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Long-Term Outcomes after Coronary Intervention with Biodegradable Polymer Stents in Patients with Acute Coronary Syndromes

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Abstract

Background: Patients with acute coronary syndromes (ACS) may have worse outcomes after percutaneous coronary intervention compared to patients without ACS.

Aims: To compare 5-year efficacy and safety outcomes in patients with and without ACS treated with biodegradable polymers, the ultrathin strut sirolimus-eluting Orsiro stent (O-SES) or the biolimus-eluting Nobori stent (N-BES).

Methods: The SORT OUT VII is a randomised trial comparing O-SES and N-BES in an all-comer setting. Of 2,525 patients, 1,329 (53%) patients had ACS and 1,196 (47%) patients were without ACS. Endpoints were target lesion failure (TLF) (a composite of cardiac death, target lesion myocardial infarction or target lesion revascularisation (TLR)) and definite stent thrombosis within 5 years.

Results: At 5-year follow up, TLF did not differ significantly between patients with and without ACS (12.3% vs. 13.2%; rate ratio (RR) 1.00; 95% confidence interval (CI): 0.70-1.44), whereas risk of definite stent thrombosis was increased in patients with ACS (2.3% vs. 1.3; RR 2.01 (95% CI: 1.01-3.98)).

In patients with ACS, rate of TLF was similar between O-SES and N-BES (12.4 % vs. 12.3%; RR 1.02; 95% CI: 0.74-1.40). The reduced risk of definite stent thrombosis in O-SES treated ACS patients within the first year (0.2% vs. 1.6%; RR 0.12; 95% CI: 0.02-0.93) was not maintained after 5 years (1.8% vs. 2.7%; RR 0.77; 95% CI: 0.37-1.63).

Conclusion: Patients with ACS had increased risk of ST regardless of stent type used. Long-term outcomes were similar for ACS patients treated with O-SES or N-BES at 5 years.

Keywords: biodegradable polymers, sirolimus, biolimus, coronary stents, myocardial infarction, stent thrombosis, target lesion failure, target lesion revascularisation

Condensed abstract

Patients with acute coronary syndromes (ACS) may have worse outcomes after percutaneous coronary intervention compared to patients without ACS. The present substudy from SORT OUT VII trial compared 5-year efficacy and safety outcomes in 1,329 patients with ACS treated with biodegradable polymers, the ultrathin strut sirolimus-eluting Orsiro stent (O-SES) or the biolimus-eluting Nobori stent (N-BES). At 5-year follow up, risk of definite stent thrombosis was twice as high in patients with ACS compared to patients without ACS. Long-term outcomes were similar for ACS patients treated with O-SES or N-BES at 5 years.

Abbreviations

ACS: acute coronary syndrome

DES: drug-eluting stent

LST: late stent thrombosis

MI: myocardial infarction

N-NES: biodegradable polymer Biolimus-eluting Nobori stent

O-SES: biodegradable polymer ultrathin strut Orsiro Sirolimus-eluting stent

PCI: percutaneous coronary intervention

RR: rate ratio

SORT OUT: Scandinavian Organisation for Randomised Trials with Clinical Outcome

ST: stent thrombosis

TLF: target lesion failure

TLR: target lesion revascularisation

TVR: target vessel revascularisation

VLST: very late stent thrombosis

Introduction

Patients with acute coronary syndromes (ACS) have increased risk of cardiac death or recurrent myocardial infarction (MI) after percutaneous coronary intervention (PCI).(1, 2) PCI in patients with ACS may be at higher risk of stent failure due to plaque characteristics, thrombus burden and persistent inflammation; all three components that contribute to delayed arterial healing, vessel remodelling, incomplete stent strut coverage and stent malapposition.(3-6)

In order to improve clinical outcomes, drug-eluting stents (DES) with release of an antiproliferative drug from a polymer surface were designed to reduce risk of restenosis.(7) However, the durable polymer has also been suggested as a trigger for chronic vessel inflammation, resulting in impaired stent strut endothelialisation and delayed arterial healing. Both mechanisms may contribute to increased risk of late and very late stent thrombosis (VLST).(8)

To improve safety of DES and decrease risk of inflammation due to durable polymers, DES with a biodegradable polymer (BP-DES) were designed, and meta-analysis shows that these BP-DES are significantly more effective than bare metal stents (BMS) and safer than first-generation DES.(9, 10) Theoretically, BP-DES would

decrease risk of inflammation and late stent thrombosis (LST), since it leaves behind a BMS after complete drug elution and polymer degradation. However, long-term follow-up studies are needed to assess the safety of newer stents.

In the SORT OUT (Scandinavian Organisation for Randomised Trials with clinical Outcome) VII trial the biodegradable ultrathin strut sirolimus-eluting stent (Orsiro; Biotronik, Bülach, Switzerland) (O-SES) was compared to the biodegradable polymer biolimus-eluting stent (Nobori, Terumo, Tokyo, Japan) (N-BES) regarding target lesion failure (TLF).(11-13) The present study aimed to assess the long-term outcomes for O-SES and N-BES in an all-comer patient population with particular attention to the ACS subgroup.

