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Long-term clinical outcomes with biodegradable polymer sirolimus-eluting stents versus durable polymer sirolimus-eluting stents

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KEYWORDS

- ACS/NSTE-ACS
- clinical research
- stable angina
- STEMI

Abstract

Aims: The purpose of this study was to compare the long-term outcomes of a biodegradable polymer, sirolimus-eluting stent (Orsiro) with a durable polymer, sirolimus-eluting stent (CYPHER) to determine if late failure of the CYPHER is caused by the polymer or sirolimus.

Methods and results: A total of 447 patients who underwent percutaneous coronary intervention (PCI) with one of the study stents were retrospectively analysed. The composite of cardiac death, stent thrombosis, and clinically driven target lesion revascularisation (TLR) within two years after PCI occurred in 3.0% of the Orsiro group and 9.6% of the CYPHER group. Multivariable Cox regression results indicated that the Orsiro stent was a significant independent predictor of a lower occurrence of the composite outcome (adjusted HR 0.37, 95% CI: 0.14-0.87), stent thrombosis (adjusted HR 0.07, 95% CI: 0.00-0.65), clinically driven TLR (adjusted HR 0.26, 95% CI: 0.09-0.69), and stent failure (adjusted HR 0.26, 95% CI: 0.09-0.69) within two years after PCI.

Conclusions: This study has demonstrated that late CYPHER failure is attributable more to its durable polymer than to the antiproliferative drug, sirolimus. This suggests that sirolimus-based, new-generation drug-eluting stents are relatively safe and are expected to show long-term outcomes superior to those of the CYPHER.

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Abbreviations

ACC	American College of Cardiology
AHA	American Heart Association
BMS	bare metal stent(s)
BP-SES	biodegradable polymer sirolimus-eluting stent(s)
CI	confidence interval
DES	drug-eluting stent(s)
DP-EES	durable polymer everolimus-eluting stent(s)
DP-SES	durable polymer sirolimus-eluting stent(s)
HR	hazard ratio
LVEF	left ventricular ejection fraction
PCI	percutaneous coronary intervention
PSS	peri-stent contrast staining
SD	standard deviation
TIMI	Thrombolysis In Myocardial Infarction
TLR	target lesion revascularisation

Introduction

First-generation drug-eluting stents (DES) with durable polymers for the controlled release of antiproliferative sirolimus have significantly reduced in-stent restenosis compared with bare metal stents (BMS)[1,2]. However, unexpectedly, first-generation DES brought new problems, i.e., late and very late stent thrombosis[3]. Synthetic non-absorbable polymers or antiproliferative drugs were considered important stimuli for vascular wall inflammation responses subsequent to a hypersensitivity reaction. According to previous pathological studies of the CYPHER® (Cordis, Cardinal Health, Milpitas, CA, USA) durable polymer sirolimus-eluting stent (DP-SES), hypersensitivity to the polymer was the most likely mechanism for the inflammatory reaction of the coronary artery wall[4,5]. Although studies were in an *in vitro* setting, there were concerns that sirolimus caused impairment of relaxation to serotonin and bradykinin of vascular smooth muscle cells subsequent to endothelial dysfunction and enhanced platelet aggregation[6-8].

Numerous trials have been undertaken to determine the factors associated with CYPHER stent failure. However, until now, there have been no head-to-head comparisons of DP and biodegradable polymers (BP) in stents with the same antiproliferative drug, sirolimus, to clarify whether CYPHER stent failure could have been caused by the polymer or the sirolimus.

Therefore, we compared the relative long-term safety and efficacy of BP-SES (Orsiro; Biotronik, Bülach, Switzerland) with DP-SES (CYPHER) in patients undergoing percutaneous coronary intervention (PCI).

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Methods

STUDY DESIGN AND PATIENTS

This retrospective, observational single-centre study was undertaken at the Seoul National University Boramae Medical Center in Seoul, Republic of Korea. A total of 447 consecutive patients who underwent PCI from May 2008 to June 2016 with one of the study stents, BP-SES Orsiro or DP-SES CYPHER, were retrospectively analysed. The enrolment period of the DP-SES was from May 2008 to May 2011, and of the BP-SES from September 2013 to July 2016. There were no limitations to the number of treated lesions, lesion length and location, reference vessel diameter, and concomitant use of other BMS or DES. As early death is rarely correlated with the scope of late complications associated with either drug or polymer and is affected by patients' disease severity at initial presentation and procedural success, patients who died within 48 hours after PCI were excluded from the analysis. The Seoul National University institutional review board and ethics committee approved the study protocol.

