EuroIntervention 2021;16:1404-1412 published online jaa September 2020

BioMatrix versus Orsiro biodegradable polymer stents in all-comer patients with coronary artery disease: the multicentre, randomised BIODEGRADE trial

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This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-20-00185

KEYWORDS

- ACS/NSTE-ACS
- drug-eluting stent
- stable angina
- STEMI

Abstract

Aims: The aim of this trial was to compare the safety and efficacy of a thin-strut biodegradable polymer sirolimus-eluting cobalt-chromium stent (Orsiro) to a thick-strut biodegradable polymer biolimus-eluting stent (BioMatrix).

Methods and results: This randomised, open-label, non-inferiority trial was conducted among patients undergoing percutaneous coronary intervention. The primary endpoint was target lesion failure (TLF). Between July 2014 and September 2017, we randomly assigned 2,341 patients to BioMatrix stents (n=1,166) or Orsiro stents (n=1,175). We analysed 2,327 patients who completed 18-month follow-up. The mean patient age was 63.5 years, and 1,565 (67.3%) patients presented with acute coronary syndrome. At 18 months, 34 (2.9%) patients with BioMatrix stents and 24 (2.1%) with Orsiro stents experienced TLF (hazard ratio [HR] 0.70, upper limit of one-sided 95% confidence interval: 1.18, p for non-inferiority <0.0001). No significant differences were noted in rates of cardiac death (16 [1.4%] vs 12 [1.0%], p=0.558), target lesion-related myocardial infarction (0 [0%] vs 3 [0.3%], p=0.250), target lesion revascularisation (18 [1.6%] vs 10 [0.9%], p=0.124), or stent thrombosis (0 [0%] vs 2 [0.2%], p=0.50).

Conclusions: In patients with a high prevalence of acute coronary syndrome, Orsiro stents were not inferior to BioMatrix stents. Both showed good clinical outcomes.

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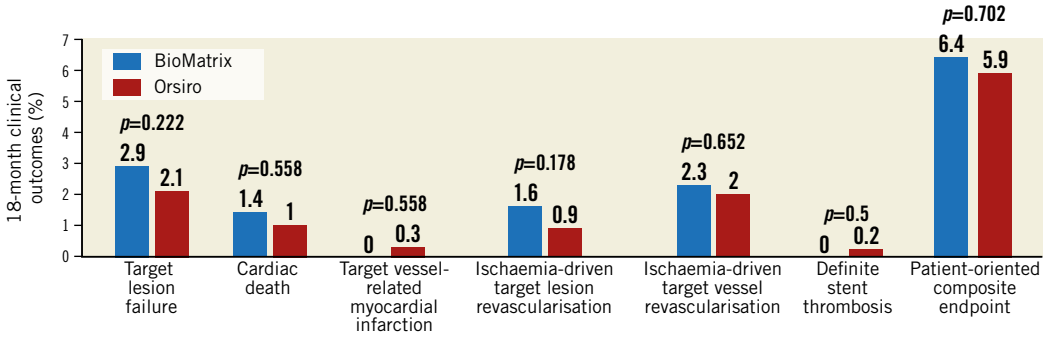
SUBMITTED ON 14/02/2020 - REVISION RECEIVED ON 1st 22/07/2020 / 2nd 11/09/2020 - ACCEPTED ON 17/09/2020

DOI: 10.4244/EIJ-D-20-00185

BIODEGRADE study
Patients with CAD requiring PCI with stents (n=2,341 randomised)

	The thick-strut biodegradable polymer stent, BioMatrix stent	The thin-strut biodegradable polymer stent, Orsiro stent
Metallic elements	316L stainless steel	Cobalt-chromium with a passive silicone carbide coating
Thickness of the stent strut	120 µm	60 or 80 µm
Biodegradable polymer	Polylactic acid	Poly-L-lactic polymer
Polymer location	Abluminal	Circumferential
Degradation time of the polymer	9 months	Over 12-24 months



Visual summary. *Comparison of the BioMatrix and Orsiro stents: summary of 18-month outcomes. Aetiopathology of debris captured by cerebral embolic protection filters during TAVI, including risk factors for greater amounts or larger particles of debris.*

Abbreviations

BP biodegradable polymer
CI confidence interval
DES drug-eluting stent(s)
PCI percutaneous coronary intervention
TLF target lesion failure

Introduction

Treatment failure rates of stents after percutaneous coronary intervention (PCI) have been decreasing since the introduction of drug-eluting stents (DES)[1-3]. Advances in stent metallic structure, polymer coating, and release of antiproliferative DES agents have improved the safety and efficacy of DES. Nevertheless, stent failure remains a substantial problem, with more PCIs being performed in cases of complex lesions[4-6].

The disappointing results of fully bioresorbable scaffolds have led to re-emerging interest in metal-based DES made of biodegradable polymers (BP) for the elution of antiproliferative agents[7-9]. The pioneer BP-DES is the BioMatrix™ stent (Biosensors, Singapore), a biolimus-eluting stent. In the LEADERS (Limus Eluted From A Durable Versus ERodable Stent Coating) trial, the definite or probable stent thrombosis rate was lower with BioMatrix (3.6%) than with the CYPHER Select® (5.2%) (Cordis, Cardinal Health, Milpitas, CA, USA)[10].

The Orsiro stent (Biotronik, Bülach, Switzerland), another BP-DES, is a sirolimus-eluting stent. It showed excellent long-term outcomes including a very low rate of stent thrombosis in several studies[11-13].

Nevertheless, few trials have compared the thin-strut Orsiro stent and the thick-strut BioMatrix/BioMatrix Flex™ stent (Biosensors). Therefore, we conducted the BIODEGRADE study (Comparison of BIoMatrix and Orsiro Drug Eluting Stent in AngioGraphic Result in patients with Coronary Artery DiseasE), a multicentre, randomised, open-label, and parallel-arm study, to determine whether the Orsiro stent is non-inferior to the BioMatrix stent.

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Methods

PATIENTS

Patients were eligible if they had chronic stable coronary artery disease or acute coronary syndromes. Inclusion and exclusion criteria as well as the characteristics of the stents are presented in detail in **Supplementary Appendix 1**. The study complied with the Declaration of Helsinki and was approved by the institutional review board of each participating centre. All patients provided written informed consent for trial participation before randomisation. This trial was registered with ClinicalTrials.gov (identifier: NCT02299011).