Methods

Study Design

The SORT OUT VII was a registry-based, randomised, prospective, two-arm, multicenter non-inferiority trial comparing O-SES and N-BES in an all-comer setting in treating atherosclerotic coronary artery lesions. A detailed description of the study has previously been reported in the main publications.(11, 12) Between November 2012 and February 2014, eligible patients were included, if they were ≥ 18 years old; had ACS or stable coronary artery disease and a lesion with ≥ 50% diameter stenosis, which required implantation of a DES. In case of multiple lesions, the allocated stent had to be used in all lesions. Exclusions criteria were life expectancy of less than a year; allergy to aspirin, clopidogrel, sirolimus or everolimus drug; participation in other randomised trials; or inability to provide written informed consent. Block randomisation was used to receive either O-SES or N-BES. All patients signed the

informed consent before randomisation. The trial is registered on Clinicaltrials.gov, number NCT01879358.

Outcome Measures

The present long-term outcome was target lesion failure (TLF), which was a composite of cardiac death, target lesion MI or clinically indicated target lesion revascularisation (TLR) with PCI or coronary artery bypass grafting (CABG). Individual components of the primary endpoint included the secondary endpoints: cardiac and all-cause death, MI, clinically indicated TLR, target vessel revascularisation (TVR), probable, possible or definite ST according to the Academic Research Consortium(14).

Clinical Event Detection

Clinically driven event detection without scheduled follow up was planned. Data on mortality, hospital admissions, coronary angiography, repeat PCI and coronary artery bypass graft (CABG) were obtained for all randomly allocated patients from the following national Danish administrative and healthcare registries: the Civil Registration System; the Western Denmark Heart Registry; the Danish National Registry of Patients, which maintain records on all hospitalisations in Denmark; and the Danish Registry of Causes of Death. The methodology has been used in previous SORT OUT publications.(11, 15) An independent event committee reviewed all end points and source documents to adjudicate causes of death, re-hospitalisation and diagnosis of MI. Two dedicated PCI operators at each center reviewed the cine films to clarify ST and TVR (either PCI or CABG).

Statistical analyses

Data on baseline characteristics are presented as mean±SD or median and interquartile range for continuous data. Continuous variables were compared using two-sample Student t test (Cochran test for cases of unequal variance) or Mann-Whitney *U* test, depending on whether the data was normally distributed. The x^2 test was used to compare distribution of categorical variables. In analyses of every end point, follow up continued until the date of an end point, death, emigration or 60 months after stent implantation, whichever came first. We constructed cumulative incidence curves, accounting for the competing risk of death. Patients who received N-BES were used as a reference group. Rate ratios (RR) were calculated for outcomes at one and 5-year follow up. A two-sided p-value of < 0.05 was considered statistically significant. In the comparison between ACS and non-ACS patients, the patient groups were not based on randomisation. Hence, we adjusted for gender, diabetes, family history of coronary artery disease, smoking, hypertension, previous myocardial infarction, previous CABG, use of glycoprotein IIb/IIIa inhibitor, hypercholesterolemia, stent delivery failure, number of stents used, reference vessel size, bivalirudin use, procedure time, age 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 standardised differences of covariates were less than 0.1. Stent delivery failure, age and family history were not balanced between the two patient groups after application of the weights. Therefore, these covariates were incorporated in a double adjustment approach as regressors in the final model.(16) For comparisons across stent types a similar approach (except double adjustment) was applied in the analysis to reduce any residual confounding that may appear despite randomisation. All analyses were conducted using SAS version 9.4 software.

Results

Patient and procedure characteristics

Of 2,525 randomised patients, 1,329 (52%) patients had ACS and were treated with O-SES (n=655) or N-BES (n=674), and 1,196 (48%) patients without ACS were treated with O-SES (n=606) and N-BES (n=590). Four patients were lost to follow-up due to emigration, and complete follow-up was available in 2,521 patients (99.8%).

Compared to patients without ACS, patients with ACS were younger (64.4 ±11.4 vs. 66.6 ± 9.9, p=0.0001), more often men (76.7% vs. 73.2%, p=0.042), current smokers (40.0% vs. 20.6%, p<0.00001), and had lower rates of diabetes mellitus (16.6% vs. 21.0%, p=0.0043), hypertension (47.3% vs. 68.1%, p<0.00001), hypercholesterolemia (40.9% vs. 75.1%, p<0.00001), previous MI (14.2% vs. 21.4%, p<0.00001) and previous revascularisation with PCI (14.0% vs. 26.0%, p<0.00001) or CABG (4.8% vs. 11.2%, p<0.00001). Data are presented in Supplemental table 1.

Baseline clinical and procedure characteristics of enrolled patients with and without ACS treated with either O-SES or N-BES are summarised in **Table 1 and 2**. The subgroups were well balanced with the exception of patients with ACS treated with N-BES, who were younger (63.7±11.5 vs. 65.1±11.3, p=0.017) and more frequently smokers compared to patients with ACS treated with O-SES.

