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**Biolimus-eluting biodegradable polymer-coated stent versus durable polymer-coated sirolimus-eluting stent in unselected patients receiving percutaneous coronary intervention (SORT OUT V)**

*a randomised non-inferiority trial*

Christiansen, Evald Høj; Jensen, Lisette Okkels; Thayssen, Per; Tilsted, Hans-Henrik; Krusell, Lars Romer; Hansen, Knud Nørregaard; Kaltoft, Anne Kjer; Maeng, Michael; Kristensen, Steen Dalby; Bøtker, Hans Erik; Terkelsen, Christian Juhl; Villadsen, Anton Boel; Ravkilde, Jan; Aarøe, Jens; Madsen, Morten; Thuesen, Leif; Lassen, Jens Flensted; Scandinavian Organization for Randomized Trials with Clinical Outcome (SORT OUT) V investigators

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# Biolimus-eluting biodegradable polymer-coated stent versus durable polymer-coated sirolimus-eluting stent in unselected patients receiving percutaneous coronary intervention (SORT OUT V): a randomised non-inferiority trial



Evald Høj Christiansen, Lisette Okkels Jensen, Per Thayssen, Hans-Henrik Tilsted, Lars Romer Krusell, Knud Nørregaard Hansen, Anne Kaltoft, Michael Maeng, Steen Dalby Kristensen, Hans Erik Bøtker, Christian Juhl Terkelsen, Anton Boel Villadsen, Jan Ravkilde, Jens Aarøe, Morten Madsen, Leif Thuesen, Jens Flensted Lassen, for the Scandinavian Organization for Randomized Trials with Clinical Outcome (SORT OUT) V investigators

## Summary

**Background** Third-generation biodegradable polymer drug-eluting stents might reduce the risk of stent thrombosis compared with first-generation permanent polymer drug-eluting stents. We aimed to further investigate the effects of a biodegradable polymer biolimus-eluting stent compared with a durable polymer-coated sirolimus-eluting stent in a population-based setting.

**Methods** This randomised, multicentre, all-comer, non-inferiority trial was undertaken at three sites across western Denmark. Eligible patients were aged 18 years or older with chronic stable coronary artery disease or acute coronary syndromes, and at least one coronary artery lesion (>50% diameter stenosis). We randomly assigned patients (1:1) using an independently managed computer-generated allocation sequence to receive either a biolimus-eluting biodegradable polymer stent (Nobori, Terumo, Tokyo, Japan) or a sirolimus-eluting permanent polymer stent (Cypher Select Plus, Cordis, Johnson & Johnson, Warren, NJ, USA). The primary endpoint was a composite of safety (cardiac death, myocardial infarction, definite stent thrombosis) and efficacy (target vessel revascularisation) at 9 months, analysed by intention to treat (non-inferiority margin of 0.02). This trial is registered with ClinicalTrials.gov, number NCT01254981.

**Findings** From July, 2009, to January, 2011, we assigned 1229 patients (1532 lesions) to receive the biolimus-eluting stent and 1239 (1555 lesions) to receive the sirolimus-eluting stent. One patient was lost to follow-up because of emigration. Intention-to-treat analysis showed that 50 (4.1%) patients who were assigned the biolimus-eluting stent and 39 (3.1%) who were assigned the sirolimus-eluting stent met the primary endpoint (risk difference 0.9% [upper limit of one-sided 95% CI 2.1%];  $p_{\text{non-inferiority}}=0.06$ ). Significantly more patients in the biolimus-eluting stent group had definite stent thrombosis at 12 months than did those in the sirolimus-eluting stent group (9 [0.7%] vs 2 [0.2%], risk difference 0.6% [95% CI 0.0–1.1];  $p=0.034$ ). Per-protocol analysis showed that 45 (3.8%) of 1193 patients who received a biolimus-eluting stent and 39 (3.2%) of 1208 who received a sirolimus-eluting stent met the primary endpoint (risk difference 0.5% [upper limit of one-sided 95% CI 1.8%];  $p_{\text{non-inferiority}}=0.03$ ).

**Interpretation** At 1 year follow-up, the biodegradable polymer biolimus-eluting Nobori stent did not improve clinical results compared with a first-generation sirolimus-eluting stent. We will need to obtain long-term data before we can make recommendations for the role of this biolimus-eluting stent in routine clinical practice.

**Funding** Terumo and Cordis (Johnson & Johnson).

## Introduction

By controlling the release of antiproliferative drugs from a polymer surface, first-generation drug-eluting stents (DES) reduce the risk of restenosis and the need for repeat revascularisation compared with bare-metal stents,<sup>1–3</sup> but at the expense of an increased risk of very late (>1 year) stent thrombosis.<sup>4,5</sup> Incomplete endothelialisation of the stent struts and positive vessel remodelling due to chronic inflammation might cause this thrombosis, because the persistence of polymer material on first-generation DES after completed drug release might trigger an inflammatory response.<sup>6,7</sup> Biodegradable polymer DES aim to overcome this problem by providing similar controlled drug release

with subsequent degradation of the polymer. Umirolimus (commonly known as biolimus)-eluting stents were designed with a biodegradable polymer applied to the non-luminal surface of the stent. After implantation, the polymer is metabolised to water and carbon dioxide within 9 months.<sup>8,9</sup> Biolimus is a highly lipophilic sirolimus analogue that inhibits proliferation of smooth muscle cells.

