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Five-year outcomes of patients with diabetes mellitus treated with a sirolimus-eluting or a biolimus-eluting stents with biodegradable polymer. From the SORT OUT VII trial

Jens Trøan[1], Evald Høj Christiansen[2], Kirstine Nørregaard Hansen[1], Ashkan Eftekhari[3], Lars Jakobsen[2], Michael Mæng[2], Phillip Freeman[3], Rebekka Vibjerg Jensen[2], Martin Kirk Christensen[3], Manijeh Noori[1], Julia Ellert-Gregersen[1], Nicolaj Brejnholt Støttrup[2], Johnny Kahlert[4], Karsten Tange Veien[1] and Lisette Okkels Jensen[1]

Abstract

Background: Diabetes mellitus is associated with higher risk of target lesion failure (TLF) after percutaneous coronary intervention. We studied the 5-year outcome in patients with diabetes mellitus treated with biodegradable polymer stents.
Methods: The SORT OUT VII was a randomised trial comparing the ultrathin sirolimus-eluting Orsiro stent (O-SES) and the biolimus-eluting Nobori stent (N-BES) in an all-comer setting. Patients (n = 2525) were randomised to receive O-SES (n = 1261, diabetes: n = 236) or N-BES (n = 1264, diabetes: n = 235). Endpoints were TLF (a composite of cardiac death, target-lesion myocardial infarction (MI), target lesion revascularization (TLR)), definite stent thrombosis and a patient related outcome (all-cause mortality, MI and revascularization) within 5 years.
Results: Patients with diabetes mellitus had higher TLF (20.6% vs 11.0%, (Rate ratio (RR) 1.85 95% confidence interval (CI): (1.42-2.40) and patient related outcome (42.0% vs 31.0%, RR 1.43 95% CI: (1.19-1.71)) compared to patients without diabetes. Among patients with diabetes mellitus, TLF after 5 years did not differ between O-SES and N-BES (21.2% vs 20.0%), RR 1.05 95% CI: (0.70-1.58), p = 0.81). Cardiac death, MI, TLR, and definite stent thrombosis did not differ between the groups.
Conclusion: In patients with diabetes mellitus, 5-year outcomes were similar among patients treated with biodegradable polymer O-SES or N-BES.
Clinical trial registration: URL: https://www.clinicaltrials.gov. Unique identifier: NCT01879358.

Keywords

Drug-eluting stent, diabetes mellitus, biodegradable polymer, target lesion failure

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Introduction

Patients with diabetes mellitus have increased risk of restenosis and adverse clinical outcomes after PCI.[1] Therefore, current guidelines recommend the use of newer generations of DES in treating patient with diabetes.[2]

Second generation DES, with thinner stent struts, have been shown to improve safety and efficacy compared to first generation DES by lowering the incidence of late stent thrombosis and restenosis.[3,4,5] The long-term persistence of a non-resorbable polymer has been suggested as a potential trigger for chronic inflammation, resulting in delayed arterial healing and a potential risk of late restenosis and stent thrombosis.[6] Newer generation DES have sought to overcome this risk by using a biodegradable polymer.

The biogradedable polymer biolimus-eluting Nobori stent (N-BES) has been found to have similar efficacy and safety as the second generation durable polymer Everolimus-eluting stent (EES), when comparing long-term results.[7] Furthermore, in a sub-study from the BIO-SCIENCE trial, comparing an ultrathin sirolimus-eluting Orsiro stent (O-SES) to a durable polymer Xience EES, there were no significant differences in long-term outcomes after 5 years in patients with diabetes, between the two stent groups.[8]

The aim of this Scandinavian Organization for Randomized Trails With Clinical Outcome (SORT OUT VII) sub-study was to evaluate the 5-year outcomes in patients with diabetes mellitus treated with the biodegradable polymer ultrathin O-SES compared to patients treated with the biodegradable polymer N-BES.

Methods and materials

The SORT OUT VII trail was a randomised, multicenter, all comer, two armed, non-inferiority study for target lesion failure (TLF) comparing the O-SES with N-BES for the treatment of coronary artery stenosis. A detailed protocol of the study is available in the main publication.[9–11] In brief, patients could be enrolled if they were older than 18 years, had a chronic stable coronary disease or acute coronary syndrome, and at least one coronary lesion with a more than 50% of diameter stenosis, requiring treatment with a DES. Patients with a life expectancy of less than 1 year; allergy to aspirin, prasugrel, clopidogrel, ticagrelor, sirolimus or biolimus could not be enrolled. There were no restrictions on number of treated lesions, number of treated vessels or length of lesions. Written consent was obtained from all patients, prior to randomization. The study was approved by the Central Region Denmark ethics committee and complied with the Declaration of Helsinki.

Randomisation

Patients were enrolled by investigators and allocated randomly to study group after diagnostic angiography and before PCI. Block randomisation by center allocated patients 1:1 to treatment with O-SES or N-BES. Randomisation was stratified by the presence of diabetes and sex. Assignment to study group was conducted using a computer run web-based system (Trialpartner).