PROCEDURES

PCI procedures were performed according to the current procedural standard. All patients received a 300 mg loading dose of aspirin and a 600 mg loading dose of clopidogrel, a 60 mg loading dose of prasugrel or a 180 mg loading dose of ticagrelor before or during PCI, unless they had previously received these antiplatelet drugs. During the PCI, weight-adjusted unfractionated heparin was given to keep the activated clotting time in the range of 250-350 seconds. The use of glycoprotein IIb/IIIa receptor inhibitors, intravascular ultrasound or post-dilatation after stent implantation was left to the operator's discretion. Pre- and post-PCI coronary flows were graded by applying Thrombolysis In Myocardial Infarction (TIMI) grading[9]. Coronary lesions were classified according to the American College of Cardiology/American Heart Association (ACC/AHA) coronary lesion classification system[10].

OUTCOMES AND DEFINITIONS

The primary outcome was the composite of cardiac death, stent thrombosis, and clinically driven target lesion revascularisation (TLR) occurring within two years of PCI. Secondary outcomes were cardiac death, stent thrombosis, clinically driven TLR, and stent failure defined as a composite of stent thrombosis and clinically driven TLR within two years of PCI. To investigate the late adverse effect of the polymer, a landmark analysis of the primary and stent failure outcomes from month 9 to month 24 post PCI was undertaken.

Cardiac death was defined as death from cardiac causes including myocardial infarction, decompensated heart failure, fatal arrhythmia, or sudden death of unknown cause. Stent thrombosis was defined as probable or definite stent thrombosis according to the Academic Research Consortium definitions[11]. TLR was defined as revascularisation with PCI or coronary artery bypass graft surgery performed for a ≥50% diameter stenosis within the index stent or within 5 mm proximal and/or distal to the implanted stents after documentation of recurrent symptoms, new electrocardiographic changes, or positive functional study suggesting ischaemia in a territory distal to the stented lesion at the time of the index procedure, or if the stenosis diameter was more than 70% in the index lesion, irrespective of the presence or absence of ischaemic signs and symptoms. Severe calcification was characterised by the presence of radiopacities noted without cardiac motion before contrast injection and generally compromising both

sides of the arterial lumen[12]. Clinical follow-up was carried out every one to six months and whenever any clinical event took place. All events were identified by the physician in charge and confirmed by the principal investigator.

STATISTICAL ANALYSIS

The results are presented as mean±standard deviation (SD) values for continuous variables and as a percentage for categorical variables. Continuous variables were analysed by using the Student's t-test. Categorical variables were analysed by using the Pearson's chi-squared test or Fisher's exact test, as appropriate. Survival curves for study outcomes were constructed by using Kaplan-Meier estimates and were compared with the log-rank test result to evaluate the difference in clinical event rates according to stent type. Cox regression analysis with Firth's penalised likelihood method was performed to determine independent associations of stents with clinical outcomes after PCI. In the multivariable analysis, prior history of myocardial infarction, clinical diagnosis, total stent length, minimal stent diameter, severe calcification of lesion, and left ventricular ejection fraction (LVEF) were included as covariates. All analyses were two-tailed, and statistical significance was defined as $p<0.05$. Statistical analyses were performed with the statistical packages SPSS, Version 20.0 (IBM Corp., Armonk, NY, USA) and R programming language version 3.3.1 with package coxphf (R Foundation for Statistical Computing, Vienna, Austria).

Results

Between May 2008 and July 2016, 447 consecutive patients with coronary artery disease underwent PCI with either Orsiro or CYPHER stents and survived for more than 48 hours after the index PCI. All were included in the analysis **(Figure 1)**. In the CYPHER group, the first case was undertaken in May 2008 when CYPHER was still popular, and the last case was in May 2011. In the Orsiro group, the first case was in September 2013, and the last case was in July 2016.

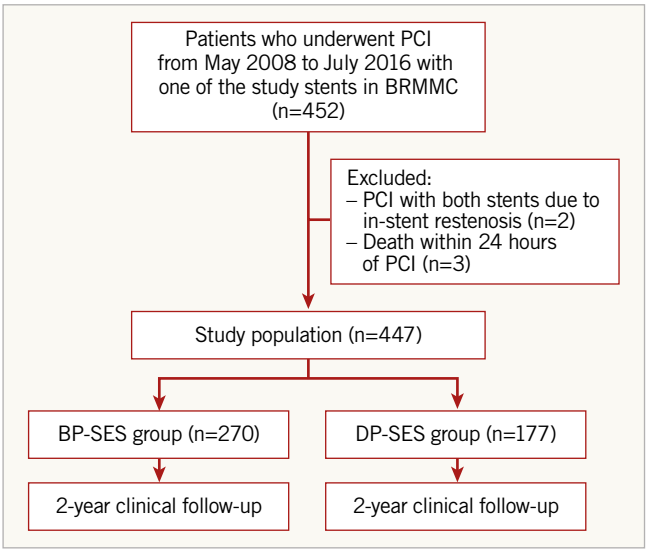

Figure 1. *Flow chart of the study groups established for analysis of stent type. BRMMC: Boramae Medical Center*