RANDOMISATION

Patients were enrolled by the investigators and randomly allocated to treatment groups after diagnostic coronary angiography and before PCI. Block randomisation by centre was used to assign patients in a 1:1 ratio to receive treatment with an Orsiro stent or a BioMatrix stent. The allocation sequence was computer-generated using a web-based randomisation program run by an independent organisation (T&W Software, Seoul, Republic of Korea).

PROCEDURES

Stents were implanted according to standard techniques. BioMatrix/BioMatrix Flex or Orsiro stents were implanted in the lesions **(Supplementary Appendix 2)**. For multiple lesions, the

assigned stent was used in at least one lesion. Other stents were used in case of device failure or in situations where the operators decided that it was in the best interest of the patient. In such cases, the patient was excluded from the per protocol (PP) analysis but was included in the intention-to-treat (ITT) analysis. Complete lesion coverage was recommended. Antithrombotic therapy was prescribed at the investigator's discretion based on the guidelines **(Supplementary Appendix 3)**.

OUTCOME MEASURES

The primary endpoint was target lesion failure (TLF), defined as a composite of cardiac death, target vessel-related myocardial infarction, or ischaemia-driven target lesion revascularisation within 18 months. Individual components of the primary endpoint comprised the secondary endpoints: cardiac death; myocardial infarction; ischaemia-driven target lesion revascularisation; all-cause death (cardiac and non-cardiac) and target vessel revascularisation; definite, probable, possible, and overall stent thrombosis according to the Academic Research Consortium definition; and a patient-oriented composite endpoint (all-cause death, all myocardial infarctions, or any revascularisation). The definitions of endpoints, event detection, site monitoring and event adjudication are described in **Supplementary Appendix 4**.

STATISTICAL ANALYSIS

The details of the rationale and methods of statistical analyses are presented in **Supplementary Appendix 5**. Briefly, the trial was powered for the non-inferiority of the Orsiro stent to the BioMatrix stent with respect to the primary endpoint at 18 months. We assumed an event rate of 5% in each stent group. We set a non-inferiority margin at 1.5, with a one-sided significance level of 0.05, 90% power and a 10% loss-to-follow-up rate. The calculated sample size was 1,192 in each treatment arm.

We constructed survival curves showing cumulative incidence rates based on time to events, accounting for the competing risk of death (in cases of death not included in the outcome). Patients who received the BioMatrix stent were deemed to be the reference group for overall and subgroup analyses. We calculated rate ratios for TLF at the 18-month follow-up for pre-specified patient subgroups (based on baseline demographic and clinical characteristics). We regarded a two-sided p-value of <0.05 as indicating statistical significance. Statistical analyses were performed using R, version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Between July 2014 and September 2017, 2,341 patients were randomly assigned to receive either the BioMatrix stent (1,166 patients [1,512 lesions]) or the Orsiro stent (1,175 patients [1,526 lesions]) **(Figure 1)** in the participating centres **(Supplementary Table 1, Supplementary Appendix 6)**. Six patients withdrew consent during follow-up, three patients were lost to follow-up at one year, and five patients were excluded because they were found to meet the exclusion criteria after enrolment. Complete follow-up data were available for 2,327 patients (99.4%) for ITT analysis and 2,262 patients for PP analysis. Baseline patient characteristics are summarised in **Table 1** and did not differ significantly between the two groups. Lesion and procedure characteristics did not differ significantly between the two stent groups except for the maximal pressure, which was lower in the BioMatrix stent group (10.25±3.71 atm vs 11.39±3.50 atm; $p<0.001$) **(Table 2)**. A high proportion of patients in both of the groups had acute coronary syndromes, multivessel disease, and complex lesions **(Table 2)**.

At 18 months, the primary endpoint, TLF, occurred in 34 (2.9%) patients in the BioMatrix group and 24 (2.1%) patients

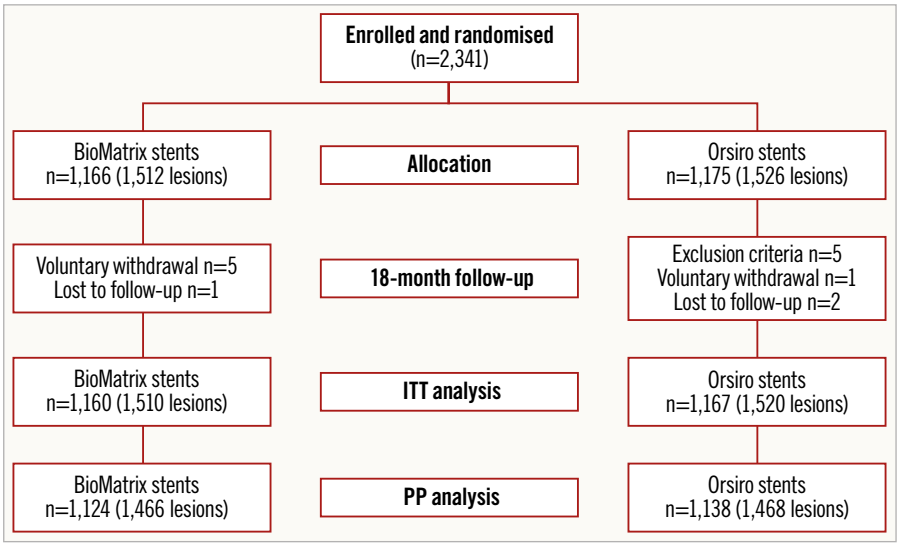

Figure 1. *Study flow chart.*

Table 1. Baseline characteristics of the study population.