A biodegradable polymer biolimus-eluting stent was assessed in the Limus Eluted from A Durable versus ERodable Stent coating (LEADERS) trial<sup>10,11</sup> and was reported to be non-inferior to the durable polymer sirolimus-eluting Cypher stent (Cordis, Miami Lakes, FL,

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USA) with respect to clinical safety and efficacy outcomes up until 4 years' follow-up. The Intracoronary Stenting and Angiographic Results (ISAR-TEST 4) trial<sup>12</sup> compared a biodegradable polymer stent (with a natural resin eluting sirolimus) with the durable polymer sirolimus-eluting Cypher stent and reported no significant differences in outcomes between the stents.<sup>12</sup>

The Scandinavian Organization for Randomized Trials with Clinical Outcome (SORT OUT) V trial aimed to further investigate the effects of a third-generation biodegradable biolimus-eluting stent compared with a first-generation durable polymer-coated sirolimus-eluting stent in a population-based setting, using registry detection of clinically driven events.<sup>13,14</sup>

## Methods

### Study design and patients

SORT OUT V is a randomised, multicentre, all-comer, two-arm, non-inferiority trial comparing a biolimus-eluting stent with a sirolimus-eluting stent to treat coronary artery stenosis, undertaken at three hospitals across western Denmark. We used western Denmark registry data<sup>15,16</sup> to compare randomised and non-randomised patients during the study period so that we could assess how generalisable our study results would be (appendix).<sup>17</sup> Eligible patients were aged 18 years or

older, had chronic stable coronary artery disease or acute coronary syndromes, and at least one coronary artery lesion with more than 50% diameter stenosis needing treatment with a DES. We did not place restrictions on the number of lesions or vessels to be treated, or lesion length. Exclusion criteria were life expectancy of less than 1 year; allergy to aspirin, clopidogrel, prasugrel, sirolimus, or biolimus; participation in another randomised trial; clinical indications of an inability to tolerate dual antiplatelet treatment for 12 months; or inability to provide written informed consent.

The study complied with the Declaration of Helsinki and was approved by the Central Region Denmark ethics committee. All patients provided written informed consent for trial participation.

### Randomisation

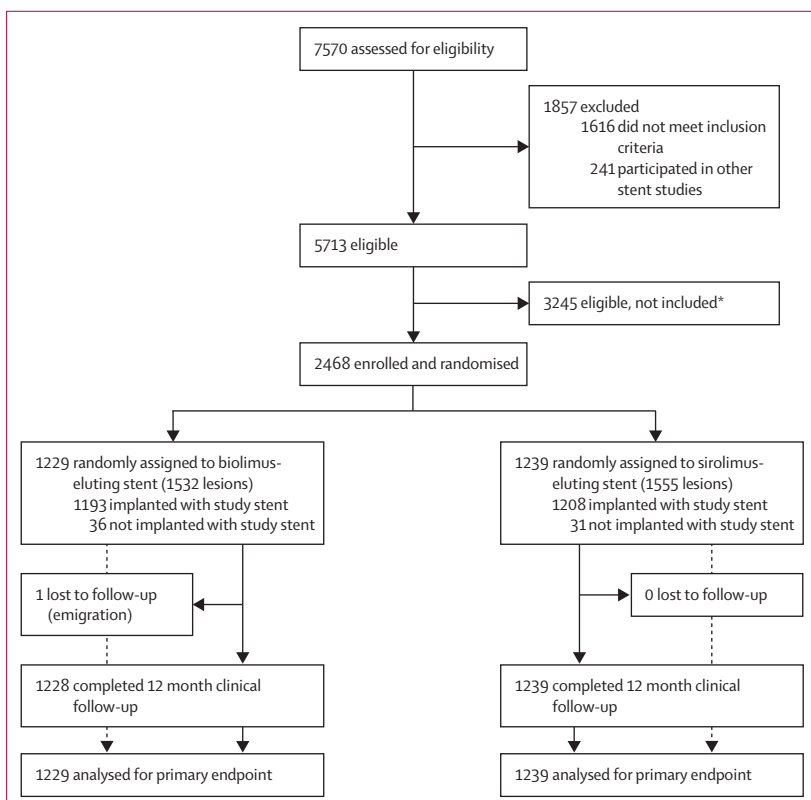
We enrolled patients and randomly allocated them to treatment groups after diagnostic coronary angiography and before percutaneous coronary intervention. Block randomisation by centre was used to assign patients (1:1) to receive a biolimus-eluting stent (Nobori, Terumo, Tokyo, Japan) or a sirolimus-eluting stent (Cypher Select Plus, Cordis, Johnson & Johnson, Warren, NJ, USA). The allocation sequence was computer-generated by an independent organisation, and was stratified by sex, presence of diabetes, and presence of ST-segment elevation myocardial infarction. Patients were assigned to treatment through an automated telephone allocation service. Although operators were not masked, all individuals analysing data were masked to treatment assignment.

### Procedures

The biolimus-eluting stent was available in three diameters (2.50 mm, 3.00 mm, 3.50 mm) and five lengths (8 mm, 14 mm, 18 mm, 24 mm, and 28 mm). The sirolimus-eluting stent was available in five diameters (2.25 mm, 2.50 mm, 2.75 mm, 3.00 mm, and 3.50 mm) and six lengths (8 mm, 13 mm, 18 mm, 23 mm, 28 mm, and 33 mm). We implanted the stents according to standard techniques. We allowed direct stenting without previous balloon dilation. We attempted full lesion coverage by implantation of one or more stents. If several lesions needed to be treated in one patient, the allocated study stent had to be used in all lesions. However, we permitted the use of DES not specified by the random allocation scheme, bare metal stents, and balloon angioplasty if the study stent could not be implanted.