DEMOGRAPHIC AND BASELINE CHARACTERISTICS

The mean age of the study patients was 67.3±11 years, 285 (63.8%) patients were male, and 372 (83.2%) patients presented with acute coronary syndrome (ACS). Among the 447 patients, 177 patients underwent PCI with DP-SES for 270 lesions, and 270 patients with BP-SES for 358 lesions. Among the previous medical history and cardiovascular risk factors, the prevalence of dyslipidaemia was higher, while that of previous myocardial infarction was lower in the BP-SES group than in the DP-SES group. In terms of clinical diagnosis, ACS was less prevalent, whereas multivessel disease was more prevalent in the BP-SES group than in the DP-SES group. At discharge, a beta-blocker was prescribed less and a statin was prescribed more in the BP-SES group than in the DP-SES group. The rate of dual antiplatelet use was similar in the two groups at one year after PCI but was significantly lower in the BP-SES group than in the DP-SES group at two years after PCI **(Table 1)**. Newer-generation antiplatelet agents such as prasugrel or ticagrelor were prescribed only in the Orsiro group, in which only 18.1% of the patients received them.

BASELINE ANGIOGRAPHIC AND PROCEDURAL CHARACTERISTICS

Total stent length was shorter, whereas post-dilatation and final TIMI flow grade 3 in the target vessel were more common in the BP-SES group than in the DP-SES group. With regard to individual lesion characteristics, the rate of thrombus-containing lesions was less prevalent whereas severely calcified lesions were more prevalent in the BP-SES group than in the DP-SES group **(Table 2)**.

CLINICAL OUTCOMES

The cumulative clinical outcomes of the study patients are summarised in **Table 3** and Kaplan-Meier survival curves are shown in **Figure 2**. The primary outcome occurred significantly less often in the BP-SES group than in the DP-SES group (BP-SES vs. DP-SES, 3.0% vs. 9.6%, hazard ratio [HR] 0.41, 95% confidence interval [CI]: 0.17-0.91, p=0.028). As for secondary outcomes, cardiac death occurred at similar rates in both groups (1.1% vs. 1.1%, HR 1.42, 95% CI: 0.27-8.84, p=0.679). However, stent thrombosis (0.0% vs. 3.4%, HR 0.07, 95% CI: 0.00-0.56, p=0.008), clinically driven TLR (1.9% vs. 9.0%, HR 0.28, 95% CI: 0.10-0.70, p=0.005), and stent failure (1.8% vs. 9.0%, HR 0.28, 95% CI: 0.10-0.70, p=0.005) occurred significantly less often in the BP-SES group than in the DP-SES group.

Among the study population, 354 (79.2%) of the 447 patients in total had a nine-month angiographic follow-up. One patient in each group had a stent fracture at the nine-month follow-up (p=0.653). Peri-stent contrast staining (PSS) was observed

Table 1. Demographic and baseline clinical characteristics of study patients.

Variables	BP-SES (n=270)	DP-SES (n=177)	*p*-value
Demographics			
Age, years	67.32±11.17	67.27±10.83	0.965
Male	178 (65.9)	107 (60.5)	0.239
Body mass index (kg/m^2)	24.50±3.29	25.99±17.62	0.188
Comorbidities and risk factors			
Hypertension	184 (68.1)	128 (72.3)	0.348
Diabetes	118 (43.7)	62 (35.0)	0.067
Dyslipidaemia	184 (68.1)	101 (57.1)	0.017
Heart failure	19 (7.0)	13 (7.3)	0.902
Cerebrovascular disease	30 (11.1)	31 (17.5)	0.054
Chronic kidney disease	15 (5.6)	9 (5.1)	0.829
Current smoker	63 (23.3)	45 (25.4)	0.614
Family history of coronary artery disease	27 (10.0)	21 (11.9)	0.534
Previous myocardial infarction	24 (8.9)	43 (18.1)	0.004
LVEF	60.16±13.28	59.28±14.50	0.512
LV dysfunction (LVEF ≤40%)	33 (12.7)	26 (15.0)	0.488
Clinical diagnosis			
Stable angina	55 (20.4)	20 (11.3)	0.002
Unstable angina	128 (47.4)	84 (47.5)	
NSTEMI	57 (21.1)	33 (18.6)	
STEMI	30 (11.1)	40 (22.6)	
Acute coronary syndrome	215 (79.6)	157 (88.7)	0.012
Total number of diseased vessels			
1 vessel	43 (15.9)	46 (26.0)	0.006
2 vessels	89 (33.0)	65 (36.7)	
3 vessels	138 (51.1)	66 (37.3)	
Multivessel disease	227 (84.1)	131 (74.0)	0.009
Left main disease	35 (13.0)	15 (8.5)	0.141
Medication at discharge			
Aspirin	270 (100.0)	177 (100.0)	–
$P2Y_{12}$ inhibitors	265 (98.1)	172 (97.2)	0.496
Newer antiplatelets (prasugrel or ticagrelor)	49 (18.1)	0 (0)	<0.001
DAPT at 1 year	129/160 (80.6)	121/138 (87.7)	0.098
DAPT at 2 years	18/66 (27.3)	76/127 (59.8)	<0.001
RAS blockers	167 (61.9)	108 (61.0)	0.859
Beta-blockers	136 (50.4)	112 (63.3)	0.007
Statin	244 (90.4)	139 (78.5)	<0.001

