical practice usually with a single hospital outpatient visit 1–3 months after stent implantation. Although the Danish healthcare 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. However, this potential to under-report events is likely to be low and should not influence differences detected between treatment groups. Biomarkers were not routinely measured in relation to the procedure, and thus we could not assess potential differences in periprocedural MI and we did not monitor bleeding complications. Finally, the study was conducted in a Danish population and whether our results are applicable to other ethnicities is unclear.

6 | CONCLUSION

The DTS was associated with an increased risk of TLR at 12 months in both patients with and without DM compared to the SES. The differences were explained by higher rates of TLR whereas rates of cardiac death and myocardial did not differ significantly between the two stent groups in patients with and without DM.

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CONFLICTS OF INTEREST

Evald H. Christiansen reports financial support was provided by Biotronik, Bülach, Switzerland. Evald H. Christiansen reports financial support was provided by OrbusNeich Medical, Fort Lauderdale, Florida, USA. Lisette O. Jensen reports a relationship with Biotronik, OrbusNeich, Biosensors, and Terumo that includes: funding grants. Michael Maeng reports a relationship with AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol Myers-Squibb, Boston Scientific, Novo Nordisk, that includes: speaking and lecture fees. Steen D. Kristensen

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Lars Jakobsen http://orcid.org/0000-0002-2522-9253
Rebekka V. Jensen http://orcid.org/0000-0001-6539-5275

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