Before implantation, patients received at least 75 mg of aspirin, a 600 mg loading dose of clopidogrel, and an unfractionated heparin dose (5000 IU or 70–100 IU/kg). Glycoprotein IIb/IIIa inhibitors were used at the operator's discretion. Recommended postprocedure dual antiplatelet regimens were 75 mg aspirin daily lifelong and clopidogrel 75 mg for 1 year. We also used prasugrel

See Online for appendix



**Figure 1: Trial profile**

\*Not all eligible patients were included because some percutaneous coronary intervention operators at participating centres did not want the choice of stent to be decided by a randomisation process.

treatment as an alternative to clopidogrel, with a loading dose of 60 mg and a daily dose of 10 mg.

The primary endpoint was a combination of safety (cardiac death, myocardial infarction, definite stent thrombosis) and efficacy (clinically indicated target vessel revascularisation) within 9 months of stent implantation. We did intention-to-treat analyses after 9 months and again at 12 months after implantation. Secondary endpoints were: total mortality; cardiac mortality; myocardial infarction; clinically indicated target lesion or vessel revascularisation; definite, probable, or possible stent thrombosis; and device delivery failure.

We defined cardiac death as any death due to an evident cardiac cause, any death related to percutaneous coronary intervention, unwitnessed death, or death from unknown causes. Myocardial infarction was defined according to the universal definition used by the European Society of Cardiology, the American College of Cardiology, the American Heart Association, and the World Heart Federation.<sup>18</sup> We did not assess biomarkers at the time of the index percutaneous coronary intervention procedure. We classified stent thrombosis as definite, probable, or possible stent thrombosis.<sup>19</sup> We defined target vessel revascularisation as any repeat percutaneous coronary intervention or surgical bypass of any segment within the entire major coronary vessel that was proximal or distal to a target lesion, including upstream and downstream branches, and the target lesion itself. We defined target lesion revascularisation as repeat revascularisation caused by a more than 50% stenosis within the stent or within a 5 mm border proximal or distal to the stent. Device failure was defined as the inability to implant the assigned study stent in a target lesion. To establish comorbidity, we obtained data on hospital diagnoses for all patients from the Danish National Registry of Patients, covering all Danish hospitals from 1977 until the implantation date,<sup>20</sup> and calculated each patient's Charlson comorbidity index score, which covers 19 major disease categories, including diabetes mellitus, heart failure, cerebrovascular diseases, and cancer.<sup>21</sup>

We used clinically driven event detection to avoid study-induced re-interventions. We obtained data on mortality, hospital admissions, coronary angiography, repeat percutaneous coronary intervention, and coronary bypass surgery for all randomly allocated patients from the following national Danish administrative and health-care registries: the Civil Registration System; the Western Denmark Heart Registry;<sup>15</sup> the Danish National Registry of Patients<sup>20</sup> (which maintains records for all hospital admissions in Denmark); and the Danish Registry of Causes of Death.<sup>22</sup> An independent event committee, masked to treatment group assignment during the adjudication process, reviewed all endpoints and source documents to adjudicate causes of death, reasons for hospital admission, and diagnosis of myocardial infarction. Two dedicated percutaneous coronary

intervention operators at each participating centre reviewed cine films for the event committee to classify stent thrombosis and target vessel revascularisation (either with percutaneous coronary intervention or coronary artery bypass grafting).

The Danish National Health Service provides universal tax-supported health care, guaranteeing residents free access to family doctors and hospitals. The Danish Civil Registration System, which is updated on a daily basis, has kept electronic records on sex, birth date, residence,

	Biolimus-eluting stent (n=1229)	Sirolimus-eluting stent (n=1239)
Age (years)	65.0 (10.6)	65.2 (10.3)
Men	917 (74.6%)	930 (75.1%)
Diabetes mellitus	185/1229 (15.1%)	189/1239 (15.3%)
Arterial hypertension	682/1180 (57.8%)	653/1189 (54.9%)
Hypercholesterolaemia	710/1179 (60.2%)	730/1190 (61.3%)
Current smoker	385/1145 (33.6%)	381/1152 (33.1%)
Body-mass index (kg/m <sup>2</sup> )	27.5 (5.2)	27.4 (5.2)
Previous myocardial infarction	209/1182 (17.7%)	206/1189 (17.3%)
Previous percutaneous coronary intervention	205/1182 (17.3%)	196/1191 (16.5%)
Previous coronary artery bypass grafting	96/1184 (8.1%)	71/1195 (5.9%)
Indication for percutaneous coronary intervention		
ST-segment elevation MI	225 (18.3%)	227 (18.3%)
Non-ST-segment elevation MI or unstable angina	372 (30.3%)	384 (31.0%)
Stable angina	608 (49.5%)	596 (48.1%)
Other	24 (2.0%)	32 (2.6%)
Number of lesions		
1	903 (73.5%)	925 (74.7%)
2	253 (20.6%)	244 (19.7%)
3	61 (5.0%)	59 (4.8%)
>3	12 (1.0%)	11 (0.9%)
Number of lesions per patient	1.25 (0.6)	1.26 (0.6)
Target vessel location		
Left main artery	21 (1.4%)	21 (1.4%)
Left anterior descending artery	623 (40.7%)	636 (40.9%)
Left circumflex artery	355 (23.2%)	350 (22.5%)
Right artery	508 (33.2%)	535 (34.4%)
Saphenous vein graft	25 (1.6%)	13 (0.8%)
Lesion type		
A	200 (13.1%)	225 (14.5%)
B1	478 (31.2%)	512 (32.9%)
B2	262 (17.1%)	242 (15.6%)
C	592 (38.6%)	576 (37.0%)
Chronic total occlusion lesions	90 (6.0%)	109 (7.2%)
Bifurcation lesions	225 (15.0%)	229 (15.1%)
Lesion length >18 mm	521 (34.1%)	522 (33.6%)
Lesion length (mm)	18.0 (12.0–27.0)	18.0 (11.0–29.0)
Reference vessel size (mm)	3.2 (3.0–3.5)	3.3 (3.0–3.6)