		BioMatrix (n=1,160)	Orsiro (n=1,167)	*p*-value
Age, years		63.6±11.1	63.4±10.7	0.583
Men		838 (72.2)	835 (71.6)	0.746
Body mass index, kg/m^2		25.1±3.3	25.1±3.3	0.644
Diabetes mellitus		393 (33.9)	384 (32.9)	0.650
Arterial hypertension		706 (60.9)	685 (58.7)	0.307
Current smoker		306 (26.4)	324 (27.8)	0.327
Dyslipidaemia		625 (53.9)	609 (52.2)	0.437
Previous percutaneous coronary intervention		147 (12.7)	135 (11.6)	0.452
Previous coronary artery bypass grafting		10 (0.9)	8 (0.7)	0.803
Previous myocardial infarction		56 (4.8)	60 (5.1)	0.801
Previous cerebrovascular accident		83 (7.2)	78 (6.7)	0.710
Atrial fibrillation		47 (4.1)	35 (3.0)	0.389
Clinical diagnosis for percutaneous coronary intervention	Silent ischaemia	65 (5.6)	55 (4.7)	0.448
	Stable angina	313 (27.0)	328 (28.1)	
	Unstable angina	424 (36.6)	424 (36.4)	
	Non-ST-segment elevation myocardial infarction	257 (22.2)	238 (20.4)	
	ST-segment elevation myocardial infarction	101 (8.7)	121 (10.4)	
IVUS/OCT-guided		273 (23.5)	265 (22.7)	0.672
Total stent length per patient lesion, mm	<35	747 (64.4)	719 (61.6)	0.177
	≥35	413 (35.6)	448 (38.4)	
Min. stent diameter per patient, mm	<3	541 (46.6)	531 (45.5)	0.611
	≥3	619 (53.4)	636 (54.5)	
Target lesion per patient	1	848 (73.1)	854 (73.2)	0.590
	2	236 (20.3)	246 (21.1)	
	3	62 (5.3)	59 (5.1)	
	>3	14 (1.2)	8 (0.7)	
	Number per patient	1.30	1.30	
Medication at discharge				
Aspirin		1,147 (99.0)	1,155 (99.0)	>0.999
Clopidogrel		961 (82.9)	961 (82.4)	0.759
Ticagrelor		140 (12.1)	152 (13.0)	0.532
Prasugrel		43 (3.7)	39 (3.3)	0.709
Renin-angiotensin system inhibitors		738 (63.7)	737 (63.2)	0.827
Beta-blocker		720 (62.2)	744 (63.8)	0.457
Statin		1,096 (94.6)	1,099 (94.2)	0.750

Table 2. Lesion and procedure characteristics.

		BioMatrix (n=1,510)	Orsiro (n=1,520)	*p*-value
Target vessel location	LM (%)	57 (3.8)	43 (2.8)	0.175
	LAD (%)	775 (51.3)	733 (48.2)	0.095
	LCX (%)	345 (22.9)	340 (22.4)	0.786
	RCA (%)	386 (25.6)	441 (29.0)	0.037
Lesion type	A	106 (7.0)	118 (7.8)	0.682
	B1	395 (26.2)	413 (27.2)	
	B2	385 (25.5)	389 (25.6)	
	C	624 (41.3)	600 (39.5)	
Chronic total occlusion		72 (4.8)	93 (6.1)	0.119
Bifurcation lesion		219 (14.5)	321 (15.2)	0.627
Lesion length, mm		21.8±10.1	21.8±10.2	0.934
Pre-stent reference vessel diameter, mm		2.50±0.71	2.50±0.74	0.916
Direct stenting		174 (11.5)	172 (11.3)	0.842
Number of stents per patient		1.45±0.74	1.47±0.76	0.477
Number of stents per lesion		1.11±0.34	1.13±0.37	0.205
Total stent length per patient lesion		34.7±21.1	35.4±21.6	0.470
Total stent length per lesion		26.67±12.2	27.1±12.8	0.294
Sum of stent length per lesion, mm	<35	1,227 (81.3)	1,192 (78.4)	0.057
	≥35	283 (18.7)	328 (21.6)	
Average of stent diameter, mm		3.00±0.41	3.03±0.44	0.071
Min. stent diameter per lesion, mm	<3	664 (44.0)	643 (42.3)	0.372
	≥3	846 (56.0)	877 (57.7)	
Maximal pressure, atm		10.1±3.7	11.4±3.5	<0.001
Minimal lumen diameter, mm		0.58±0.39	0.59±0.42	0.384
Diameter stenosis, %		77.7±14.1	77.7±14.3	0.970
Post-stent minimal lumen diameter, mm		2.66±0.56	2.68±0.57	0.327
Post-stent reference diameter, mm		3.06±0.61	3.07±0.06	0.706
Post-stent diameter stenosis, %		13.5±7.1	13.2±7.3	0.228
Acute gain, mm		2.08±0.62	2.09±0.61	0.826
Delivery failure		0 (0)	1 (0.07)	0.319
IVUS/OCT-guided		346 (22.9)	345 (22.7)	0.921

in the Orsiro group **(Figure 2, Table 3)**. The non-inferiority of the Orsiro stent was confirmed with a risk ratio of 0.70 and an upper limit of the one-sided 95% confidence interval (CI) of 1.17 (p<0.001 in one-sided non-inferiority test). No significant differences were noted in the rates of cardiac death, target vessel-related myocardial infarction, ischaemia-driven target lesion revascularisation, and the patient-oriented composite endpoint **(Figure 2, Table 3)**. Only two (0.2%) patients in the Orsiro stent group had late definite stent thrombosis (one patient at 60 days and the other at 270 days after index PCI). The two patients were taking dual antiplatelet therapy with aspirin and clopidogrel.

The results on a PP basis were not different from the ITT analyses **(Supplementary Table 2)**. We also analysed the cumulative incidence rate of TLF and a competing risk of non-cardiac death to avoid a possible upward biased estimate of the true cumulative incidence rate. In the analysis considering the competing risk, the primary endpoint was not different between the stent groups **(Supplementary Figure 1)**.