Values are n (%) or mean±standard deviation. ACC: American College of Cardiology; AHA: American Heart Association; DAPT: dual antiplatelet therapy; LV: left ventricle; LVEF: left ventricular ejection fraction; NSTEMI: non-ST-segment elevation myocardial infarction; RAS: renin-angiotensin system; RVD: reference vessel diameter; STEMI: ST-segment elevation myocardial infarction

in six patients in the CYPHER group only (p=0.017) **(Figure 3)**. However, none of them experienced any clinical event during the whole follow-up period.

Among 447 patients, 344 patients were followed up from nine months to two years after PCI and were included in the nine months to 24 months landmark analysis of clinical outcomes after PCI. The composite of cardiac death, stent thrombosis, and clinically driven TLR occurred significantly less often in the BP-SES group than in the DP-SES group (2.1% vs. 7.7%, HR 0.33, 95% CI: 0.10-0.91, p=0.032). Similarly, stent failure after nine months of PCI occurred significantly less in the BP-SES group than in the DP-SES group (1.6% vs. 7.7%, HR 0.25, 95% CI: 0.06-0.74, p=0.011). Interestingly, even patients who did not take the newer antiplatelet therapy experienced fewer primary outcomes in the BP-SES group than in the DP-SES group (2.7% vs. 10.7% during the whole follow-up period, p=0.001; 2.1% vs. 9.0% during the nine-month landmark analysis, p=0.009). Additionally, the 49 patients who had received the newer antiplatelet therapy did not experience any cardiac death, stent thrombosis, or TLR events after discontinuation of the prasugrel or ticagrelor after 12 months.

The results of the multivariable Cox regression analysis revealed that BP-SES was a significant independent predictor of a lower occurrence of the primary outcome (adjusted HR 0.37, 95% CI: 0.14-0.87, p=0.022), stent thrombosis (adjusted HR 0.07, 95% CI: 0.00-0.65, p=0.015), clinically driven TLR (adjusted HR 0.26, 95% CI: 0.09-0.69, p=0.006), and stent failure (adjusted HR 0.26, 95% CI: 0.09-0.69, p=0.006) within two years after PCI. The multivariable Cox regression analysis for outcomes from nine months to 24 months after PCI demonstrated similar results. Compared to the DP-SES, the use of the BP-SES was significantly associated with a lower occurrence of the composite of cardiac death, stent thrombosis, or clinically driven TLR (adjusted HR 0.34, 95% CI: 0.10-0.97, p=0.043) and stent failure (adjusted HR 0.23, 95% CI: 0.06-0.74, p=0.012) from nine months to 24 months after PCI **(Table 4)**.

To determine whether the outcomes according to stent type were consistent, we calculated the HR for the primary outcome in various subgroups. The results revealed that there were no significant interactions between stent type and primary outcome in any of the subgroups even though, in subgroups of patients without diabetes, with severely calcified lesions, with a lesion longer than 24 mm, and with LVEF more than 40%, the BP-SES patients had significantly better clinical outcomes than the DP-SES patients **(Figure 4)**.

Discussion

In this observational study, we showed that the clinical efficacy of DP stents was inferior to that of BP stents with the same antiproliferative drug, sirolimus. The incidence of clinical outcomes, including stent thrombosis, clinically driven TLR, and other composite outcomes was significantly higher in the DP-SES group than in the BP-SES group during the two-year follow-up period. In particular, the differences in outcomes increased at and after

Table 2. Angiographic and procedural characteristics.