Endpoints

The primary endpoint was TLF after 5 years, which was a composite of cardiac death, myocardial infarction (MI) or target lesion revascularization (TLR).

The secondary endpoints were the individual components of the primary endpoint, stent thrombosis (Academic Research Consortium definition[12]), and a patient related composite endpoint (all-cause death, MI and all revascularization).

Data collection

Clinical driven event detection was used to prevent study induced reintervention. Danish registry data was used to obtain data on mortality, hospital admissions, repeat PCI, coronary artery bypass graft (CABG), for all randomised patients. This method has previously been described in earlier publications of SORT OUT studies.[9–11]

An independent event committee, blinded to allocation group, reviewed all endpoints and sources of documentation for cause of death, diagnosis of MI and reasons for hospital admissions. Two PCI operators from each participating center reviewed cine films for the event committee for classification of stent thrombosis and target vessel revascularization (PCI or CABG).

Statistics

Categorical data was compared using the Chi squared test. Continuous data was compared using a two sided Student´ st-test or Mann-Whitney U-test, when data was not normally distributed. Follow-up, for all endpoints, continued until death, emigration or 5 years after stent implantation, whichever came first. Cumulative incidence curves were constructed, accounting for the risk of death (when not included in outcome). Using a modified Poisson regression analysis with the sandwich method, incidence rate ratios were calculated for all endpoints after 0-5 years, 0-1 year and 1-5 years. The N-BES group was used as reference for all analyses. The comparison between patients with diabetes and without diabetes was not based on randomisation. Hence, we adjusted for gender, acute coronary syndrome, family history of coronary artery disease, smoking,

hypertension, previous MI, previous CABG, use of Glycoprotein IIb/IIIa inhibitor, hypercholesterolemia, stent delivery failure, number of lesions greater than 1, reference vessel size under 2.75 mm, Bivalirudin use, procedure time, age above 65 and body mass index. We applied propensity scores, using the inverse probability treatment weighting (IPTW) approach to balance the two patient groups for potential confounding. Covariates were considered balanced when standardized differences of covariates were less than 0.1. Weight trimming down to the 99.5th percentile was applied to reduce the importance of large weights. Completeness of covariates was high (>90%). While missing values in categorical covariates were assigned to their own sub-group, median values were imputed for missing values in continuous variables. The intention to treat principle was applied. A two sided *p*-value of 0.05 was considered statistically significant. Analyses were conducted using the SAS version 9.4 software.

Results

Patients were included between 21 November 2012 and 9 February 2014. In total, 2525 patients were included, with 1261 (1590 lesions) receiving the O-SES, while 1264 (1588 lesions) received the N-BES. Of the 2525 patients, 471 (18.6%) had diabetes mellitus, with 236 patients receiving the O-SES and 235 patients receiving the N-BES. At 5 years, four patients were lost during follow-up due to emigration (Figure 1).

Patient and lesion characteristics of patients with diabetes receiving O-SES and N-BES are summarized in Table 1. Patients with diabetes receiving the O-SES were significantly older (67.3 ± 10.6 vs 65.0 ± 10.0, $p = 0.02$). No other baseline characteristics differed significantly between study groups.

Patients with diabetes had significantly higher TLF compared to patients without diabetes at 5 years, 20.6% versus 11.0%, Rate ratio (RR) 1.85 95% Confidence interval (CI): 1.42-2.40, $p < 0.0001$. This difference was driven by all components of TLF (Cardiac death: 10.2% vs 3.9%, $p < 0.0001$, MI: 10.0% vs 6.9%, $p = 0.014$, TLR: 10.8% vs 6.2%, $p = 0.008$).

At 5 years, the patient related endpoint (all-cause mortality, all MI and all revascularization) was significantly higher in patients with diabetes compared to patients without diabetes (42.0% vs 31.0%, RR 1.43 95% CI: (1.19-1.71), $p < 0.0001$) (Figure 2(A)). This difference was both seen within the first year and also from 1 to 5 years (0-1 year: 16.6% vs 13.3%, $p = 0.02$ and 1-5 years: 30.6% vs 20.4%, $p = 0.002$). All components of the endpoint differed significantly between patients with diabetes compared to patients without diabetes after 5 years (All death: 18.5% vs 11.0%, $p < 0.001$, all MI: 10.0% vs 6.7%, $p = 0.01$, Any revascularization: 26.8% vs 20.6%, $p = 0.005$).

At 5-year, the primary endpoint of TLF did not differ significantly in patients with diabetes treated with the O-SES compared to patients receiving the N-BES (21.2% vs 20.0% RR 1.05 95% CI: (0.70 -1.58), $p = 0.82$). There was no significant difference between the two groups in TLF within the first year or from 1 year to 5 years (Table 2, Figure 2(B)).

The individual components of the primary endpoint cardiac death, MI and TLR did not differ significantly between the O-SES group and the N-BES group in patients with diabetes mellitus. There was no significant difference in the patient related endpoint between the two study groups (Table 2, Figure 2(C)–(D)).