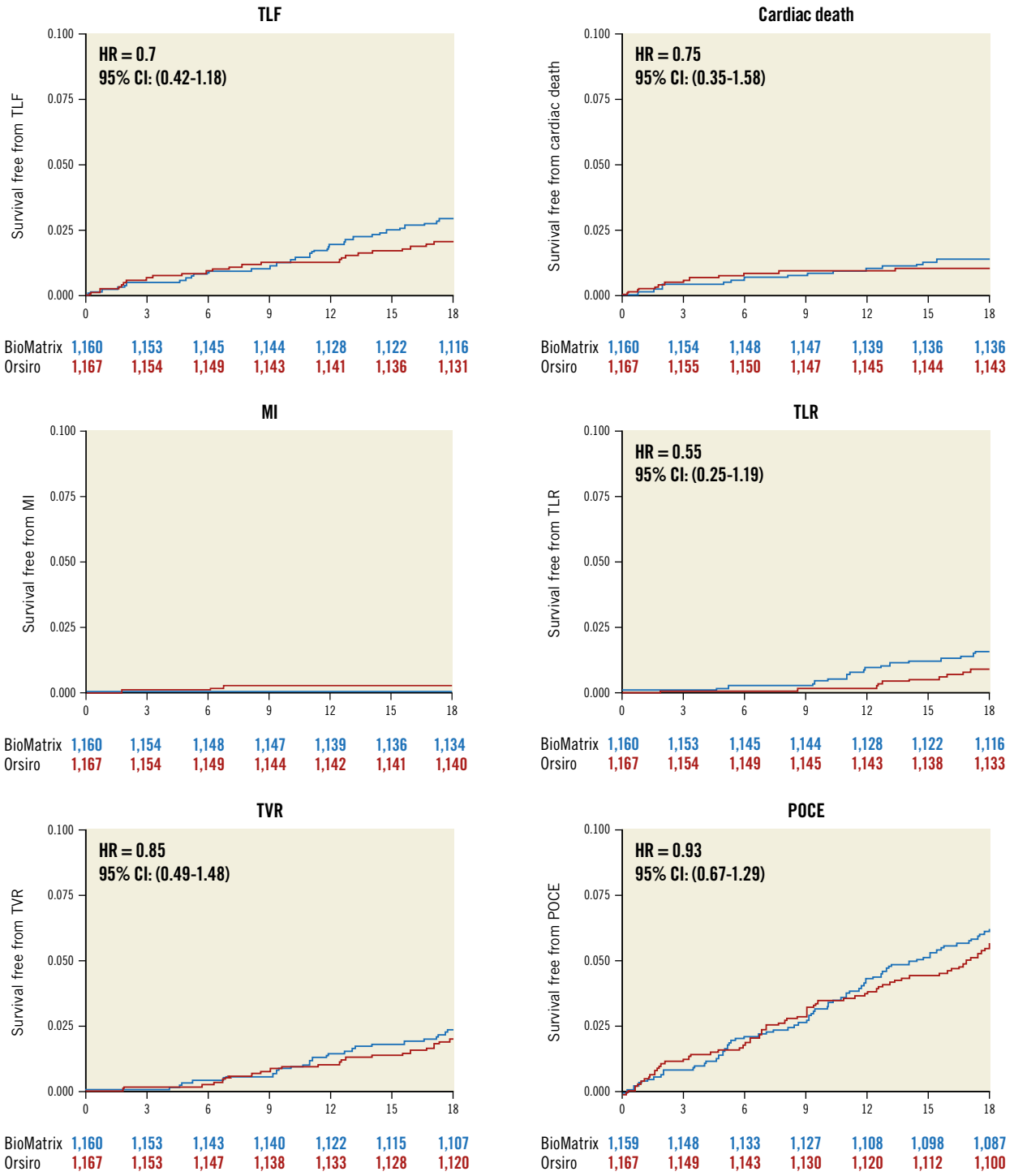

Figure 2. *Clinical outcomes during the 18-month follow-up period. MI: target vessel-related myocardial infarction; POCE: patient-oriented composite endpoint; TLF: target lesion failure; TLR: ischaemia-driven target lesion revascularisation; TVR: ischaemia-driven target vessel revascularisation*

In various subgroup analyses, the findings for TLF were consistent across the pre-specified subgroups except for diabetes mellitus **(Figure 3)**. In patients without diabetes mellitus, TLF occurred less frequently in the Orsiro stent group than in the BioMatrix stent group (hazard ratio [HR] 0.42, 95% CI: 0.20-0.89, p=0.024, p for interaction=0.041), which was driven mainly by lower ischaemia-driven target lesion revascularisation (HR 0.15, 95% CI: 0.03-0.66, p=0.012).

Discussion

In this BIODEGRADE study, the biodegradable polymer thin-strut Orsiro stent was non-inferior to the biodegradable polymer

Table 3. Clinical outcomes.

	BioMatrix (n=1,160)	Orsiro (n=1,167)	*p*-value	HR (95% CI)
Target lesion failure	34 (2.9)	24 (2.1)	0.222	0.70 (0.42-1.18)
Death				
All-cause death	26 (2.2)	24 (2.1)	0.869	0.92 (0.53-1.60)
Cardiac death	16 (1.4)	12 (1.0)	0.558	0.75 (0.35-1.58)
Non-cardiac death	10 (0.9)	12 (1.0)	0.841	1.20 (0.52-2.77)
Target vessel-related myocardial infarction	0 (0.0)	3 (0.3)	0.250	–
Any myocardial infarction	2 (0.2)	9 (0.8)	0.071	4.49 (0.97-20.80)
Ischaemia-driven target lesion revascularisation	18 (1.6)	10 (0.9)	0.178	0.55 (0.25-1.19)
Ischaemia-driven target vessel revascularisation	27 (2.3)	23 (2.0)	0.652	0.85 (0.49-1.48)
Any repeat revascularisation	47 (4.1)	43 (3.7)	0.725	0.91 (0.60-1.37)
Stent thrombosis*	0 (0.0)	2 (0.2)	0.500	–
Patient-oriented composite endpoint	74 (6.4)	69 (5.9)	0.702	0.93 (0.67-1.29)
Bleeding	28 (2.4)	27 (2.3)	0.979	0.96 (0.56-1.63)

*Stent thrombosis: 1st case, definite late stent thrombosis leading to myocardial infarction; 2nd case, definite late stent thrombosis causing unstable angina.

thick-strut BioMatrix stent for TLF at 18 months. All secondary outcomes including cardiac mortality, target vessel-related myocardial infarction, target lesion revascularisation, and stent thrombosis did not differ between the two groups.