Data are mean (SD), number (%), or median (IQR). Previous percutaneous coronary intervention and reference vessel size differed significantly between groups at baseline (p=0.039 and p=0.031, respectively). Some of the 1229 participants' data is missing for some variables because it was not recorded in the Western Denmark Heart Registry. MI=myocardial infarction.

**Table 1: Baseline characteristics of the study population**

	Biolimus-eluting stent (n=1229)	Sirolimus-eluting stent (n=1239)	p value
More than one stent			
Per patient	448 (36.5%)	450 (36.3%)	0.56
Per lesion	279 (18.3%)	300 (19.2%)	0.79
Total stent length (mm)			
Per patient	22.0 (14.0–32.0)	23.0 (13.0–33.0)	0.22
Per lesion	15.0 (10.0–20.0)	15.0 (10.0–20.0)	0.51
Direct stenting	329 (21.6%)	345 (22.4%)	0.60
Stent delivery failure	26 (1.7%)	31 (2.0%)	0.54
Maximum pressure (atm)	16.0 (14.0–20.0)	18.0 (15.0–20.0)	<0.0001
Length of procedure (min)	24.0 (16.0–38.0)	24.0 (15.0–38.0)	0.94
Fluoroscopy time (min)	6.5 (4.0–12.0)	6.9 (4.0–12.2)	0.27
Contrast (mL)	100.0 (60.0–130.0)	100.0 (60.0–140.0)	0.64
Use of glycoprotein IIb/IIIa inhibitors	195 (15.9%)	209 (16.9%)	0.50

Data are number (%) or median (IQR).

**Table 2: Procedure characteristics**

emigration date, and vital status changes since 1968;<sup>20</sup> the ten-digit civil registration number assigned at birth and used in all registries allows accurate record linkage. The Civil Registration System provided vital status data for our study participants and minimised loss to follow-up. The National Registry of Causes of Deaths and the Danish National Registry of Patients provided information on causes of death and diagnoses made during hospital admissions (coded according to the International Classification of Diseases, 10th revision).<sup>22</sup>

### Statistical analysis

The trial was powered for assessing non-inferiority of the biolimus-eluting stent compared with the sirolimus-eluting stent with respect to the primary endpoint at 9 months. On the basis of results from the SORT OUT III trial,<sup>13</sup> we assumed an event rate of 3% in the sirolimus-eluting stent group. No valid estimate for event rate in an all-comer population after treatment with the biolimus-eluting Nobori stent was available. With a sample size of 1200 patients in each treatment group, a two-group large-sample normal approximation test of proportions with a one-sided 0.05 significance level would have 90% power to detect non-inferiority with a predetermined non-inferiority margin of 0.02. The sample size of 1200 in each group assumes 0% of patients are lost to follow-up, since we used the Civil Registration System.

A Farrington-Manning test was used to test for non-inferiority. We compared distributions of continuous variables between study groups using the two-sample *t* test (or Cochran test for cases of unequal variance) or the Mann-Whitney *U* test, depending on whether the data followed a normal distribution. We analysed distributions of categorical variables using the  $\chi^2$  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. We constructed survival curves based on time to events, accounting for the competing risk of death.<sup>23</sup> Patients who received the sirolimus-eluting stent were used as the reference group for overall and subgroup analyses. We calculated risk differences for major adverse cardiac events at 12 month follow-up for prespecified patient subgroups (based on baseline demographic and clinical characteristics). The intention-to-treat principle was used in all analyses. Except for the inferiority testing of the primary endpoint, we regarded a two-sided *p* value of less than 0.05 to indicate statistical significance. We used Cox proportional hazards regression analysis to assess whether difference detected at baseline had any effect on the result. We did analyses using SAS software (version 9.2). This trial is registered with ClinicalTrials.gov, number NCT01254981.