Clinical outcomes

At 5-year follow up, TLF did not differ significantly between patients with and without ACS (12.3% vs. 13.2%; rate ratio (RR) 1.00; 95% confidence interval (CI): 0.70-1.44). Definite ST occurred more frequently in patients with ACS (2.3% vs. 1.3; RR 2.01 (95% CI: 1.01-3.98)) compared to patients without ACS. Cardiac death and

target lesion MI did not differ significantly among patients with ACS and without ACS. (**Figure 1-2)**

In patients with ACS, TLF was similar in the O-SES and the N-BES groups at 5-year follow up (12.4% vs. 12.3%; RR 1.02 (95% CI: 0.74-1.40). **(Table 3)** There were no statistically significant differences between the two stent groups regarding cardiac death, target lesion MI and TLR. Definite ST occurred less often in ACS patients treated with O-SES compared to N-BES within the first year (0.2% vs. 1.6%, p=0.043), but this significant difference was not maintained up to 5 years. **(Table 3 and Figure 1).**

In patients without ACS, TLF at 5 year follow up was similar between O-SES and N-BES group (12.4% vs. 14.1%; RR 0.80 (95% CI: 0.58-1.11). Definite ST occurred with same rates at 5 year follow up in patients without ACS treated with O-SES or N-BES (1.2% vs. 1.4%; RR 0.81 (0.29-2.27). Cardiac death, target lesion MI and TLR did not differ significantly between the two stent groups.

Discussion

The ACS substudy of the SORT OUT VII trial focused on safety and efficacy of biodegradable polymer O-SES and N-BES, and found similar rates of TLF at 5-year follow up in patients with ACS. Patients with ACS had two-fold risk of definite ST compared to patients without ACS, but there were no significant differences regarding cardiac death, target lesion MI and TLR. On stent level, patients with ACS treated with O-SES or N-BES had similar rates of TLF.

Despite improvement in efficacy and safety of DES, patients with ACS still have a higher incidence of adverse clinical outcomes after PCI compared to patients without ACS. Factors such as altered thrombotic and inflammatory environment inside the

culprit lesion might delay the vessel healing at culprit sites contributing to higher risk for stent-related adverse events such as ST in patients with ACS.(17-19) DES with biodegradable polymers have been shown to improve device- and patient-oriented clinical outcomes up to 5 years of follow-up compared to BMS and early generation polymer-based DES.(20, 21) A meta-analysis comparing biodegradable polymer DES with durable polymer DES concluded, that biodegradable polymer DES might be more favorable, when treating patients with ACS.(9, 22)

The long-term clinical benefits of complete polymer degradation has been assessed in a 5-year report from the "Ultrathin Strut Biodegradable Polymer Sirolimus-Eluting Stent Versus Durable Polymer Everolimus-Eluting Stent for Percutaneous Coronary Revascularisation" (BIOSCIENCE) trial(23) in patients with ACS. TLF in patients with ACS treated with O-SES was 16.9% compared to 12.4% in current study at five-year follow up, which was mainly explained by a higher rate of TLR (8.9% vs. 5.9%). Rates of cardiac death (8% vs. 6%) and target lesion MI (5.2% vs. 4.6%) were comparable to the rates in in the current study.

Definite ST at 5-year follow-up among patients with ACS treated with O-SES was1.4% in the BIOSCIENCE study, 1.5% in the "Comparison of Biodegradable Polymer and Durable Polymer Drug-Eluting Stents in an All Comers Population" (BIO-RESORT) (24) and 1.8% in the current study. In all three studies, definite ST mainly occurred as VLST, and this might be due to slow degradation of polymer in the O-SES group (12-24 months) almost acting like DES with durable polymer, triggering a chronic inflammatory reaction in the vessel wall.(23) O-SES has one of the thinnest stent struts available in clinical use, and hence less thrombogenic and may reduce the risk of early stent thrombosis. This inflammation response to the slowly degradation of the polymer may potentially cause delayed arterial healing with

incomplete re-endotheliasation, neoatherosclerosis, hypersensitivity reaction and most importantly positive vessel remodelling, resulting in acquired stent malapposition and increased risk of ST. (25) On the other hand, rates of definite ST within the first year were similar to durable polymer EES in several studies ranging between 1.4% in BIOSCIENCE (23) and 1.0% in BIOSTEMI (26), while the rate of ST in current study was incomprehensibly low at 0.2%.

While biodegradable polymer O-SES had similar clinical outcomes compared to the second-generation durable polymer Everolimus-eluting stent (EES), and showed promising results in patients with ACS, N-BES has in several trials been associated with higher risk of early definite ST. (27-30). In the current study, definite ST at 5-year follow up in ACS patients treated with N-BES was 2.7%, and mainly occurred within the first year (1.6%)(11), while VLST was similar for the N-BES and O-SES groups. At 5-year follow up in the "Comparison of Biolimus Eluted From an Erodible Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction" (COMFORTABLE AMI)(21) definite ST was 2.2% and VLST 1.3% in N-BES, which is in accordance with the current study. VLST occurred with similar rate in the BMS group (1.6%), supporting the theory of complete polymer degradation beyond 9-12 month in N-BES.(21)

In the "Biolimus-eluting biodegradable polymer-coated stent versus durable polymer-coated sirolimus-eluting stent in unselected patients receiving percutaneous coronary intervention" (SORT OUT V)(31) with half of the study population presenting with ACS, definite ST at 5-year follow up was 1.9% in the N-BES group, while rates of LST and VLST was 0.8% and 1.1% respectively. The "Abluminal Biodegradable Polymer Biolimus-Eluting Stent Versus Durable Polymer Everolimus-Eluting Stent" (COMPARE II) (27, 28) had similar rates of LST (0.8%) and VLST (0.8%) in N-BES

group. In both studies, the N-BES had higher rates of LST as in comparison to SES and EES.