The BIODEGRADE study was designed to confirm the non-inferiority of the Orsiro stent to the BioMatrix stent, which is currently the leading BP-DES. Compared with the BioMatrix stent, the sirolimus-eluting Orsiro stent has improved stent design with hypothetical benefit: a silicone carbide coating, thinner stent struts (60-80 µm vs 120 µm), slower drug release (12 weeks vs four weeks), and more delayed polymer degradation (after 12-24 months vs 6-9 months) than the BioMatrix stent. The thin-strut Orsiro stent recently showed better efficacy than the second-generation thick-strut DES[12-14]. Definite stent thrombosis was absent in the Orsiro stent[12], and the 12-month TLF rate was lower with the Orsiro stent than with the XIENCE stent (Abbott Vascular, Santa Clara, CA, USA). In addition, patients with the Orsiro stent in small coronary vessels showed notably less three-year TLF than those with second-generation zotarolimus-eluting stents[14]. These studies compared the thin-strut BP-DES to the second-generation DES with durable polymer in which BP-DES showed superiority. However, the trials comparing thinner DES and the thicker BioMatrix stent did not show superiority of the thin-strut DES[15]. Similarly, in our study, we compared two BP-DES with different strut thicknesses and found that there was no difference in the outcomes. We think that the durability of the polymer may have a more important role in the inferior clinical outcome than has the thickness. However, we need more data to conclude the thickness hypothesis.

While we were recruiting patients, the result of SORT-OUT VII was reported, i.e., that the Orsiro stent had better efficacy than the Nobori® stent (Terumo, Tokyo, Japan)[16]. The one-year TLF rate was 3.8% (48 patients) in the Orsiro group and 4.6% (58 patients)

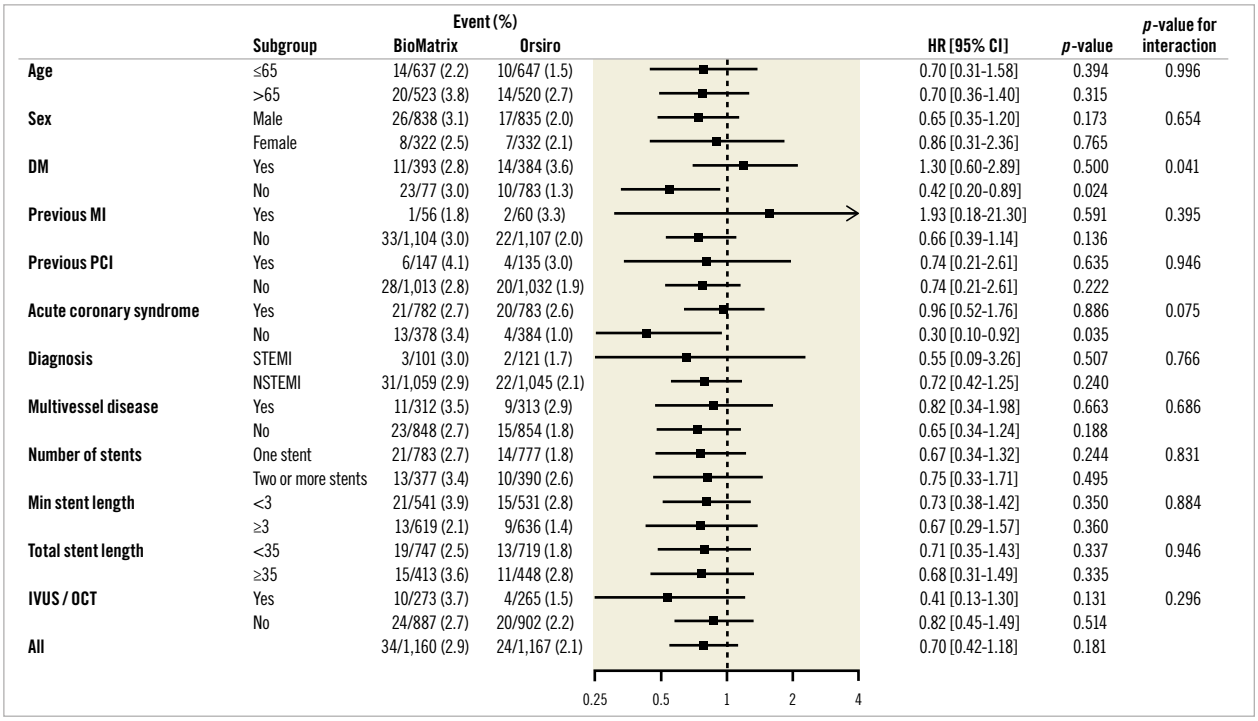

Figure 3. *Subgroup analysis. DM: diabetes mellitus; MI: myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; RR: risk ratio; STEMI: ST-segment elevation myocardial infarction*

in the Nobori group, and that of definite stent thrombosis was 0.4% (5 patients) in the Orsiro group and 1.2% (15 patients) in the Nobori group (p=0.034). Nobori and BioMatrix stents are similar in all aspects, except for the presence of an ultra-thin non-degradable parylene coating between the stent and the polymer on the Nobori stent. The Nobori stent, unlike the BioMatrix stent, failed to show non-inferiority to the CYPHER® stent (Cordis) within one year in the SORT OUT V trial[17]. In the COMPARE II trial, definite or probable stent thrombosis was higher in the Nobori stent group than in the second-generation XIENCE stent group[18]. However, the thick-strut BioMatrix stent showed no difference with respect to TLF and stent thrombosis compared to the thin-strut everolimus-eluting SYNERGY™ stent (Boston Scientific, Marlborough, MA, USA) with biodegradable polymers[15]. It is not certain whether the parylene coating influences the stent thrombosis. It is certain, however, that the Nobori and BioMatrix stents showed different clinical outcomes.

We observed less ischaemia-driven target lesion revascularisation in Orsiro stent-treated patients without diabetes mellitus. The five-year outcomes of the BIOFLOW-II study revealed an interaction with the stents and diabetes mellitus: the Orsiro stent was associated with a significantly higher target lesion revascularisation than the XIENCE stent in patients with diabetes mellitus[12]. However, there was no interaction with diabetes mellitus in the SORT OUT VII study[16]. It may be interesting to elucidate whether the Orsiro stent performs better in patients without diabetes mellitus. However, this is only a hypothesis-generating finding, and could have been an incidental finding.