### Role of the funding source

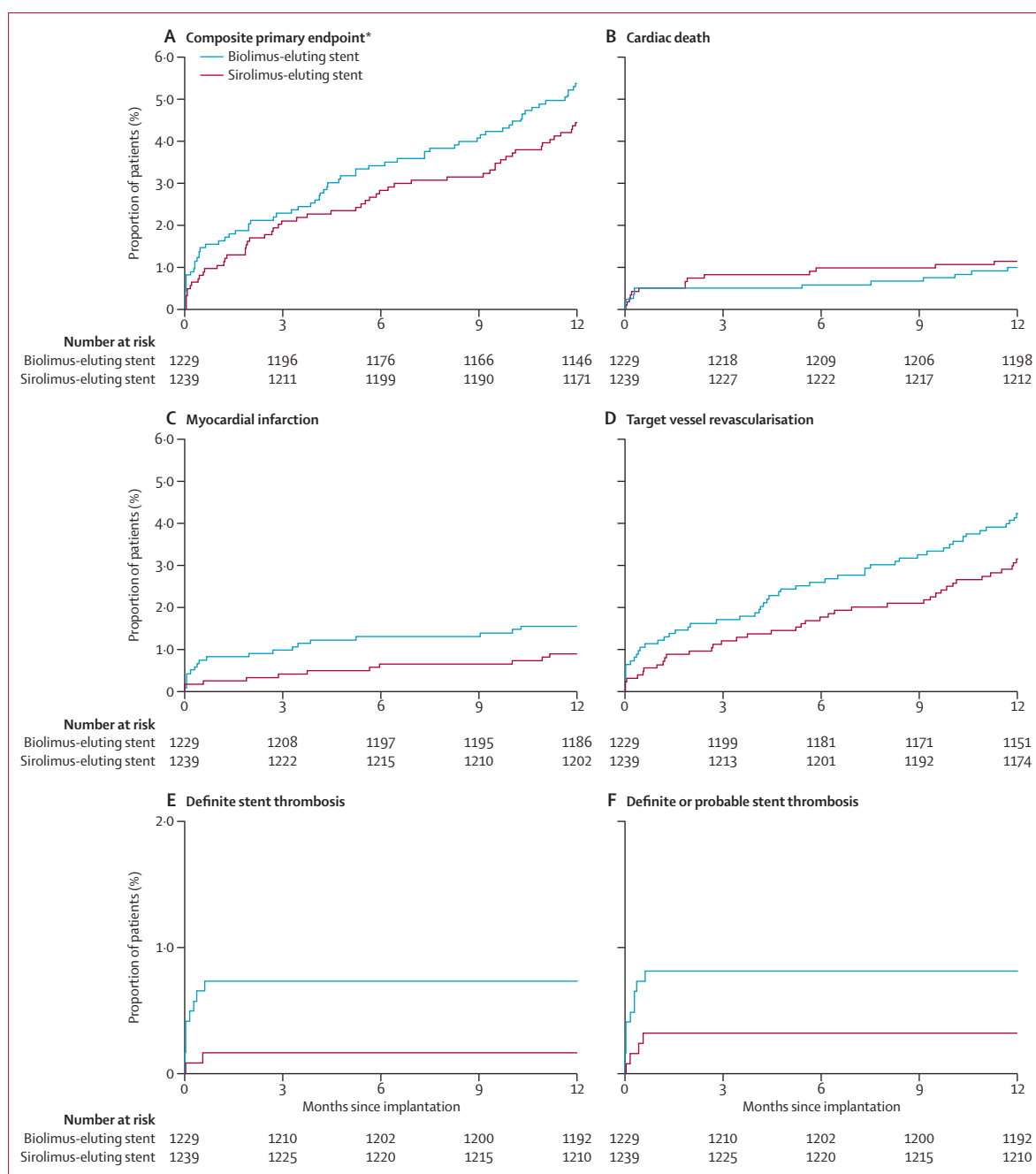
The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. They also did not have access to the clinical trial database, nor any opportunity to review the manuscript. The corresponding author had full access to all the data in the study and final responsibility for the decision to submit for publication.

### Results

Between July, 2009, to January, 2011, we screened 7570 patients and randomly assigned 2468 patients with 3087 lesions to receive either the biolimus-eluting stent (1229 patients with 1532 lesions) or the sirolimus-eluting stent (1239 patients with 1555 lesions; figure 1). 3245 eligible patients were not enrolled, mainly because some operators at the participating centres preferred not to leave stent selection to a randomised process. One patient was lost to follow-up on day 112 because of emigration.

Baseline demographic and clinical characteristics in the two study groups were well balanced except for a slightly higher rate of previous coronary artery bypass grafting in the biolimus-eluting stent group (table 1). A high proportion of patients in both groups had acute coronary syndromes, multivessel disease, and complex lesions (table 1). Diabetes was equally distributed and reported in 15% of patients. Apart from a higher maximum stent implantation pressure (table 2) and larger reference vessel diameter in the sirolimus-eluting group, procedure results (such as the rate of device delivery failure and indices of procedure duration, fluoroscopy time, and use of contrast) and lesion characteristics were similar in the study groups (table 2).

The 9 month composite primary endpoint occurred in 50 (4.1%) of 1229 patients in the biolimus-eluting stent group and in 39 (3.1%) of 1239 patients in the sirolimus-eluting stent group (figure 2). With an absolute risk difference of 0.9% and the upper limit of the one-sided 95% CI at 2.1% (one-sided  $p_{\text{non-inferiority}}=0.06$ ),



**Figure 2: Time-to-event curves for major adverse cardiac events**

\*Cardiac death, myocardial infarction, definite stent thrombosis, and target vessel revascularisation.

non-inferiority of the biolimus-eluting stent versus the sirolimus-eluting stent was not shown. Rates of death, cardiac death, myocardial infarction, and clinically driven target vessel revascularisation at 9 months did not differ significantly between the two stent groups (table 3). The result was similar for the composite endpoint at 12 months, which occurred in 66 (5.4%) patients in the biolimus-eluting stent group and in 55 (4.4%) patients in the sirolimus-eluting stent group

(table 3 and figure 2). Definite stent thrombosis occurred within 12 months in nine (0.7%) patients in the biolimus-eluting stent group and in two (0.2%) patients in the sirolimus-eluting stent group ( $p=0.034$ ). We did not detect late definite stent thrombosis in any patient. At 12 month follow-up, definite or probable stent thrombosis did not differ between the two groups (table 3). Clinically driven target lesion revascularisation occurred within 9 months in 30 (2.4%) patients in the