Definite stent thrombosis did not differ significantly after 5 years, with an incidence of 2.1% in the O-SES group and 3.4% in the N-BES group (RR 0.61 95%CI: (0.20, 1.88), $p = 0.39$). There was neither a difference in definite stent thrombosis within the first year nor from 1-year to 5-year between the two groups (Table 2, Figure 2(E)).

Discussion

This SORT OUT VII sub-study compared long-term outcomes of the O-SES with that of the N-BES in patients with diabetes. The primary endpoint of TLF and a patient related outcome was significantly higher in patients with diabetes compared to patients without diabetes after 5 years. However, TLF, cardiac death, MI, definite stent thrombosis and a patient related endpoint did not differ significantly between the two stent groups in patients with diabetes mellitus.

Biodegradable polymers DES were developed to overcome the safety risks of the durable polymer in second generation DES. The remnants of polymer left after drug release may impair vascular healing and potentiate inflammation, and potentially create long-term complications of delayed restenosis and late thrombosis seen in DES. In a pooled analysis of several studies (ISAR-TEST 3, ISAR-TEST 4 and LEADERS), the first generation of biodegradable polymer DES was compared to durable second generation DES.[13] The study showed similar safety and efficacy, with significantly reduced stent thrombosis rates.

In the present study, both stents are covered with a biodegradable polymer. However, the two stents still differ in several ways. In addition to the difference in the drug coating, the rate of drug release also differs, lasting 12 weeks in the O-SES versus 4 weeks in the N-BES. Furthermore, the degradation rate of the biodegradable polymer also differs between the two stents. While the biodegradable polymer in the O-SES is degraded in approximately 12-24 months, the N-BES polymer degrades at a faster rate of 6-9 months. Stent strut thickness also differs between the stents and may influence the amount of shear wall stress and thrombogenicity of the

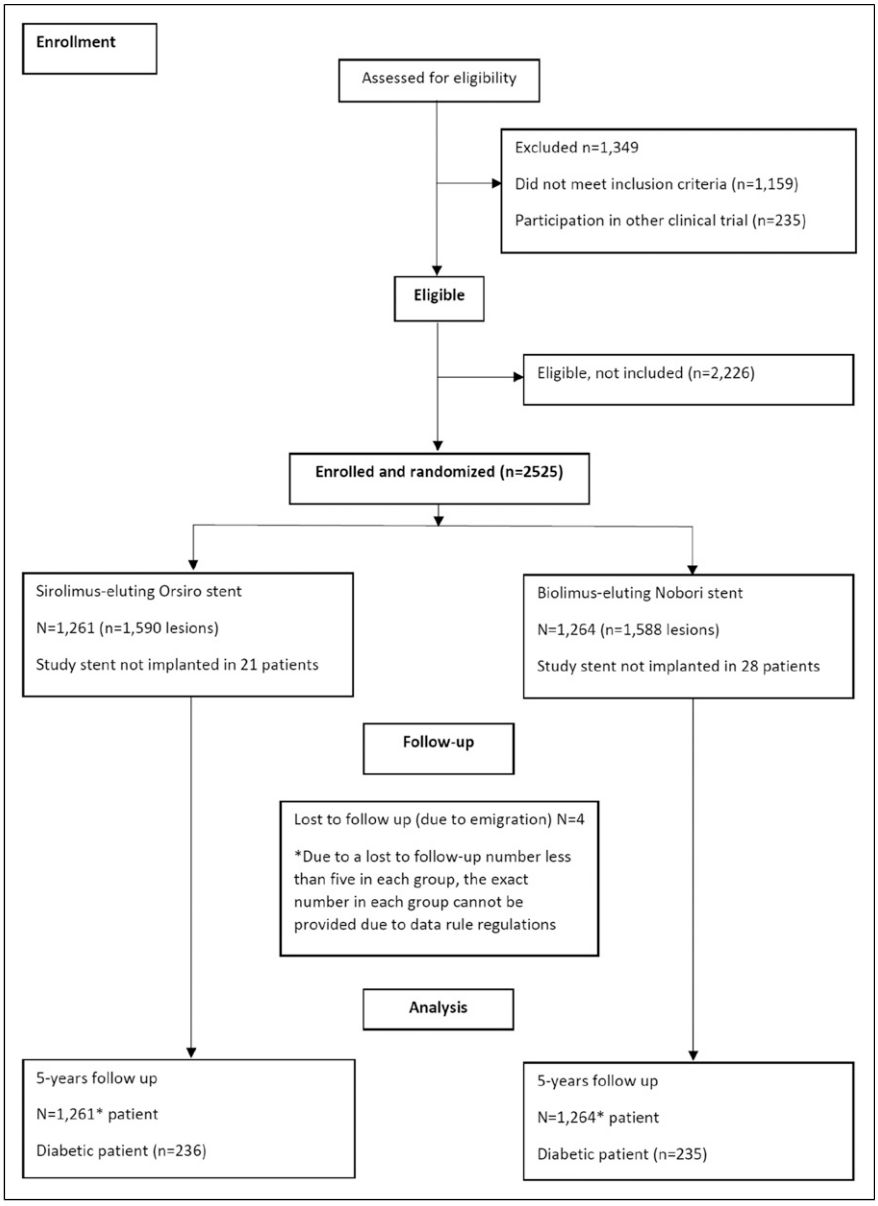

Figure 1. CONSORT diagram for the scandinavian organization for randomized trails with clinical outcome (SORT OUT) VII trail.