Variables		BP-SES	DP-SES	*p*-value
Per patient characteristics		**n=270**	**n=177**	
Total number of stents		1.53±0.84	1.66±0.95	0.136
Total stent length (mm)		36.01±23.62	43.09±26.26	0.003
Minimal stent diameter (mm)		2.88±0.42	2.82±0.33	0.069
At least 1 vessel RVD ≤2.75 mm		149 (55.2)	113 (63.8)	0.069
At least 1 lesion length >24 mm		84 (31.1)	71 (40.1)	0.051
At least 1 ACC/AHA B2 or C lesion		199 (73.7)	130 (73.4)	0.952
At least 1 preprocedural TIMI flow grade 0-2		56 (20.7)	47 (26.6)	0.153
At least 1 moderate or severe angulation		18 (6.7)	6 (3.4)	0.133
At least 1 chronic total occlusion		17 (6.3)	12 (6.8)	0.839
At least 1 severe calcification		88 (32.6)	47 (26.6)	0.174
At least 1 ostial lesion		57 (21.1)	37 (20.9)	0.958
Adjuvant ballooning of all treated lesions		185 (68.5)	84 (47.5)	<0.001
Post-procedural TIMI flow grade 3 of all vessels		267 (98.9)	170 (96.0)	0.047
Per lesion characteristics		**n=358**	**n=270**	
Target lesion coronary artery	Left main	15 (4.2)	12 (4.4)	0.551
	Left anterior descending	150 (41.9)	106 (39.3)	
	Left circumflex	87 (24.3)	69 (25.6)	
	Right coronary artery	106 (29.6)	81 (30.0)	
	Bypass graft	0 (0.0)	2 (0.7)	
ACC/AHA lesion class	A	31 (8.7)	33 (12.2)	0.502
	B1	84 (23.5)	63 (23.3)	
	B2	118 (33.0)	88 (32.6)	
	C	125 (34.9)	86 (31.9)	
	B2 or C lesions	243 (67.9)	174 (64.4)	0.367
Preprocedural TIMI flow grade	0	34 (9.5)	37 (13.7)	0.392
	1	5 (1.4)	4 (1.5)	
	2	20 (5.6)	12 (4.4)	
	3	299 (83.5)	217 (80.4)	
	Preprocedural TIMI flow grade 0-2	59 (16.5)	53 (19.6)	0.307
Lesion angulation	Mild (<45°)	340 (95.0)	264 (97.8)	0.150
	Moderate (≥45° and <90°)	16 (4.5)	6 (2.2)	
	Severe (≥90°)	2 (0.6)	0 (0.0)	
	Angulated lesion (≥45°)	18 (5.0)	6 (2.2)	0.069
Total occlusion	No	322 (89.9)	230 (85.2)	0.107
	<3 months	19 (5.3)	26 (9.6)	
	≥3 months	17 (4.7)	14 (5.2)	
	Chronic total occlusion	17 (4.7)	14 (5.2)	0.803
Lesion calcification	No	187 (52.2)	195 (72.2)	<0.001
	Mild	26 (7.3)	3 (1.1)	
	Moderate	37 (10.3)	11 (4.1)	
	Severe	108 (30.2)	61 (22.6)	
Other characteristics	Severely calcified lesion	108 (30.2)	61 (22.6)	0.034
	Thrombus present	40 (11.2)	86 (31.9)	<0.001
	Ostial lesion	62 (17.3)	45 (16.7)	0.830
	Adjuvant ballooning after stent implantation	257 (71.8)	152 (56.3)	<0.001
	Long lesion (>24 mm)	156 (43.6)	157 (58.1)	<0.001
	Small vessel (RVD ≤2.75 mm)	178 (49.7)	156 (57.8)	0.045
	Post-procedural TIMI flow grade 3	355 (99.2)	262 (97.0)	0.063

Values are n (%) or mean±standard deviation. ACC: American College of Cardiology; AHA: American Heart Association; RVD: reference vessel diameter; TIMI: Thrombolysis In Myocardial Infarction