	Biolimus-eluting stent (n=1229)	Sirolimus-eluting stent (n=1239)	Risk difference (95% CI)	p value
<b>Events at 30 days</b>				
All-cause mortality	8 (0.7%)	7 (0.6%)	0.1% (-0.5 to 0.7)	0.78
Cardiac death	6 (0.5%)	6 (0.5%)	0.0% (-0.5 to 0.6)	0.99
Myocardial infarction	10 (0.8%)	3 (0.2%)	0.6% (0.0 to 1.1)	0.050
Target vessel revascularisation	14 (1.1%)	8 (0.6%)	0.5% (-0.2 to 1.2)	0.19
Target lesion revascularisation	11 (0.9%)	7 (0.6%)	0.3% (-0.3 to 1.0)	0.34
Definite stent thrombosis	9 (0.7%)	2 (0.2%)	0.6% (0.0 to 1.1)	0.034
<b>Events at 9 months</b>				
Composite primary endpoint*	50 (4.1%)	39 (3.1%)	0.9% (-0.6 to 2.4)	0.22
All-cause mortality	22 (1.8%)	22 (1.8%)	0.0% (-1.0 to 1.1)	0.98
Cardiac death	8 (0.7%)	12 (1.0%)	-0.3% (-1.0 to 0.4)	0.38
Myocardial infarction	16 (1.3%)	8 (0.6%)	0.7% (-0.1 to 1.4)	0.097
Definite stent thrombosis†	9 (0.7%)	2 (0.2%)	0.6% (0.0 to 1.1)	0.034
Target vessel revascularisation	40 (3.3%)	26 (2.1%)	1.2% (-0.1 to 2.4)	0.075
Target lesion revascularisation	30 (2.4%)	16 (1.3%)	1.1% (0.1 to 2.2)	0.035
<b>Events at 12 months</b>				
Composite endpoint*	66 (5.4%)	55 (4.4%)	0.9% (-0.8 to 2.6)	0.28
All-cause mortality	30 (2.4%)	27 (2.2%)	0.3% (-0.9 to 1.4)	0.67
Cardiac death	12 (1.0%)	14 (1.1%)	-0.2% (-1.0 to 0.7)	0.71
Composite endpoint based on all-cause mortality‡	82 (6.7%)	68 (5.5%)	1.2% (-0.7 to 3.1)	0.22
Myocardial infarction	19 (1.5%)	11 (0.9%)	0.7% (-0.2 to 1.5)	0.14
Stent thrombosis‡				
Definite	9 (0.7%)	2 (0.2%)	0.6% (0.0 to 1.1)	0.034
Acute (<24 h)	5 (0.4%)	1 (0.1%)	0.3% (-0.1 to 0.7)	0.10
Subacute (24 h to 30 days)	4 (0.3%)	1 (0.1%)	0.2% (-0.1 to 0.6)	0.18
Late (31 days to 12 months)	0	0	NA	NA
Probable	1 (0.1%)	2 (0.2%)	-0.1% (-0.4 to 0.2)	0.57
Definite or probable	10 (0.8%)	4 (0.3%)	0.5% (-0.1 to 1.1)	0.11
Possible	3 (0.2%)	5 (0.4%)	-0.2% (-0.6 to 0.3)	0.75
Target vessel revascularisation	52 (4.2%)	39 (3.1%)	1.1% (-0.4 to 2.6)	0.15
Target lesion revascularisation	40 (3.3%)	25 (2.0%)	1.2% (0.0 to 2.5)	0.055

Data are number (%) unless otherwise indicated. Two-sided CIs have been used for all endpoints. \*Cardiac death, myocardial infarction, definite stent thrombosis, and clinically-driven target vessel revascularisation. †All-cause mortality, myocardial infarction, definite stent thrombosis, and clinically-driven target vessel revascularisation. ‡Academic Research Consortium definition.

Table 3: Clinical outcomes

biolimus-eluting stent group and 16 (1.3%) patients in the sirolimus-eluting stent group ( $p=0.035$ ).

Findings for the primary endpoint were consistent across prespecified subgroups (figure 3). Specifically, the primary endpoint did not differ significantly between the two stent groups in patients with and without diabetes mellitus. Due to the small imbalance in proportion of patients with previous coronary artery bypass graft and difference in reference vessel diameter between groups, we adjusted for these variables with Cox proportional hazards regression analysis. This did not change the results (data not shown).

Results of per-protocol analysis showed that 45 (3.8%) of 1193 patients who received a biolimus-eluting stent

and 39 (3.2%) of 1208 patients who received the sirolimus-eluting stent met the primary endpoint (risk difference 0.5% [upper limit of one-sided 95% CI 1.8%];  $P_{\text{non-inferiority}}=0.03$ ).