Study limitations

First, the observed 18-month TLF rate was 2.9% for the control group (the BioMatrix stents), which was lower than the assumed 5% used in the study power calculation. If we had assumed an expected event rate of 2.9% instead of 5%, the statistical power of this study to detect non-inferiority would have been as low as 76%. Second, despite the all-comer nature of the study population with wide inclusion criteria and very few exclusion criteria, the event rates were very low. There was also follow-up loss, which may raise the question of underreporting. However, this limitation may not have biased the results because the follow-up loss was negligible (only 0.6%) and evenly distributed between the treatment groups, and periodic monitoring and data audits were thoroughly performed during this trial. One possible reason for the low event rates may be the selection bias during screening of eligible patients because we excluded patients with cardiogenic shock with Killip class IV, symptomatic heart failure, or non-cardiac comorbid conditions that may result in life expectancy <1 year or protocol non-compliance. We did not measure post-PCI cardiac enzyme routinely in the study, which may have led to the lower incidence of events such as periprocedural myocardial infarction. There might also be an ethnic or genetic factor, as trials conducted in East Asian populations have consistently reported lower event rates[19,20]. Finally, our primary endpoint might be limited by the relatively short follow-up period. Therefore, we will assess the TLF at three years, as previously set out in the design of the trial.

Conclusions

The Orsiro stent was not inferior to the BioMatrix stent in patients with minimum exclusion criteria and a high proportion of acute coronary syndromes. Both BP-DES showed good clinical outcomes.

Impact on daily practice

In this trial, we randomly assigned 1,175 and 1,166 patients to treatment with thin-strut sirolimus-eluting stents (Orsiro), and treatment with thick-strut biolimus-eluting stents (BioMatrix), respectively. Both the thin-strut Orsiro stents and the thick-strut BioMatrix stents showed good intermediate-term clinical outcomes. The stent design of biodegradable polymer may have limited effects on outcomes.

Funding

This research was supported by grants from the Korean Health Technology R&D Project, Ministry of Health and Welfare (HI17C1799, HI18C0493, and HI19C0655) and grants from BIOTRONIK Korea, Seoul, Republic of Korea, and DIO Korea, Seoul, Republic of Korea.

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Conflict of interest statement

The authors/study collaborators have no conflicts of interest to declare.

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Supplementary data

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The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-20-00185

Supplementary data

Supplementary Appendix 1. Inclusion and exclusion criteria

Patients were eligible if they were at least 20 years old, had chronic stable coronary artery disease or acute coronary syndromes, and had at least one lesion of the coronary arteries or venous or arterial bypass grafts with >50% diameter stenosis that required treatment with a DES. Moreover, the subjects had to have evidence of myocardial ischaemia (e.g., stable, unstable angina, recent infarction, silent ischaemia, positive functional study, or a reversible change in the electrocardiogram consistent with ischaemia). In subjects with diameter stenosis >70%, evidence of myocardial ischaemia did not have to be documented. Angiographically, target lesion(s) had to be located in arteries with diameters of ≥2.5 mm and ≤4.5 mm and had to be amenable to PCI.

The exclusion criteria were life expectancy of <1 year; allergy to aspirin, clopidogrel, ticagrelor, prasugrel, sirolimus, or biolimus; participation in another randomised stent trial; inability to provide written informed consent; cardiogenic shock with Killip class IV; symptomatic heart failure; or non-cardiac comorbid conditions that may result in life expectancy <1 year or protocol non-compliance (per site investigator's medical judgement).

Supplementary Appendix 2. The characteristics of the stents

The Orsiro stent is a cobalt-chromium stent with ultra-thin strut thickness (60 μm for stent diameters of 2.25–3.00 mm and 80 μm for stent diameters of 3.50-4.00 mm). It has a passive silicone carbide stent coating and an active biodegradable poly-L-lactic polymer in a circumferential pattern. The poly-L-lactic polymer is degraded over 12-24 months. The antiproliferative agent, sirolimus, is fully eluted at three months [10]. The BioMatrix stent is made of 316L stainless steel with 120 μm thickness and a polylactic acid abluminal polymer that is degradable at nine months. The antiproliferative agent is biolimus, which is eluted over six months [10].

Supplementary Appendix 3. Antithrombotic therapy

All patients were administered aspirin and one $P2Y_{12}$ inhibitor (clopidogrel, prasugrel, or ticagrelor) before the procedure according to the investigator's discretion. The dose of each drug was at the discretion of each investigator. Aspirin was administered indefinitely and clopidogrel, prasugrel, or ticagrelor was administered for at least one year thereafter. Unfractionated heparin (70-100 IU/kg) was administered before the procedure. Glycoprotein IIb/IIIa inhibitors were used at the operator's discretion.

Supplementary Appendix 4. The definition of endpoints, event detection, site monitoring and event adjudication

Definitions

Cardiac death was defined as any death due to an evident cardiac cause, any death related to PCI, an unwitnessed death, or death from unknown causes. Myocardial infarction was defined according to the third universal definition of myocardial infarction [15]. Myocardial infarction not related to other than the target vessel was defined as any myocardial infarction that was not clearly attributable to a non-target vessel. Target lesion revascularisation was defined as repeat revascularisation with PCI or surgical bypass due to >50% stenosis within the stent or within a 5 mm border proximal or distal to the stent. Target vessel revascularisation was defined as any repeat PCI 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. Revascularisation was considered to be ischaemia-driven if angiography during follow-up showed a diameter stenosis ≥50% with at least one of the following: 1) history of recurrent angina pectoris, presumably related to the target vessel; 2) objective signs of ischaemia at rest or during exercise test by electrocardiography, presumably related to the target vessel; or 3) abnormal test results of invasive functional diagnostic test (fractional flow reserve). Stent thrombosis was defined as definite, probable, or possible stent thrombosis according to the Academic Research Consortium definition [16].