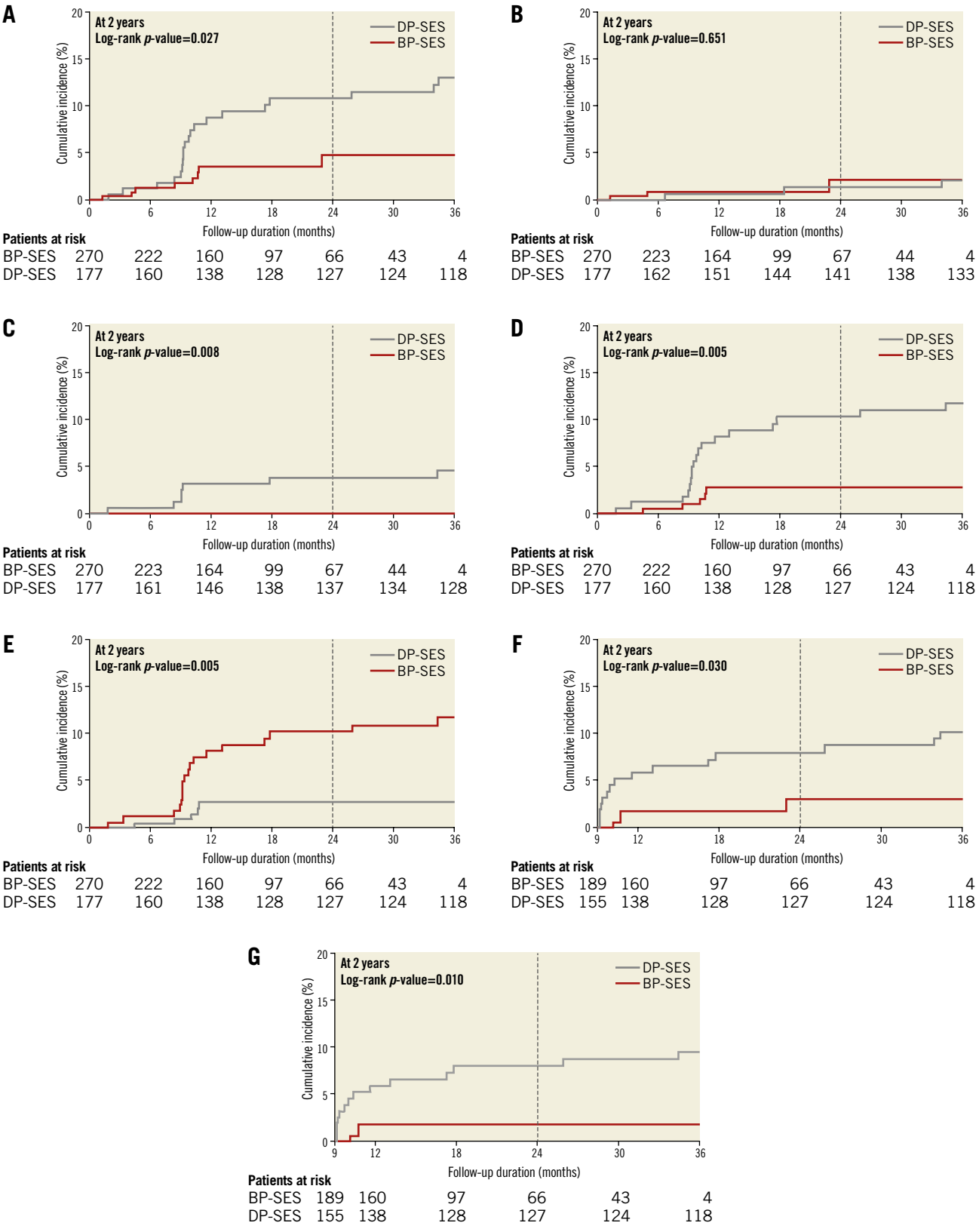

Figure 2. *Kaplan-Meier curves of clinical outcomes. A) Cumulative incidence of the primary outcome, a composite of cardiac death, stent thrombosis, and target lesion revascularisation (TLR). B) Cumulative incidence of cardiac death. C) Cumulative incidence of stent thrombosis. D) Cumulative incidence of TLR. E) Cumulative incidence of the composite of stent thrombosis or TLR. F) Cumulative incidence of the composite of cardiac death, stent thrombosis, and TLR at and after nine months of PCI. G) Cumulative incidence of stent thrombosis or TLR at and after nine months of PCI.*

Table 3. Clinical outcomes at 2-year follow-up.

Variables	BP-SES (n=270)	DP-SES (n=177)	HR (95% CI)	*p*-value
Cardiac death, stent thrombosis or clinically driven TLR	8 (3.0)	17 (9.6)	0.41 (0.17-0.91)	0.028
Cardiac death	3 (1.1)	2 (1.1)	1.42 (0.27-8.84)	0.679
Stent thrombosis	0 (0.0)	6 (3.4)	0.07 (0.00-0.56)	0.008
Clinically driven TLR	5 (1.9)	16 (9.0)	0.28 (0.10-0.70)	0.005
Stent thrombosis or clinically driven TLR	5 (1.9)	16 (9.0)	0.28 (0.10-0.70)	0.005
Cardiac death, stent thrombosis or clinically driven TLR after 9 months	4/189 (2.1)	12/155 (7.7)	0.33 (0.10-0.91)	0.032
Stent thrombosis or clinically driven TLR after 9 months	3/189 (1.6)	12/155 (7.7)	0.25 (0.06-0.74)	0.011

Values are n (%), unless otherwise stated. Hazard ratio provided as hazard BP-SES/hazard DP-SES. Stent thrombosis defined as probable or definite stent thrombosis according to the Academic Research Consortium definition. Target lesion revascularisation defined as revascularisation by percutaneous or surgical methods. CI: confidence interval; HR: hazard ratio; TLR: target lesion revascularisation

Table 4. Adjusted hazard ratios of clinical outcomes in multivariable model.