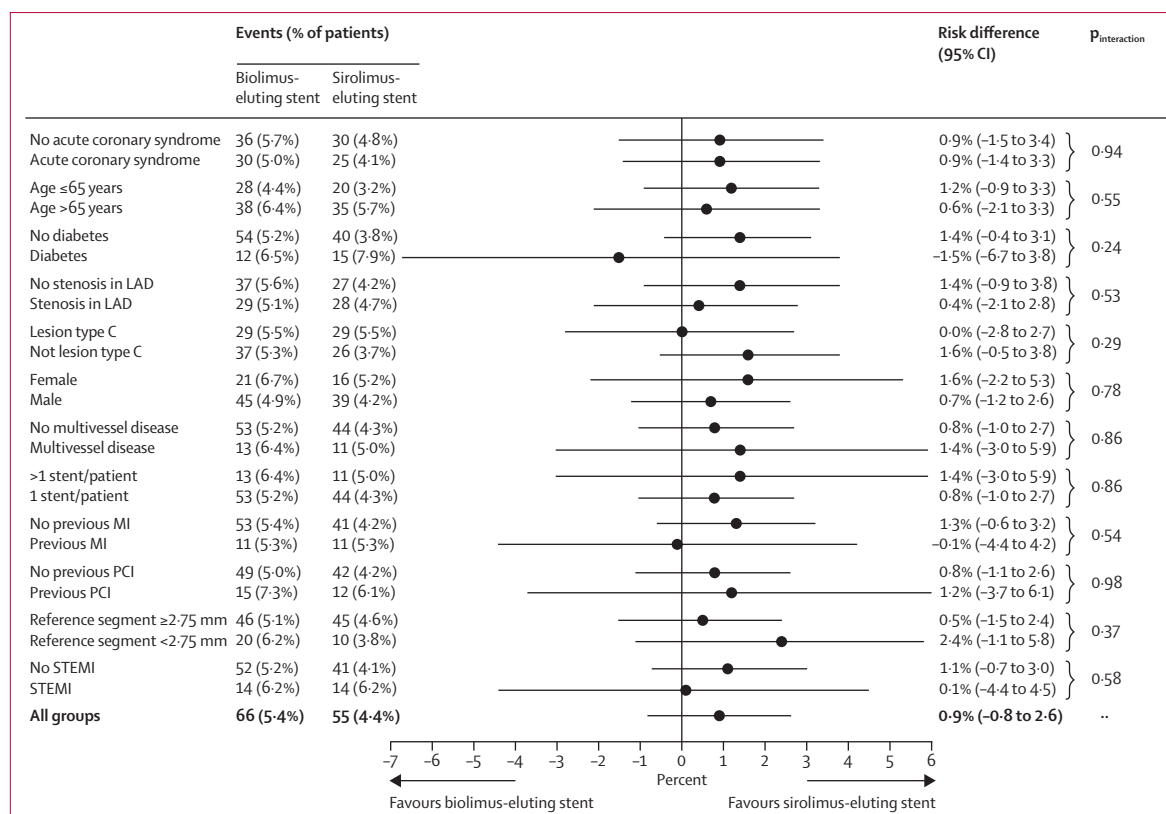
## Discussion

Our SORT OUT V trial is the largest head-to-head comparison of the biodegradable polymer-coated biolimus-eluting Nobori stent and the permanent polymer-coated sirolimus-eluting Cypher stent.<sup>9</sup> At 9 and 12 month assessment of clinical safety and efficacy, the results of the study did not show non-inferiority of the biolimus-eluting stent compared with the sirolimus-eluting stent.

This result contrasts with that of the LEADERS trial, which also compared a biolimus-eluting biodegradable polymer-coated stent with the sirolimus-eluting Cypher stent.<sup>10</sup> The biodegradable stent of the LEADERS trial (BioMatrix Flex, Biosensors, Newport Beach, CA, USA) is almost identical to the Nobori stent used in our study. The stent platforms are made of the same stainless steel alloy and the biodegradable polymer is the same. However, the Nobori stent has an ultra-thin non-degradable parylene coating between the stent and the biodegradable polymer to assure polymer attachment to the stent struts.

In the LEADERS trial, the event rate for the primary endpoint for both stents was almost twice as high as in SORT OUT V, and the investigators concluded that the biodegradable polymer study stent was non-inferior to the sirolimus-eluting stent.<sup>10</sup> By contrast with the LEADERS trial, we did not routinely assess procedural biomarkers, and did not record asymptomatic and electrocardiograph silent procedure-related myocardial damage. The higher rate of new revascularisations in the LEADERS trial (4.4% with the biolimus-eluting stent vs 5.5% with the sirolimus-eluting stent) compared with our trial (3.3% vs 2.1%) might be explained by the fact that 25% of patients in the LEADERS trial had a prescheduled angiography follow-up.<sup>24</sup> Furthermore, the rate of diabetes was twice as high in the LEADERS trial as in our trial in which 15% of patients had diabetes, a rate that is characteristic for interventional studies in Nordic countries.

We cannot explain why, in our trial, the 12 month event rates in the biolimus-eluting stent group were higher than those in the sirolimus-eluting stent group. Although non-significant, the difference was noted in all elements of the combined endpoint and across patient subgroups. The differences seemed to occur mainly during the first month and were most pronounced in the endpoints of stent thrombosis, myocardial infarction, and new revascularisations (figure 2). We cannot exclude that the non-degradable parylene coating between the stent and the biodegradable polymer, covering the entire stent, might be a causal factor. Other explanations might be the significant, but small, difference in implantation pressures between the two groups, with a possibly improved apposition



**Figure 3: Prespecified subgroup analysis for the composite endpoint\* at 12 months**

Data are number of events (% of patients). Major adverse cardiac events are a composite of cardiac death, myocardial infarction, definite stent thrombosis, and target vessel revascularization. LAD=left anterior descending artery. MI=myocardial infarction. PCI=percutaneous coronary intervention. STEMI=ST-elevation myocardial infarction. \*Cardiac death, myocardial infarction, definite stent thrombosis, and clinically indicated target vessel revascularisation.

between stent struts and vessel wall in the patients who received the sirolimus-eluting stent.