DES.[14] Due to this observation, ultrathin strut stents have been proposed to potentially decrease long-term complications associated with stent strut thickness, like definite or probable stent thrombosis. The O-SES has ultrathin stent struts with a thickness of 60-80 µm, while the N-BES has significantly greater strut thickness of 120 µm. These differences could potentially explain the observed numerically lower number of definite and probable stent thrombosis seen in the O-SES group in our study, in addition to the influence of non-stent factors like glycemic control and life style management.

This study compared two different DES in patients with diabetes. While, DES have been shown to be more efficient and safe than the BMS in patients with diabetes,[15] no such differences have been found between the different generations of DES.

The N-BES have previously been compared to second generation stents, showing promising results in patients with diabetes. In a sub-study of the COMPARE-II study comparing the N-BES with the durable polymer EES in patients with diabetes, no significant difference in major adverse cardiac events or secondary endpoints between the two stent groups were found.[16] The results of the N-BES were comparable to our study, with just slightly higher TLF (22.3% COMPARE-II vs 20.0% SORT OUT VII), lower Definite/Probable stent thrombosis (2.8% COMPARE-II vs 3.8% SORT

Table 1. Patients characteristics and procedure characteristics.

	O-SES (n = 236)	N-BES (n = 235)	p-value
Age (years), mean (SD)	67.3 ± 10.6	65.0 ± 10.0	0.02
Sex (male), n (%)	180 (76.3)	181 (77.0)	0.85
Hypertension, n (%)	182 (81.3)	177 (77.3)	0.30
Hypercholesterolemia, n (%)	178 (78.8)	183 (79.6)	0.83
Active smoking, n (%)	53 (24.1)	64 (28.4)	0.30
Body mass index (kg/m^2), mean (SD)	29.2 (5.3)	29.0 (5.3)	0.80
Prior MI, n (%)	56 (24.8)	54 (23.5)	0.75
Prior PCI, n (%)	62 (26.7)	71 (30.5)	0.37
Prior CABG, n (%)	29 (12.6)	26 (11.1)	0.63
Acute coronary syndromes, n (%)	106 (44.9)	114 (48.5)	
Charlson comorbidity score, n (%)			0.84
0	67 (28.4)	72 (30.6)	
1-2	107 (45.3)	101 (43.0)	
≥3	62 (26.3)	62 (26.4)	
Number of lesions	298	302	
Target lesions per patient, n (%)			0.21
1	174 (73.7)	183 (77.9)	
2	57 (24.2)	43 (18.3)	
3	5 (2.1)	7 (3.0)	
>3	0 (0.0)	2 (0.9)	
Number of stents			
Per patient, mean (SD)	1.5 ± 0.8	1.5 ± 0.8	0.95
Per lesion, mean (SD)	1.2 ± 0.5	1.2 ± 0.5	0.38
Stent length			
Per patient, mean (SD)	26.1 ± 15.8	26.0 ± 15.2	0.98
Per lesion, mean (SD)	21.5 ± 12.4	20.8 ± 11.5	0.53
Use of GP2A3B inhibitor, n (%)	7 (3.0)	6 (2.6)	0.78
Use of bivalirudin, n (%)	31 (14.3)	43 (19.6)	0.14

Patient characteristics for patients with diabetes at baseline. O-SES = sirolimus-eluting Orsiro stent, N-BES = biolimus-eluting Nobori stent, MI = myocardial infarction, PCI = percutaneous coronary intervention, CABG = coronary artery bypass graft, STEMI = ST-elevation myocardial infarction, NSTEMI = Non-ST-elevation myocardial infarction, uAP = unstable angina pectoris, sAP = stable angina pectoris.

OUT VII) and lower cardiac death (7.1% COMPARE-II vs 10.6% SORT OUT VII).

A non-randomised efficacy and safety study comparing the N-BES with the durable polymer EES, looked at outcomes in patients with diabetes after 20 months. The study found no differences between the two stent groups, including in stent thrombosis.[17]

In a pooled analysis of the BIOFLOW II, IV and V, patients with diabetes treated with an O-SES were compared to the durable polymer EES 1 year after implantation. The primary outcome TLF was found to be similar across the two stent groups. The rate of TLF was similar to, but higher than in the present study, that is a TLF of 6.3% compared to our 4.7%.[18] However, in the 5-year outcomes of the BIOFLOW II study, a post hoc analysis of diabetic patients showed a numerically, but not statistically significant, difference in TLF of 15.9% in the O-SES group versus 11.5% in the EES group. This difference was mainly driven by the numerically higher number of TLR in the O-SES group (13.5% vs 4.5%, $p = 0.138$), while the O-SES group had significantly lower stent thrombosis (0% vs 6.9%). These results differ from the present study by lower TLF and stent thrombosis in the O-SES group. The study excluded patient presenting with acute MI, which may explain the lower events compared to our study.[19] The non-randomised, single arm BIOFLOW III study, found a TLF of the O-SES of 14%, similar to the BIOFLOW II study and lower than our study.[20] This difference may also be explained be the lower number of patients presenting with acute MI, with approximately 30% in the BIOFLOW III compared 46% in this present study.