Variables	Adjusted HR*	95% CI	*p*-value
Cardiac death, stent thrombosis or clinically driven TLR (primary endpoint)	0.37	0.14-0.87	0.022
Cardiac death	2.13	0.25-26.66	0.484
Stent thrombosis	0.07	0.00-0.65	0.015
Clinically driven TLR	0.26	0.09-0.69	0.006
Stent thrombosis or clinically driven TLR	0.26	0.09-0.69	0.006
Cardiac death, stent thrombosis or clinically driven TLR after 9 months	0.34	0.10-0.97	0.043
Stent thrombosis or clinically driven TLR after 9 months	0.23	0.06-0.74	0.012

Hazard ratio provided as hazard BP-SES/hazard DP-SES. *adjusted for previous myocardial infarction, clinical diagnosis, total stent length, minimal stent diameter, severe lesion calcification, and left ventricular ejection fraction. CI: confidence interval; HR: hazard ratio; TLR: target lesion revascularisation

nine months post PCI. The differences were mainly driven by the contribution of the clinically driven TLR outcome. Notably, there was an absence of stent thrombosis in the BP-SES group, whereas there were six stent thromboses in the DP-SES group. All stent thrombosis cases were proven by performing coronary angiography and all were successfully revascularised with PCI.

Sirolimus has potent immunosuppressant properties and an antiproliferative action that inhibits both cytokine- and growth factor-mediated proliferation and migration of vascular smooth muscle cells[13]. These antiproliferative and antimigratory properties are responsible for the efficacy of sirolimus therapy, which results from the suppression of neointimal hyperplasia in the PCI field[14].

The superiority of SES over BMS in late lumen loss was described in previous trials[1,2]. Although DES significantly reduced in-stent angiographic (binary) restenosis and repeat revascularisation compared with the levels associated with BMS, some data from large registries have indicated a high risk for late and very late stent thrombosis with first-generation DES, which is rarely seen with BMS[15,16].

Several factors, including procedure-, patient-, lesion-, and stent-related factors, are thought to have a role in stent thrombosis in DES[15,17,18]. Of the stent-related factors, the drugs eluted from stents play an important role. Sirolimus not only reduces neointimal formation by impeding vascular smooth muscle cell proliferation and migration, but also impairs endothelialisation and the normal healing processes of the injured arterial wall[19]. Another stent-related factor, the polymer that carries the antiproliferative drug, was also doubted as a key factor associated with late stent thrombosis. Polymers have been shown to cause delayed healing, impaired endothelialisation on stent struts, and hypersensitivity reactions[4,5]. Preclinical experience in a pig model showed a progressive increase of granulomatous reactions, including eosinophilic infiltrate, starting at 28 days after CYPHER DP-SES

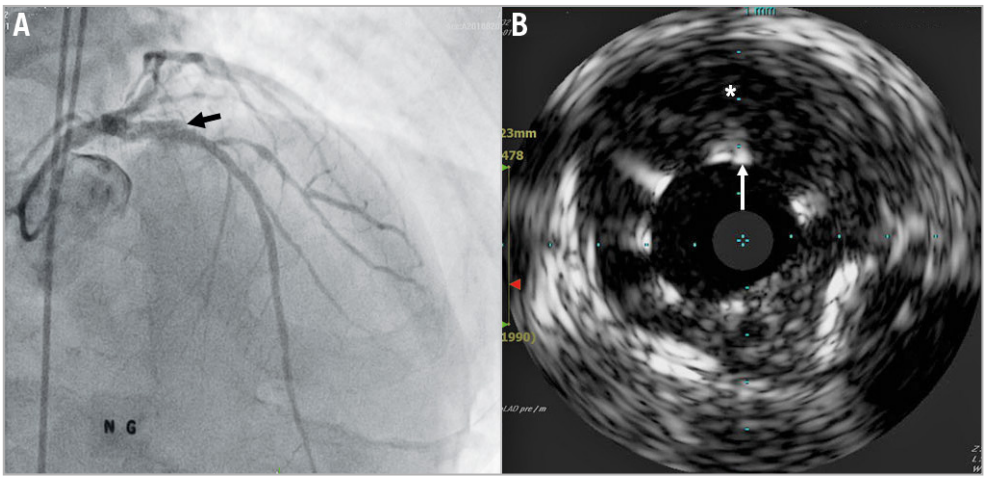

Figure 3. *A typical example of peri-stent staining and very late malapposition in the CYPHER group. A) Black arrow indicates peri-stent contrast staining. B) White arrow indicates a stent strut; the asterisk denotes peri-stent space formed by malapposition.*