The SORT OUT IV study documented similar safety and efficacy between the sirolimus-eluting Cypher stent and the second-generation everolimus-eluting Xience V stent.<sup>14</sup> The COMPARE II trial randomly assigned 2707 patients (2:1) to the biolimus-eluting Nobori stent or an everolimus-eluting stent (Xience V or Prime, Abbott Vascular, Santa Clara, CA, USA, or Promus, Boston Scientific, Natick, MA, USA; panel).<sup>25</sup> Although the event rates in the biolimus-eluting stent group were numerically higher than in the everolimus-eluting stent group, the study showed non-inferiority of the biolimus-eluting stent. At 12 months, rates of major cardiac events at 12 months were 5.2% with the biolimus-eluting stent versus 4.8% with the everolimus-eluting stent and the rates of definite stent thrombosis were 0.7% versus 0.4%. These results are similar to those reported in our study (5.4% with the biolimus-eluting stent vs 4.4% with the sirolimus-eluting stent for major cardiac events and 0.7% vs 0.2% for definite stent thrombosis), so despite our study not showing non-inferiority, our results are backed up by 12 month safety and efficacy data from COMPARE II, which also compared an older-generation DES with the biolimus-eluting Nobori stent.

### Panel: Research in context

#### Systematic review

We searched PubMed, EuroPCR, and Transcatheter Cardiovascular Therapeutics (TCT) conferences for reports on randomised trials comparing the biolimus-eluting biodegradable polymer-coated Nobori stent with durable polymer stents powered for clinical endpoints with the search terms “Nobori”, “stent”, “randomised”, or “randomized”, published between Jan 1, 2003, and June 1, 2012. We identified the COMPARE II trial,<sup>25</sup> which randomly assigned (2:1) 2707 patients to the biolimus-eluting Nobori stent or an everolimus-eluting stent. At 12 months, the rates of major adverse cardiac events and definite stent thrombosis were higher in the biolimus-eluting stent group than in the everolimus-eluting stent group, but using a non-inferiority margin of 4%, the investigators concluded non-inferiority of the biolimus-eluting stent. We identified additional reports cited in this Article by searching PubMed with the term “biolimus-eluting stent”.

#### Interpretation

Our study and the COMPARE II trial show that at 1 year, the biodegradable polymer biolimus-eluting Nobori stent does not improve clinical results compared with the first-generation sirolimus-eluting or everolimus-eluting durable polymer stents. However, long-term data will be needed before we can make recommendations for the role of the Nobori stent in routine clinical practice.

Very late stent thrombosis (generally defined as occurring >1 year after implantation) has been a weakness of first-generation DES. Therefore, our follow-up



of 12 months is too short to offer a complete description of the safety profile of the biolimus-eluting stent. In the NOBORI 2 study,<sup>26</sup> which assessed the biolimus-eluting Nobori stent, very low stent thrombosis rates were seen 12–24 months (0·10%)<sup>26</sup> and 24–36 months (0·10%) after implantation.<sup>27</sup> By contrast, results of the LEADERS trial showed that the sirolimus-eluting Cypher stent has a yearly incidence of very late stent thrombosis of about 0·6%.<sup>10</sup> Therefore, we postulate that our results might show non-inferiority of the biolimus-eluting stent versus the sirolimus-eluting stent in the longer term. Accordingly, a meta-analysis of three randomised clinical trials with 2 or more years' follow-up reported that biodegradable, as compared with durable, polymer DES were associated with a reduced risk of definite stent thrombosis and target lesion revascularisation.<sup>28</sup> The second-generation everolimus-eluting stent with a permanent fluoropolymeric polymer seems to be an exception to this finding, and so far it has not been associated with long-term safety problems.<sup>29</sup>

In conclusion, the SORT OUT V study did not show non-inferiority of the biolimus-eluting Nobori stent compared with the sirolimus-eluting Cypher stent at 12 months.

#### Contributors

The steering committee formulated the study design, which all authors subsequently accepted. EHC and MoM were responsible for data management and for design and implementation of the statistical analysis. All other authors enrolled patients and contributed to data collection. EHC, LOJ, PT, LT, and JFL contributed to the design of the statistical analysis and the interpretation of results. EHC, LOJ, MiM, LT, and JFL drafted the report, which was subsequently reviewed by all authors. All authors saw the final submitted report and agreed with its contents.

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#### Conflicts of interest

EHC has received honoraria from Terumo and Cordis and travel grants from both companies. LOJ has received unrestricted grants from Terumo for her institution and honoraria from Cordis (Clinical Event Committee member). PT, ABV, and JA have received unrestricted grants from Terumo and Cordis for their institutions. H-HT has received travel grants from Terumo and Cordis for his institution, and he is married to a Terumo employee. AK has received unrestricted grants from Abbott Vascular, Boston Scientific, and Cordis for her institution, and honoraria from Cordis. MiM has received travel grants from Cordis, Medtronic, and Boston Scientific. SDK has received honoraria from AstraZeneca, Eli Lilly,

Daichii Sankyo, and The Medicines Company. JR has received unrestricted grants from Terumo, Abbott Vascular, and Cordis for his institution, and honoraria from Abbott Vascular. LT has received unrestricted grants from Abbott Vascular, Boston Scientific, and Cordis for his institution and honoraria from Abbott Vascular, Cordis, and Boston Scientific. JFL has received unrestricted grants from Abbott Vascular, Boston Scientific, and Cordis for his institution and speaking honoraria from Abbott Vascular, Cordis, Medtronic, Eli Lilly, Boston Scientific, and AstraZeneca. LRK, KNH, HEB, CJT, and MoM declare that they have no conflicts of interest.

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