In the BIOSCIENCE trial, 5 years outcomes of patients with diabetes treated with the O-SES was compared to patients treated with the durable polymer EES, and TLF did not differ significantly between the two stents group.[8] The study found a 5-year TLF of 31.0% for the O-SES group which is higher than the TLF found in our study. This difference may be due to the inclusion of procedure related

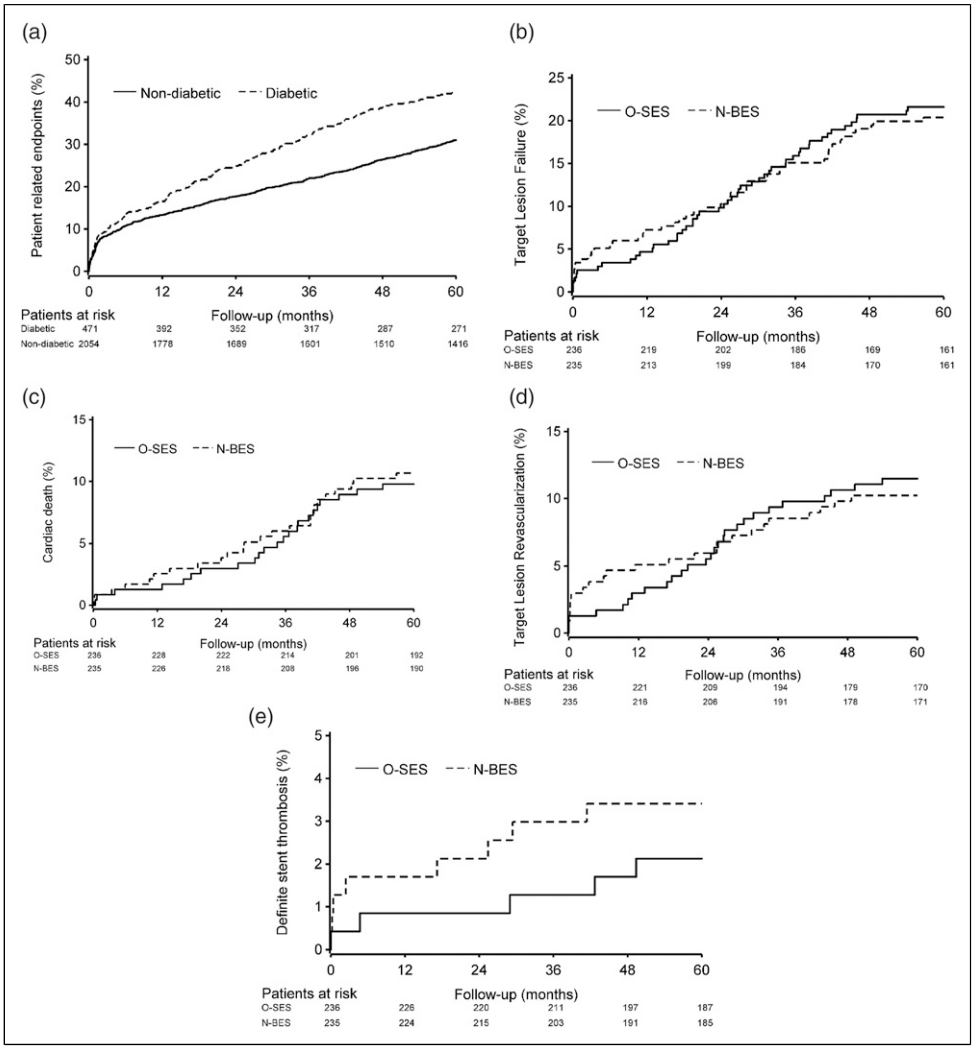

Figure 2. Time to event curves for endpoints at 5-year. (A): Patient related composite endpoint in patients with or without diabetes. (B): Target lesion failure in patients with diabetes treated with O-SES and N-BES. (C): Cardiac death in patient with diabetes treated with O-SES and N-BES. (D): Target lesion revascularization in patients with diabetes treated with O-SES and N-BES. E: Definite stent thrombosis in patients with diabetes treated with O-SES and N-BES.