It is important to highlight, that ST in ACS patients treated with N-BES mainly occurred within the first year, and that there were no differences regarding rates of ST in patients without ACS treated with N-BES. The mechanism of higher risk of early and late ST in ACS patients receiving N-BES may be related to factors such as: 1) thicker stent struts (71-91 µm in O-SES vs. 120 µm in N-BES); 2) rapid polymer degradation (12-24 months in O-SES and 6-9 months in N-BES); 3) rapid drug release (12 weeks in O-SES vs. 4 weeks in N-BES); 4) an ultra-thin non-degradable parylene-C coating between the stent struts and polymer, which assures polymer attachment to the stent struts; 5) thrombotic and inflammatory environment in culprit lesions. It is therefore most likely that the inflammatory thrombotic environment in culprit lesions of ACS patients along with the design of N-BES contributed to the higher risk of ST compared to O-SES. With low risk of ST in newer DES in general, larger studies and meta-analysis including patients with ACS treated with N-BES should be performed in order to make a recommendation for the role of N-BES in routine clinical practise, but caution needs to be exercised, when using N-BES in patients with ACS. The N-BES has been used in many patients worldwide, which makes long-term follow up relevant. Both in the present study and in previous SORT OUT study (32) we have shown, that the traditional 1-year primary endpoint assessment therefore might be insufficient to predict 5-year clinical outcomes in patients treated with coronary DES implantation. A substudy from the "Limus Eluted From A Durable Versus ERodable Stent Coating" LEADERS trial(22) compared biodegradable polymer Biomatrix Flex biolimus-eluting stent with SES in patients with STEMI and NSTEMI. The BioMatrix Flex has similarities to the N-BES (same

stainless steel alloy, same strut thickness and coated with biodegradable polymer, which elutes Biolimus). At five-year follow up the rate of definite ST was 4.3% in patients treated with BioMatrix Flex stent (mainly occurring as early ST), while the rate in the present study was 2.7% in patients with ACS treated with N-BES. The high percentage of ST in LEADERS trial might be due to only two-third of patients were on dual antiplatelet therapy the first year, which comprised aspirin and clopidogrel.

Despite improvements with thinner-strut stent platforms and biodegradable polymers, long-term adverse clinical outcomes such as ST continues to occur with similar rates as in patients treated with the durable polymer EES. Even though biodegradable polymer DES are designed to reduce inflammation and promote faster endothelialisation, patients with ACS are susceptible to thrombosis and at a higher risk of short and long-term adverse events.

Limitations

The SORT OUT trials use a register-based outcome without clinical follow-up, and even though Danish healthcare databases capture events of sufficient severity, the event rate might be underestimated compared to rates of events registered by a dedicated trial staff. The SORT VII was powered to compare O-SES or N-BES in an all-comers undergoing PCI at one year of follow-up. However, it is important to report long-term follow-up of biodegradable polymer drug-eluting stent in particular in ACS patients.

Conclusion

Patients with ACS had increased risk of ST regardless of stent type used. Long-term outcomes were similar for ACS patients treated with O-SES or N-BES at 5 years.

Patients with ACS treated with N-BES had higher risk of ST within the first year, but the difference did not maintain at 5 years.

Impact on daily practice

Biodegradable polymer drug-eluting stents is thought to be more favourable, when treating patients with acute coronary syndromes, compared to durable polymer drug-eluting stents. The study provides clinical data on five-year follow-up in patients with and without acute coronary syndromes treated with the biodegradable polymer ultrathin strut sirolimus-eluting stent and compared to the biodegradable polymer biolimus-eluting stent, and shows comparable clinical outcomes regarding target lesion failure with absence of definite stent thrombosis. Patients with ACS treated with biodegradable polymer biolimus-eluting stent had higher risk of stent thrombosis the first year, but the difference was not maintained after 5 years. Caution needs to be exercised, when using N-BES in patients with ACS. Further larger randomised studies are needed to clarify the impact of acute coronary syndromes on safety and efficacy of biodegradable polymer drug-eluting stent.