Clinical event detection

Clinically, follow-up of the patients occurred at predetermined schedules at 1, 6, 12 and 18 months. Follow-up comprised preferentially office visits, but telephone contact was also allowed. During the follow-up visits, data on angina class and adverse ischaemic, neurologic, and bleeding events were collected. Original source documents were submitted for any clinical events (death, myocardial infarction, revascularisation, stroke, or any other serious adverse events). If the patient was readmitted in a non-study hospital, all efforts were made to obtain original source documents from that hospital. For myocardial infarctions, electrocardiogram and cardiac enzyme (creatine kinase, creatine kinase MB, and troponin) data were obtained and recorded.

Site monitoring

A designated trial monitor at appropriate intervals reviewed investigational data for accuracy and completeness and to ensure compliance with the protocol. If necessary, this trial monitor inspected all documents and required records that are maintained by the investigator/site, including medical records (office, clinic, or hospital) for the subjects in this trial.

Clinical event adjudication

With the exception of all-cause mortality, most endpoints required clear, pre-specified criteria, and centralised review by an independent clinical events adjudication committee (CEAC) blinded to treatment allocation. These endpoints were captured during patient interview, supplemented by death certificates; hospital record abstracts and related reports (angiography, echocardiography and other clinical information). First, all required

documents, reports, hospital records were identified, made anonymous, and copied to the data coordinating centre (DCC) by clinical staff. Second, the DCC checked to ensure confidentiality and, if required, had the records centrally abstracted onto standard forms by trained DCC staff. Third, centrally prepared forms and documents were circulated to CEAC members for assessment.

Supplementary Appendix 5. Statistical analysis

The trial was powered for the non-inferiority of the Orsiro stent to the BioMatrix stent with respect to the primary endpoint at 18 months. Target lesion failure of second-generation DES at one year had been reported 2.9%-5.6% in Korea [15,16]. We designed 18-month follow-up and recruited centres had performed PCI for acute coronary syndrome at a high percentage. Therefore, we assumed an event rate of 5% in each stent group. The hazard ratio of the historical placebo (bare metal stent) versus DES was 3.22 (95% confidence interval [CI]: 2.04-5.0) [17]. In a recent study showing the inferiority of a DES versus another DES, the hazard ratio was 2.43 (95% CI: 1.50-3.94) [18]. Therefore, we set a non-inferiority margin at 1.5, which was lower than the lower bound of the hazard ratio of the previous inferior DES and was much lower than that of a bare metal stent. Non-inferiority would be acknowledged if the upper limit of the one-sided 95% CI of the risk ratio of TLF was not greater than 1.5. With a sample size of 1,073 patients in each treatment arm, a two-group survival non-inferiority with a one-sided significance level of 0.05 would have 90% power to detect the non-inferiority with a predetermined non-inferiority margin of 1.5. The sample size with 1,192 in each treatment arm assumed a 10% loss-to-follow-up rate.

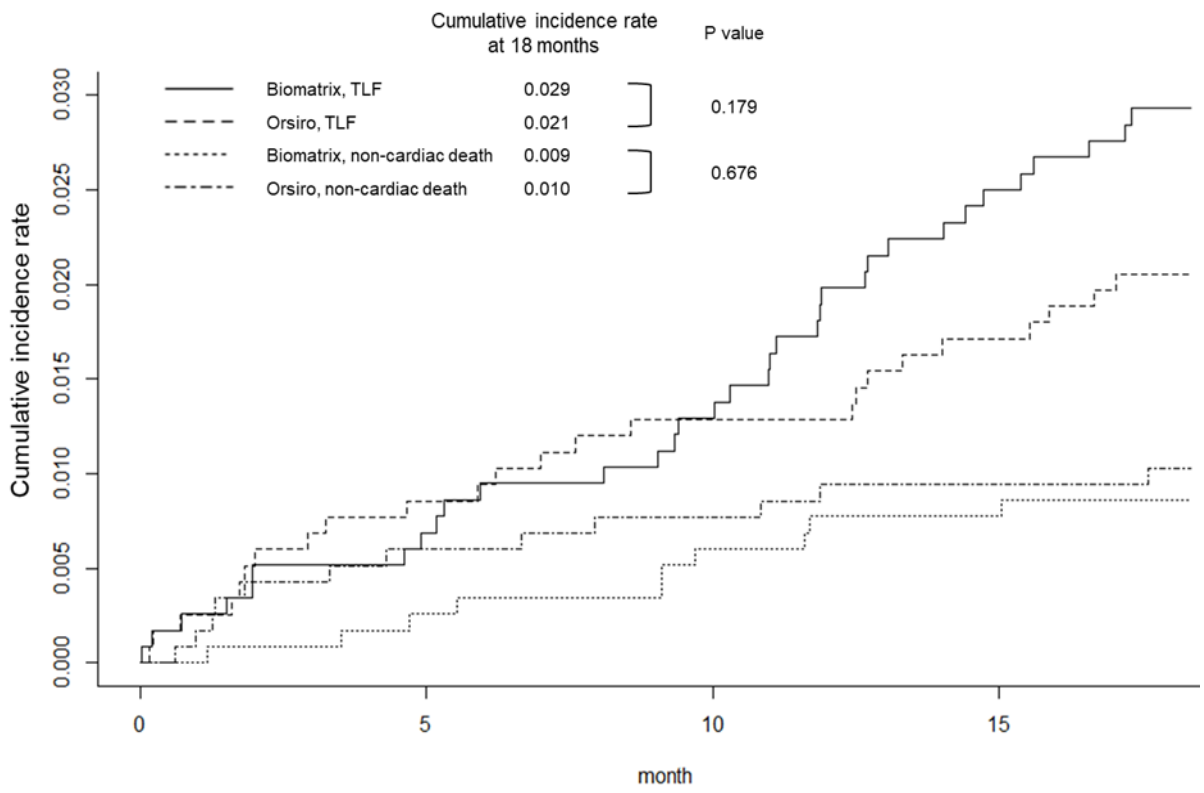
We compared continuous variables between the study groups using the two-sample t-test or the Mann-Whitney U test, depending on whether the data followed a normal distribution. We analysed distributions of categorical variables using the χ^2 test. In the analyses of every endpoint, follow-up continued until the date of an endpoint event, death, or 18 months after stent implantation, whichever came first. We constructed survival curves displaying cumulative incidence rates based on time to events, accounting for the competing risk of death (in cases of death not included in the outcome). Patients who received the BioMatrix stent were used as the reference group for overall and subgroup analyses. We calculated rate ratios for TLF at the 18-month follow-up for pre-specified patient subgroups (based on baseline demographic and clinical characteristics). The intention-to-treat (ITT) principle was used for all analyses. We also performed per-protocol (PP) analyses. Except for the inferiority testing of the primary endpoint, we regarded a two-sided p-value of <0.05 as indicating statistical significance. Statistical analyses were performed using R, version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria). All the analyses were performed by a professional statistician (S.H. Kim).