MI as a part of TLF, which was not a part of the TLF s definition of our study. However, the BIOSCIENCE trial also reported a high incidence of 11.5% for definite and probable stent thrombosis, while our study found an incidence of 2.5% in the O-SES group. The difference in definite/probable stent thrombosis was mainly driven by a rather large difference in probable stent thrombosis. This difference was found at both the interval of 0-1 and 1-5 years. The target lesion revascularization was also higher in the BIOSCIENCE sub-study, reporting 18.2 % in the O-SES group, while the present study only reported 11.4 % after 5 years.

Patients with diabetes have an increased risk of adverse outcomes after PCI compared to patients without diabetes.[2] This effect is especially true for the long-term outcomes. Our study found a significantly increased burden of disease in patient with diabetes, with a patient related endpoint of 42.0% versus 31.0% in patients without diabetes. This difference was driven by all individual components of the endpoint. The BIOSCIENCE study (biodegradable polymer O-SES vs durable polymer EES) found a similar high patient related endpoint (41.4% vs 28.2%) in patients with diabetes compared to patients without diabetes. Similar to the present study, they did not find any difference between the two stent groups. In the present study, the patient related endpoint for patients with diabetes started to diverge already within the first year compared to patients without diabetes, and continued to increase throughout the 5 years. In the BIOSCIENCE study, their patient related endpoint was also significantly higher after 1 year, and persisted throughout the 5 years[8,21] These

Table 2. Outcomes after 5 years in patients with diabetes mellitus.

	O-SES, *n* (%)	N-BES, *n* (%)	RR, (95%CI)	*p*-value
Target lesion failure				
0-5	50 (21.2)	47 (20.0)	1.05 (0.70 - 1.58)	0.81
0-1	11 (4.7)	17 (7.2)	0.63 (0.29 - 1.36)	0.24
1-5	39 (17.8)	30 (14.1)	1.29 (0.80 - 2.08)	0.30
All-cause death				
0-5	43 (18.2)	44 (18.7)	0.96 (0.63 - 1.46)	0.85
0-1	7 (3.0)	9 (3.8)	0.78 (0.29 - 2.09)	0.62
1-5	36 (15.8)	35 (15.5)	1.01 (0.63 - 1.60)	0.98
Cardiac death				
0-5	23 (9.7)	25 (10.6)	0.90 (0.51 - 1.59)	0.73
0-1	3 (1.3)	6 (2.6)	0.50 (0.12 - 2.01)	0.33
1-5	20 (8.8)	19 (8.4)	1.03 (0.55 - 1.93)	0.93
Non-cardiac death				
0-5	20 (8.5)	19 (8.1)	1.03 (0.55 - 1.93)	0.91
0-1	4 (1.7)	3 (1.3)	1.33 (0.30 - 5.94)	0.71
1-5	16 (7.0)	16 (7.1)	0.98 (0.49 - 1.95)	0.95
MI not related to other than index				
0-5	14 (5.9)	12 (5.1)	1.15 (0.53 - 2.51)	0.72
0-1	3 (1.3)	7 (3.0)	0.42 (0.11 - 1.65)	0.22
1-5	11 (4.9)	5 (2.3)	2.17 (0.75 - 6.28)	0.15
MI				
0-5	24 (10.2)	23 (9.8)	1.03 (0.58 - 1.84)	0.92
0-1	4 (1.7)	10 (4.3)	0.40 (0.12 - 1.27)	0.12
1-5	20 (8.9)	13 (6.0)	1.52 (0.75 - 3.07)	0.24
Definite stent thrombosis				
0-5	5 (2.1)	8 (3.4)	0.61 (0.20 - 1.88)	0.39
0-1	2 (0.8)	4 (1.7)	0.50 (0.09 - 2.74)	0.42
1-5	3 (1.3)	4 (1.8)	0.73 (0.16 - 3.26)	0.68
Probable stent thrombosis				
0-5	1 (0.4)	1 (0.4)	0.98 (0.06 - 15.8)	0.99
0-1	1 (0.4)	1 (0.4)	1.00 (0.06 - 16.1)	1.0
1-5	0 (0.0)	0 (0.0)	-	
Possible stent thrombosis				
0-5	11 (4.7)	8 (3.4)	1.35 (0.55 - 3.35)	0.51
0-1	0 (0.0)	1 (0.4)	-	-
1-5	11 (4.8)	7 (3.1)	1.54 (0.60 - 3.96)	0.37
Definite or probable stent thrombosis				
0-5	6 (2.5)	9 (3.8)	0.65 (0.23 - 1.85)	0.42
0-1	3 (1.3)	5 (2.1)	0.60 (0.14 - 2.52)	0.48
1-5	3 (1.3)	4 (1.8)	0.73 (0.16 - 3.26)	0.68
Target vessel revascularization				
0-5	40 (16.9)	35 (14.9)	1.13 (0.71 - 1.80)	0.62
0-1	13 (5.5)	19 (8.1)	0.67 (0.33 - 1.37)	0.27
1-5	27 (12.6)	16 (7.7)	1.66 (0.89 - 3.11)	0.11
Target lesion revascularization				
0-5	27 (11.4)	24 (10.2)	1.11 (0.64 - 1.94)	0.71
0-1	7 (3.0)	12 (5.1)	0.57 (0.22 - 1.46)	0.24
1-5	20 (9.0)	12 (5.6)	1.65 (0.80 - 3.39)	0.17
Patient related endpoint[a]				
0-5	102 (43.2)	96 (40.9)	1.04 (0.78 - 1.40)	0.78
0-1	33 (14.0)	45 (19.1)	0.69 (0.43 - 1.10)	0.12
1-5	69 (34.2)	51 (26.8)	1.35 (0.93 - 1.95)	0.11