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Figure legends

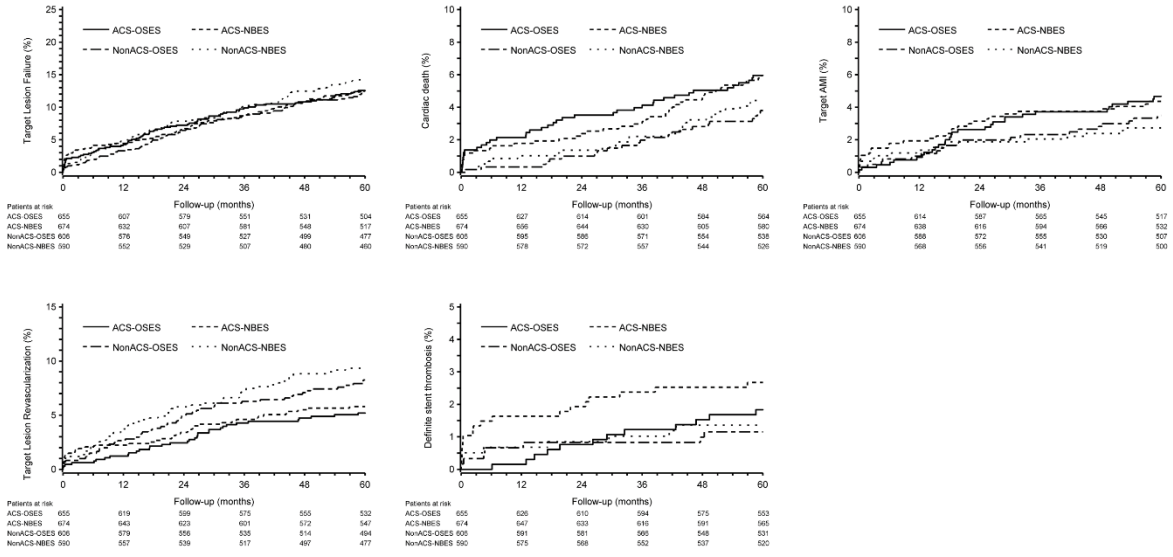

Figure 1. **Cumulative incidence of end points.** Time-to-event curves for clinical outcomes in patients with acute coronary syndromes (ACS) vs. without ACS treated with sirolimus-eluting Orsiro stent (O-SES) or biolimus-eluting Nobori stent (N-

BES). Target lesion failure is a composite of cardiac death, target lesion myocardial infarction, target lesion revascularisation.

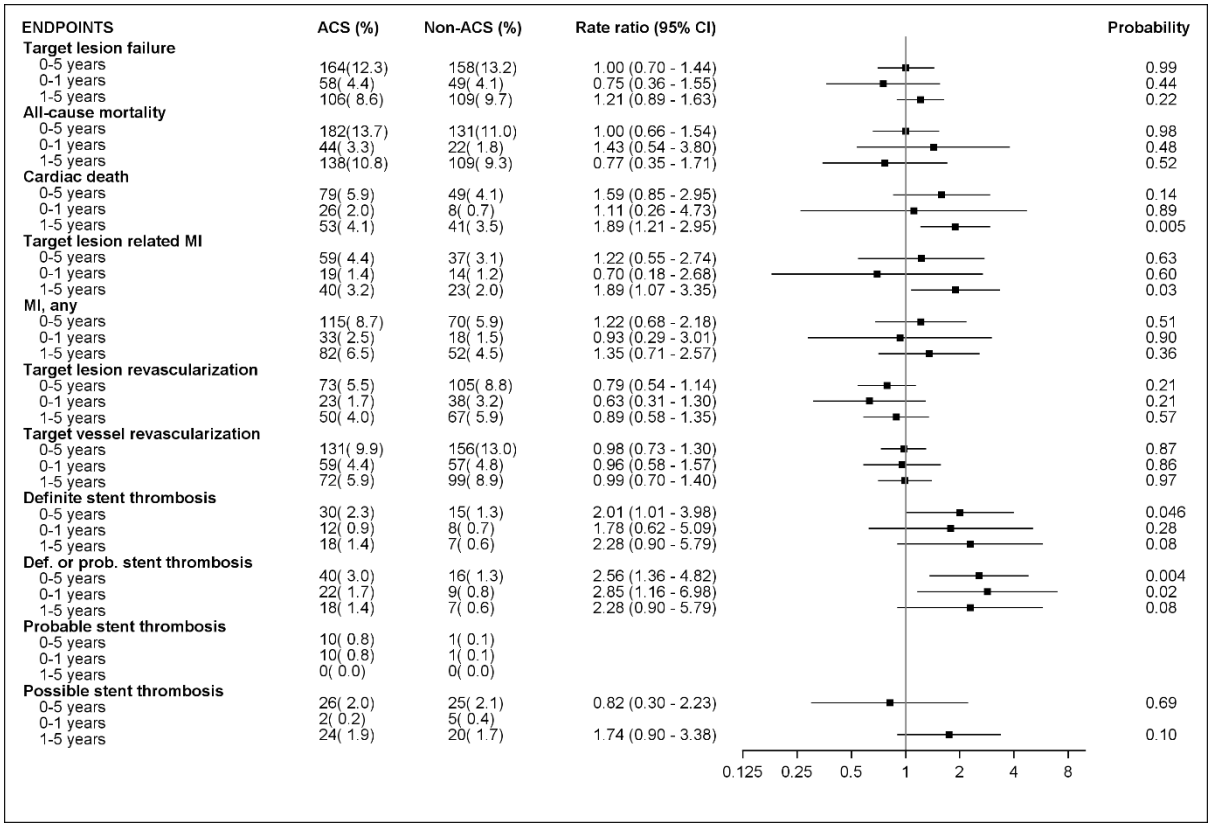

Figure 2. **Five-year clinical outcomes in randomised patients with and without acute coronary syndromes.** Forest plot of pre-specified subgroup analysis for the primary endpoints at 5 year-follow up in patients with and without acute coronary syndromes (ACS) treated with with sirolimus-eluting Orsiro stent (O-SES) or biolimus-eluting Nobori stent (N-BES). Values are presented as the number of patients (%). CI: confidence interval, MI: myocardial infarction.