Supplementary Appendix 6. A list of centres and investigators

In-Ho Chae[1], MD; Young Jin Choi[2], MD; Myeong-Kon Kim[3], MD; Kwang Soo Cha[4], MD; Seung-Hwan Lee[5], MD; Bum-Kee Hong[6], MD; Seung-Woon Rha[7], MD; Woong Chol Kang[8], MD; Jae-Hwan Lee[9], MD; Sang-Hyun Kim[10], MD; Nam-Ho Lee[11], MD; Kyung-Joo Ahn[12], MD; Hun-Sik Park[13], MD; Dae-Gyun Park[14], MD; Doo-Il Kim[15], MD; Hee-Yeol Kim[16], MD; Sang-Uk Lym[17], MD; Yong Sung Seo[18], MD; Ki-Yuk Chang[19], MD; Tae-Jun Cha[20], MD; Byeong-Hee Hwang[21], MD; Byung-Ryul Cho[22], MD; Byoung-Eun Park[23], MD; Hee-Kyung Jeon[24], MD; Jong-Seon Park[25], MD

1. Seoul National University Bundang Hospital, Seongnam, Republic of Korea;
2. Sejong General Hospital, Bucheon, Republic of Korea;
3. Catholic Kwandong University International St. Mary's Hospital, Incheon, Republic of Korea;
4. Pusan National University Hospital, Pusan, Republic of Korea;
5. Wonju Severance Hospital, Yonsei University College of Medicine, Republic of Korea;
6. Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea;
7. Korea University Guro Hospital, Seoul, Republic of Korea;
8. Gacheon University Gil Medical Center, Incheon, Republic of Korea;
9. Chungnam National University Hospital, Daejeon, Republic of Korea;
10. Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul, Republic of Korea;
11. Hallym University Kangnam Sacred Heart Hospital, Seoul, Republic of Korea;
12. KEPCO Medical Center, Seoul, Republic of Korea;
13. Kyoungpook National University Hospital, Daegu, Republic of Korea;
14. Hallym University Kangdong Sacred Heart Hospital, Seoul, Republic of Korea;
15. Inje University Paik Hospital, Pusan, Republic of Korea;
16. The Catholic University of St. Mary's Hospital, Bucheon, Republic of Korea;
17. Cha University Bundang Cha Medical Center, Seongnam, Republic of Korea;
18. Myongji Hospital, Goyangsi, Republic of Korea;
19. The Catholic University of St. Mary's Hospital, Seoul, Republic of Korea;
20. Kosin University Gospel Hospital, Pusan, Republic of Korea;
21. The Catholic University of St Paul's Hospital, Seoul, Republic of Korea;
22. Kangwon National University Hospital, Chuncheon, Republic of Korea;
23. Dankook University Hospital, Cheonan, Republic of Korea;
24. The Catholic University of St. Mary's Hospital, Uijeongbu, Republic of Korea;
25. Yongnam University Medical Center, Daegu, Republic of Korea

Supplementary figure. Cumulative incidence rates with a competing risk, non-cardiac death



Supplementary Figure 1. The cumulative incidence rate of the primary endpoint and a competing risk, non-cardiac death.

Supplementary Table 1. The number of patients per centre.

ID	Centre	Number
1	Seoul National University Bundang Hospital	923
2	Sejong General Hospital	143
3	Catholic Kwandong University International St. Mary's Hospital	139
4	Pusan National University Hospital	124
5	Wonju Severance Hospital, Yonsei University College of Medicine	122
6	Gangnam Severance Hospital, Yonsei University College of Medicine	104
7	Korea University Guro Hospital	96
8	Gacheon University Gil Medical Center	84
9	Chungnam National University Hospital	81
10	Seoul Metropolitan Government Seoul National University Boramae Medical Center	77
11	Hallym University Kangnam Sacred Heart Hospital	73
12	KEPCO Medical Center	71
13	Kyoungpook National University Hospital	62
14	Hallym University Kangdong Sacred Heart Hospital	50
15	Inje University Paik Hospital, Pusan	30
16	The Catholic University of St. Mary's Hospital, Bucheon	29
17	Cha University Bundang Cha Medical Center	26
18	Myongji Hospital	19
19	The Catholic University of St. Mary's Hospital, Seoul	18
20	Kosin University Gospel Hospital	14
21	The Catholic University of St Paul's Hospital	13
22	Kangwon National University Hospital	12
23	Dankook University Hospital, Cheonan	10
24	The Catholic University of St. Mary's Hospital, Uijeongbu	5
25	Yongnam University Medical Center	2

Supplementary Table 2. The results on a per-protocol basis.

	BES	**SES**	HR (95% CI)	*p*-value
TLF	34 (2.9)	24 (2.1)	0.70 (0.41-1.17)	0.175
Cardiac death	16 (1.4)	12 (1.1)	0.74 (0.35-1.57)	0.436
MI	0 (0.0)	3 (0.3)	-	-
TLR	18 (1.6)	10 (0.9)	0.55 (0.25-1.18)	0.125
All-cause death	26 (2.2)	23 (2.0)	0.88 (0.50-1.54)	0.643
TVR	10 (0.9)	15 (1.3)	1.49 (0.67-3.31)	0.331
RR (TLR or TVR)	26 (2.3)	22 (1.9)	0.84 (0.47-1.47)	0.534
CVA	11 (1.0)	7 (0.6)	0.63 (0.24-1.62)	0.335
ST	0 (0.0)	2 (0.2)	-	-
BL	27 (2.4)	27 (2.4)	0.99 (0.58-1.68)	0.964