O-SES = sirolimus-eluting Orsiro stent, N-BES = biolimus-eluting Nobori stent, RR = Rate ratio, MI = myocardial infarction.
[a](All death, all MI or any revascularization).

results indicate that the increased complications seen in patients with diabetes start early after implantation of a stent and persist. In the present study the TLF accounted for approximately half of the patient related outcomes in patient with diabetes, while only accounting for around one third in patient without diabetes. This difference indicates that the increased burden of disease, seen in patients with diabetes, is associated with stent and vessel factors. Similarly, a higher event rate was found in the BIOSCIENCE study, in which two thirds of the patient related endpoint was to due TLF after 5 years[8]

PCI with DES plays an important role in the revascularization of patients with diabetes. However, surgical management of coronary artery disease is still a crucial part of the treatment. Several previous studies have found a benefit of surgical management compared to PCI in patients with diabetes, especially in patients with multi-vessel disease.[22,23] Therefore, in patients with diabetes and multi-vessel disease, CABG is recommended over complex PCI, after considering patient factors such as frailty and surgical risk.[3]

Limitations

This study, like the previous SORT OUT studies, used registry-based outcome detection. The Danish health care databases and registries are updated daily and detect events of sufficient severity for patients to seek medical attention. This could potentially underestimate the results of this study as lower detection rate of events in patients with none or few symptoms is possible compared to follow-up detection. However, this potential underestimation of events is likely to be low, and unlikely to affect differently in the two stent groups, limiting the effect on the results of this study. Another limitation is that the N-BES is no longer commercially available in several countries. However, there is still a large number of patients previously implanted with the N-BES whom may benefit from the knowledge generated in the present study. Finally, a limitation of this study is the lack of information on glycemic control and medical management. Glycemic control is an important prognostic factor of outcomes in diabetic patients, and may influence the results of the study. However, due to the randomization process it is unlikely to influence differently in the two study groups.

Conclusion

In patients with diabetes mellitus, 5-year outcomes were similar among patients treated with the biodegradable polymer O-SES or N-BES.

Declaration of conflicting interests

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References

1. Billinger M, Räber L, Hitz S, et al. Long-term clinical and angiographic outcomes of diabetic patients after revascularization with early generation drug-eluting stents. *Am Heart J* 2012; 163: 876–886. DOI: 10.1016/j.ahj.2012.02.014.
2. Marx N, Federici M, Schütt K, et al. ESC Guidelines for the management of cardiovascular disease in patients with diabetes: developed by the task force on the management of cardiovascular disease in patients with diabetes of the European Society of Cardiology (ESC). *Eur Heart J*. 2023; 44: 4043–4140. doi:10.1093/eurheartj/ehad192.
3. Palmerini T, Benedetto U, Biondi-Zoccai G, et al. Long-term safety of drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *J Am Coll Cardiol* 2015; 65: 2496–2507. DOI: 10.1016/j.jacc.2015.04.017.
4. Jensen LO, Thayssen P, Maeng M, et al. Three-year outcomes after revascularization with everolimus- and sirolimus-eluting stents from the SORT OUT IV trial. *JACC Cardiovasc Interv* 2014; 7: 840–848. DOI: 10.1016/j.jcin.2014.02.014.
5. Smits PC, Vlachojannis GJ, McFadden EP, et al. Final 5-year follow-up of a randomized controlled trial of everolimus- and paclitaxel-eluting stents for coronary revascularization in daily practice: the COMPARE trial (A trial of everolimus-eluting stents and paclitaxel stents for coronary