Table 1 - Baseline patient characteristics

	ACS			Non-ACS			p value
	N-BES (n=674)	O-SES (n=655)	p-value	N-BES (n=590)	O-SES (n=606)	p-value	ACS versus non-ACS

Age, mean (SD), y	63.7 ± 11.5	65.1 ± 11.3	0.017	66.1±9.8	67.1±10.0	0.093	0.0001
Male gender, (%)	525 (77.9)	495 (75.6)	0.32	426 (72.2)	450 (74.3)	0.42	0.042
Family history of coronary artery disease	274 (44.5)	272 (45.0)	0.85	296 (53.8)	294 (53.9)	0.97	0.00001
Diabetes mellitus, (%)	114 (16.9)	106 (16.2)	0.72	121 (20.5)	130 (21.5)	0.69	0.0043
Arterial hypertension, (%)	302 (45.8)	310 (48.8)	0.28	397 (68.3)	403 (68)	0.89	<0.00001
Hypercholesterolemia, (%)	270 (40.8)	262 (41.1)	0.92	436 (74.7)	449 (75.5)	0.75	< 0.00001
Current smoker, (%)	282 (42.9)	233 (36.9)	0.028	117 (20.5)	122 (20.7)	0.91	< 0.00001
Body mass index ≥ 25 (kg/m^2)	439 (67.7)	429 (68.1)	0.89	401 (69.5)	418 (71.8)	0.38	0.14
Previous myocardial infarction, (%)	103 (15.5)	83 (12.8)	0.17	119 (20.4)	132 (22.5)	0.38	< 0.00001
Previous percutaneous coronary intervention, (%)	102 (15.2)	83 (12.8)	0.20	154 (26.2)	154 (25.8)	0.86	< 0.00001
Previous coronary artery bypass grafting, (%)	32 (4.8)	31 (4.8)	0.98	64 (10.9)	69 (11.5)	0.74	< 0.00001
Comorbidity index score 0 1-2 ≥ 3	 439 (65.1) 183 (27.2) 52 (7.7)	 424 (64.7) 174 (26.6) 57 (8.7)	0.80	 324 (54.9) 205 (34.7) 61 (10.3)	 319 (52.6) 224 (37.0) 63 (10.4)	0.71	< 0.00001

Data are presented as mean ± standard deviation or number of patients (%).

ACS = Acute Coronary Syndrome; N-BES = biolimus-eluting Nobori stent; O-SES = sirolimus-eluting Orsiro stent

Table 2 - Baseline lesion and procedure characteristics

	ACS			Non-ACS			p Value
	N-BES (n= 820)	O-SES (n=800)	p-value	N-BES (n=768)	O-SES (n=790)	p-value	ACS versus non-ACS
Treated coronary artery Left main artery Left anterior descending artery Left circumflex artery Right coronary artery Saphenous vein graft	6 (0.7) 348 (42.4) 181 (22.1) 278 (33.9) 7 (0.9)	4 (0.5) 347 (43.4) 166 (20.8) 272 (34.0) 11 (1.4)	0.78	6 (0.8) 324 (42.2) 168 (21.9) 258 (33.6) 12 (1.6)	14 (1.8) 339 (42.9) 171 (21.8) 254 (32.2) 11 (1.4)	0.50	0.30
Lesion type A B1 B2 C	98 (12.0) 271 (33.0) 259 (31.6) 192 (23.4)	89 (11.1) 285 (35.6) 230 (28.8) 196 (24.5)	0.51	105 (13.7) 278 (36.2) 234 (30.5) 151 (19.7)	128 (16.2) 260 (32.9) 240 (30.4) 162 (20.5)	0.39	0.0062
Chronic total occlusion lesions	12 (1.5)	11 (1.4)	0.86	53 (7.1)	51 (6.6)	0.74	<0.00001
Bifurcation lesions	101 (12.5)	102 (12.8)	0.86	97 (12.9)	90 (11.7)	0.47	0.76
No. of lesions treated per patient 1 > 1	553 (82.0) 121 (18.0)	529 (80.8) 126 (19.2)	0.55	442 (74.9) 148 (25.1)	449 (74.1) 157 (25.9)	0.74	0.00003
No. of stents used per patient 1 > 1	464 (68.8) 203 (30.1)	449 (68.5) 200 (30.5)	0.96	382 (64.7) 204 (34.6)	380 (62.7) 222 (36.6)	0.76	0.015
Visual estimation of lesion length (mm)	20.1 ± 13.7	19.9 ± 12.8	0.81	21.8±15.2	22.1±16.2	0.71	0.0007
Lesion length > 18 mm	263 (32.1)	232 (29.1)	0.19	267 (34.8)	251 (31.8)	0.21	0.11
Reference vessel size (mm)	3.2±0.5	3.2±0.5	0.23	3.1±0.5	3.1±0.6	0.035	<0.00001
Stent length (mm)	24.8 ± 16.2	24.0 ± 13.6	0.37	26.6±17.0	26.5±17.3	0.88	0.001
Direct stenting	119 (14.9)	100 (13.0)	0.28	92 (12.4)	121 (15.9)	0.056	0.89
Maximum pressure (atm)	15.9±4.2	15.8±4.1	0.41	15.9±4.1	16.0±3.9	0.42	0.49
Stent delivery failure	18 (2.2)	16 (2.0)	0.78	14 (1.8)	10 (1.3)	0.37	0.24
Flouro time (minutes)	7.2 ± 7.0	7.4 ± 7.2	0.64	9.4±9.2	9.9±9.3	0.27	0.0001
Contrast volume used (mL)	89.8 ± 63.1	88.5 ± 58.0	0.69	109.3±79.6	112.2±76.5	0.53	0.0001
Procedure time (minutes)	23.7 ± 18.4	24.3 ± 17.1	0.55	28.2±21.8	30.1±37.4	0.28	0.0001