revascularization in daily practice). *JACC Cardiovasc Interv* 2015; 8: 1157–1165. DOI: 10.1016/j.jcin.2015.03.028.
6. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol* 2006; 48: 193–202. DOI: 10.1016/j.jacc.2006.03.042.
7. Vlachojannis GJ, Smits PC, Hofma SH, et al. Long-term clinical outcomes of biodegradable polymer biolimus-eluting stents versus durable polymer everolimus-eluting stents in patients with coronary artery disease: three-year follow-up of the COMPARE II (Abluminal biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent) trial. *EuroIntervention* 2015; 11: 272–279. DOI: 10.4244/eijv11i3a53.
8. Iglesias JF, Heg D, Roffi M, et al. Five-year outcomes in patients with diabetes mellitus treated with biodegradable polymer sirolimus-eluting stents versus durable polymer everolimus-eluting stents. *J Am Heart Assoc* 2019; 8: e013607. DOI: 10.1161/jaha.119.013607.
9. Ellert J, Christiansen EH, Maeng M, et al. Impact of diabetes on clinical outcomes after revascularization with sirolimus-eluting and biolimus-eluting stents with biodegradable polymer from the SORT OUT VII trial. *Cathet Cardiovasc Interv* 2019; 93: 567–573. DOI: 10.1002/ccd.27891.
10. Hansen KN, Jensen LO, Maeng M, et al. Five-year clinical outcome of the biodegradable polymer ultrathin strut sirolimus-eluting stent compared to the biodegradable polymer biolimus-eluting stent in patients treated with percutaneous coronary intervention: from the SORT OUT VII trial. *Circ Cardiovasc Interv* 2023; 16: e012332. DOI: 10.1161/circinterventions.122.012332.
11. Jensen LO, Thayssen P, Maeng M, et al. Randomized comparison of a biodegradable polymer ultrathin strut sirolimus-eluting stent with a biodegradable polymer biolimus-eluting stent in patients treated with percutaneous coronary intervention: the SORT OUT VII trial. *Circ Cardiovasc Interv.* 2016; 9: e003610. doi:10.1161/circinterventions.115.003610.
12. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007; 115: 2344–2351. DOI: 10.1161/circulationaha.106.685313.
13. de Waha A, Stefanini GG, King LA, et al. Long-term outcomes of biodegradable polymer versus durable polymer drug-eluting stents in patients with diabetes a pooled analysis of individual patient data from 3 randomized trials. *Int J Cardiol* 2013; 168: 5162–5166. DOI: 10.1016/j.ijcard.2013.07.263.
14. Kolandaivelu K, Swaminathan R, Gibson WJ, et al. Stent thrombogenicity early in high-risk interventional settings is driven by stent design and deployment and protected by polymer-drug coatings. *Circulation* 2011; 123: 1400–1409. DOI: 10.1161/circulationaha.110.003210.
15. Bangalore S, Kumar S, Fusaro M, et al. Outcomes with various drug eluting or bare metal stents in patients with diabetes mellitus: mixed treatment comparison analysis of 22,844 patient years of follow-up from randomised trials. *BMJ* 2012; 345: e5170. DOI: 10.1136/bmj.e5170.
16. Paradies V, Vlachojannis GJ, Royaards KJ, et al. Abluminal biodegradable polymer biolimus-eluting versus durable polymer everolimus-eluting stent in patients with diabetes mellitus: 5 years follow-up from the COMPARE II trial. *Int J Cardiol* 2019; 290: 40–44. DOI: 10.1016/j.ijcard.2019.04.054.
17. Sprimont P, Pierard S, Vanoverschelde JL, et al. Efficacy and safety of biodegradable polymer biolimus A9-eluting stent versus durable polymer everolimus-eluting stent in diabetic patients: a prospective non-randomized single-centre long-term comparison. *Acta Cardiol* 2014; 69: 523–531. DOI: 10.1080/ac.69.5.3044879.
18. Waksman R, Shlofmitz E, Windecker S, et al. Efficacy and safety of ultrathin, bioresorbable-polymer sirolimus-eluting stents versus thin, durable-polymer everolimus-eluting stents for coronary revascularization of patients with diabetes mellitus. *Am J Cardiol* 2019; 124: 1020-1026. DOI: 10.1016/j.amjcard.2019.06.021.
19. Lefèvre T, Haude M, Neumann FJ, et al. Comparison of a novel biodegradable polymer sirolimus-eluting stent with a durable polymer everolimus-eluting stent: 5-year outcomes of the randomized BIOFLOW-II trial. *JACC Cardiovasc Interv* 2018; 11: 995–1002. DOI: 10.1016/j.jcin.2018.04.014.
20. Waltenberger J, Brachmann J, van der Heyden J, et al. Five-year results of the bioflow-III registry: real-world experience with a biodegradable polymer sirolimus-eluting stent. *Cardiovasc Revascularization Med* 2020; 21: 63–69. DOI: 10.1016/j.carrev.2019.03.004.
21. Franzone A, Pilgrim T, Heg D, et al. Clinical outcomes according to diabetic status in patients treated with biodegradable polymer sirolimus-eluting stents versus durable polymer everolimus-eluting stents: prespecified subgroup analysis of the BIOSCIENCE trial. *Circ Cardiovasc Interv.* 2015; 8: e002319. doi:10.1161/circinterventions.114.002319.
22. Farkouh ME, Domanski M, Dangas GD, et al. Long-term survival following multivessel revascularization in patients with diabetes: the FREEDOM follow-on study. *J Am Coll Cardiol* 2019; 73: 629–638. DOI: 10.1016/j.jacc.2018.11.001.
23. Kappetein AP, Head SJ, Morice MC, et al. Treatment of complex coronary artery disease in patients with diabetes: 5-year results comparing outcomes of bypass surgery and percutaneous coronary intervention in the SYNTAX trial. *Eur J Cardio Thorac Surg* 2013; 43: 1006–1013. DOI: 10.1093/ejcts/ezt017.