Glycoprotein IIb/IIIa inhibitor	22 (3.3)	21 (3.2)	0.95	10 (1.7)	13 (2.1)	0.57	0.039
Bivalirudin	256 (40)	246 (39.6)	0.89	4 (0.8)	7 (1.3)	0.40	<0.00001

Data are presented as mean ± standard deviation or number of lesions (%).

ACS = Acute Coronary Syndrome; N-BES = biolimus-eluting Nobori stent; O-SES = sirolimus-eluting Orsiro stent

Table 3 - 5-year clinical outcomes in patients with and without ACS treated with O-SES or N-BES.

	ACS (n=1,329)				**Non-ACS (n=1,196)**			
Outcomes	**O-SES (n=655)**	**N-BES (n=674)**	**RR (95% CI)**	**P value**	**O-SES (n=606)**	**N-BES (n=590)**	**RR (95% CI)**	**P value**
Target lesion failure								
0-5 years	81 (12.4)	83 (12.3)	1.02 (0.74-1.40)	0.92	75 (12.4)	83 (14.1)	0.80 (0.58-1.11)	0.19
0-1 year	28 (4.3)	30 (4.5)	1.01 (0.60-1.72)	0.96	20 (3.3)	29 (4.9)	0.61 (0.33-1.11)	0.10
1-5 years	53 (8.7)	53 (8.4)	1.02 (0.69-1.50)	0.93	55 (9.5)	54 (9.8)	0.92 (0.63-1.35)	0.67
All-cause mortality								
0-5 years	90 (13.7)	92 (13.6)	0.94 (0.70-1.27)	0.69	68 (11.2)	63 (10.7)	0.94 (0.66-1.33)	0.72
0-1 year	27 (4.1)	17 (2.5)	1.60 (0.86-2.97)	0.14	11 (1.8)	11 (1.9)	0.90 (0.38-2.09)	0.80

1-5 years	63 (10.0)	75 (11.4)	0.79 (0.56-1.11)	0.17	57 (9.6)	52 (9.0)	0.95 (0.65-1.39)	0.78
Cardiac death								
0-5 years	39 (6.0)	40 (5.9)	0.97 (0.62-1.53)	0.91	23 (3.8)	26 (4.4)	0.79 (0.45-1.39)	0.41
0-1 year	14 (2.1)	12 (1.8)	1.24 (0.56-2.72)	0.59	2 (0.3)	6 (1.0)	0.34 (0.07-1.74)	0.20
1-5 years	25 (4.0)	28 (4.3)	0.86 (0.49-1.48)	0.58	21 (3.5)	20 (3.5)	0.92 (0.50-1.72)	0.80
Non-cardiac death								
0-5 years	51 (7.8)	52 (7.7)	0.92 (0.62-1.36)	0.67	45 (7.4)	37 (6.3)	1.05 (0.67-1.62)	0.84
0-1 year	13 (2.0)	5 (0.7)	2.42 (0.86-6.83)	0.095	9 (1.5)	5 (0.8)	1.56 (0.52-4.68)	0.43
1-5 years	38 (6.1)	47 (7.2)	0.75 (0.49-1.16)	0.20	36 (6.1)	32 (5.5)	0.96 (0.59-1.56)	0.88
Target lesion myocardial infarction								
0-5 years	30 (4.6)	29 (4.3)	1.13 (0.67-1.91)	0.65	21 (3.5)	16 (2.7)	1.09 (0.54-2.22)	0.81
0-1 years	6 (0.9)	13 (1.9)	0.48 (0.18-1.28)	0.14	6 (1.0)	8 (1.4)	0.58(0.18-1.83)	0.35

1-5 years	24 (3.9)	16 (2.5)	1.63 (0.85-3.10)	0.14	15 (2.6)	8 (1.4)	1.77 (0.74-4.23)	0.20
Myocardial infarction								
0-5 years	58 (8.9)	57 (8.5)	1.09 (0.75-1.59)	0.65	36 (5.9)	34 (5.8)	0.95 (0.58-1.55)	0.83
0-1 year	13 (2.0)	20 (3.0)	0.73 (0.36-1.48)	0.38	7 (1.2)	11 (1.9)	0.53 (0.19-1.48)	0.23
1-5 years	45 (7.3)	37 (5.8)	1.28 (0.82-1.99)	0.28	29 (4.9)	23 (4.0)	1.18 (0.68-2.05)	0.56
Target lesion revascularization								
0-5 years	34 (5.2)	39 (5.8)	0.95 (0.59-1.52)	0.83	50 (8.3)	55 (9.3)	0.87 (0.58-1.29)	0.48
0-1 year	8 (1.2)	15 (2.2)	0.63 (0.26-1.50)	0.29	16 (2.6)	22 (3.7)	0.69 (0.36-1.33)	0.27
1-5 years	26 (4.2)	24 (3.7)	1.12 (0.64-1.97)	0.69	34 (5.9)	33 (5.9)	0.99 (0.61-1.62)	0.98
Target vessel revascularization								
0-5 years	60 (9.2)	71 (10.5)	0.88 (0.62-1.25)	0.47	81 (13.4)	75 (12.7)	1.06 (0.76-1.46)	0.74
0-1 year	24 (3.7)	35 (5.2)	0.76 (0.45-1.28)	0.30	27 (4.5)	30 (5.1)	0.85 (0.50-1.45)	0.55

1-5 years	36 (6.0)	36 (5.8)	0.99 (0.62-1.58)	0.96	54 (9.5)	45 (8.2)	1.21 (0.81-1.81)	0.36
Definite stent thrombosis								
0-5 years	12 (1.8)	18 (2.7)	0.77 (0.37-1.63)	0.49	7 (1.2)	8 (1.4)	0.81 (0.29-2.27)	0.69
0-1 year	1 (0.2)	11 (1.6)	0.12 (0.02-0.93)	0.043	4 (0.7)	4 (0.7)	0.99 (0.24-3.99)	0.98
1-5 years	11 (1.8)	7 (1.1)	1.68 (0.64-4.39)	0.29	3 (0.5)	4 (0.7)	0.64 (0.14-2.95)	0.57
Probable stent thrombosis								
0-5 years	5 (0.8)	5 (0.7)	1.03 (0.30-3.59)	0.96	1 (0.2)	0 (0.0)		
0-1 year	5 (0.8)	5 (0.7)	1.03 (0.30-3.60)	0.96	1 (0.2)	0 (0.0)		
1-5 years	0 (0.0)	0 (0.0)			0 (0.0)	0 (0.0)		
Definite or probable stent thrombosis								
0-5 years	17 (2.6)	23 (3.4)	0.83 (0.44-1.58)	0.57	8 (1.3)	8 (1.4)	0.96 (0.35-2.60)	0.93
0-1 year	6 (0.9)	16 (2.4)	0.43 (0.17-1.11)	0.081	5 (0.8)	4 (0.7)	1.28 (0.34-4.84)	0.71

1-5 years	11 (1.8)	7 (1.1)	1.68 (0.64-4.39)	0.29	3 (0.5)	4 (0.7)	0.64 (0.14-2.95)	0.57
Possible stent thrombosis								
0-5 years	12.8 (1.8)	14 (2.1)	0.90 (0.41-1.98)	0.80	11 (1.8)	14 (2.4)	0.70 (0.31-1.57)	0.39
0-1 year	2 (0.3)	0 (0.0)			1 (0.2)	4 (0.7)	0.23 (0.03-2.13)	0.20
1-5 years	10 (1.6)	14 (2.1)	0.69 (0.30-1.57)	0.37	10 (1.7)	10 (1.7)	0.90 (0.37-2.20)	0.82
In-stent restenosis								
0-5 years	30 (4.6)	25 (3.7)	1.26 (0.74-2.16)	0.39	44 (7.3)	48 (8.1)	0.85 (0.56-1.30)	0.46
0-1 year	6 (0.9)	6 (0.9)	1.04 (0.33-3.25)	0.95	11 (1.8)	15 (2.5)	0.71 (0.32-1.57)	0.39
1-5 years	24 (3.9)	19 (2.9)	1.33 (0.72-2.45)	0.36	33 (5.7)	33 (5.9)	0.92 (0.56-1.51)	0.75
All revascularization								
0-5 years	152 (23.2)	143 (21.2)	1.14 (0.89-1.46)	0.31	135 (22.3)	119 (20.2)	1.11 (0.86-1.43)	0.44
0-1 year	96 (14.7)	92 (13.6)	1.13 (0.84-1.54)	0.42	46 (7.6)	47 (8.0)	0.91 (0.60-1.38)	0.64

1-5 years	56 (10.5)	51 (9.0)	1.13 (0.77-1.66)	0.54	89 (16.2)	72 (13.5)	1.24 (0.91-1.71)	0.18
Patient related endpoints								
0-5 years	236 (36.0)	229 (34.0)	1.09 (0.89-1.33)	0.40	199 (32.8)	170 (28.8)	1.09 (0.88-1.35)	0.44
0-1 year	125 (19.1)	112 (16.6)	1.19 (0.91-1.57)	0.21	58 (9.6)	57 (9.7)	0.90 (0.61-1.32)	0.59
1-5 years	111 (21.0)	117 (20.9)	0.98 (0.75-1.28)	0.89	141 (25.7)	113 (21.2)	1.19 (0.92-1.53)	0.18

Data are presented as numbers and percentages.

Patient related endpoints: all deaths, all myocardial infarction and all revascularization.

ACS = Acute Coronary Syndrome; N-BES = biolimus-eluting Nobori stent; O-SES = sirolimus-eluting Orsiro stent