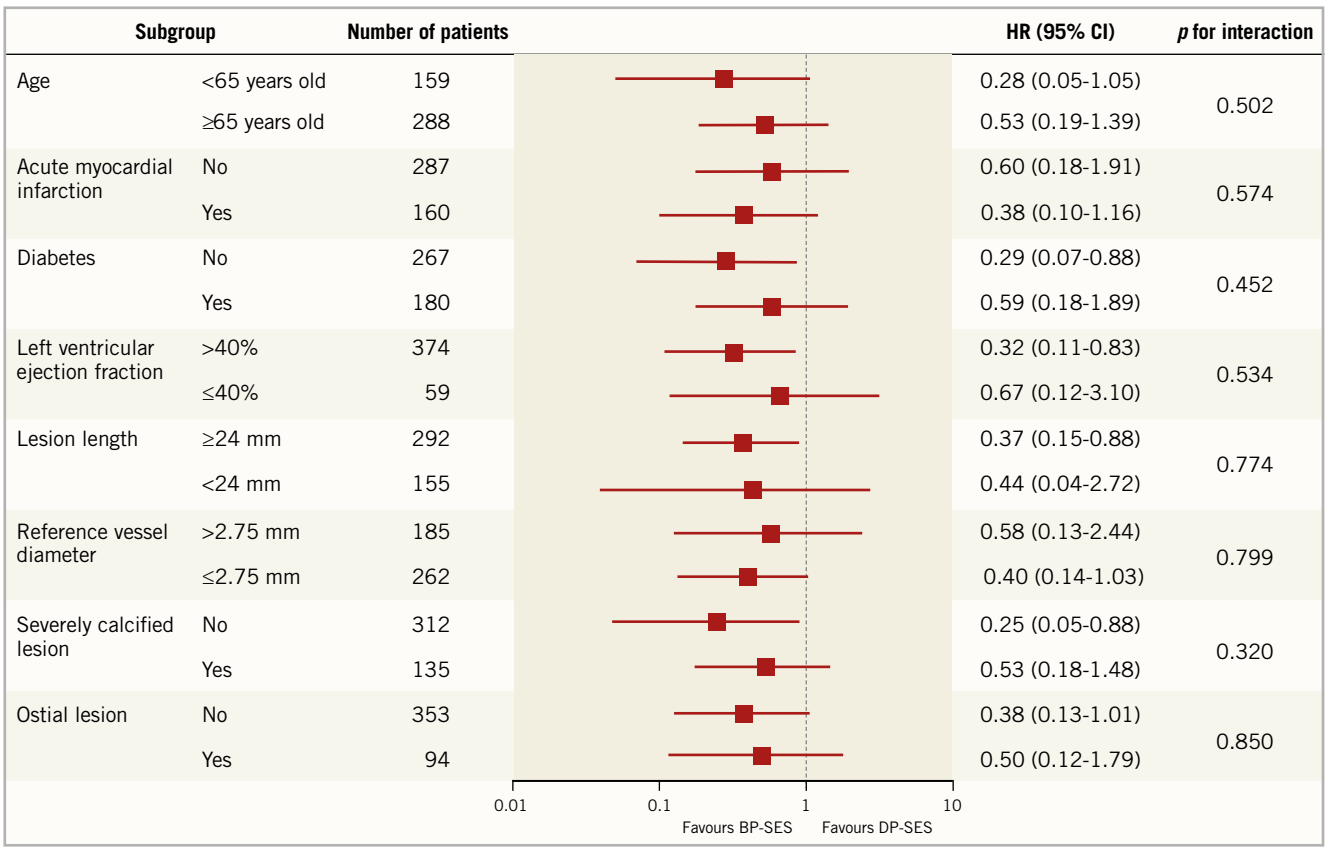

Figure 4. *Forest plot of the composite of cardiac death, stent thrombosis, and target lesion revascularisation.*

implantation. This finding suggests that the hypersensitivity reaction peaks after the complete release of the eluted drugs and is probably related to the polymer[20].

There were some clinical trials investigating the efficacy and safety of second-generation DES with newer polymers and antiproliferative drugs. However, despite extensive and thorough studies, researchers could not determine which stent feature (antiproliferative agent or polymer type) was more causative of late stent-related adverse events since all of the studies compared stents with different antiproliferative drugs and/or different polymers.

To the best of our knowledge, this study is the first to compare the safety of stents with different polymers (durable versus biodegradable) but the same antiproliferative drug, sirolimus. As shown in our results, the use of a BP-SES has been demonstrated to be more efficacious and safer than that of a DP-SES. This indicates that the late failures associated with the CYPHER DP-SES were more likely to be caused by the DP than the sirolimus.

Despite our results showing superiority of BP-DES over DP-DES, it is uncertain whether a BP is safer than all DP because there are different kinds of DP than that used in CYPHER stents. The present study simply indicates that the specific DP used in the CYPHER stent is vasculotoxic. Actually, some clinical studies have shown other types of DP to be safe when compared to other BPs[21-24].

At present, SES are produced by a variety of manufacturers and are used in the treatment of coronary patients, though the CYPHER DP-SES is no longer commercially available due to safety concerns. However, a clinical implication of the present study is that sirolimus is quite effective as an antiproliferative drug for use in DES, even though many kinds of antiproliferative drug are available. Therefore, recently developed SES adopting other drug-carrier technologies, whether DP or BP, should be investigated with the results of this study in mind.

Limitations

There are several limitations in this study. First, the present study was not a randomised study. Thus, the results may have been subject to bias, even though multiple potential variables were adjusted in the analyses. In particular, mean stent length, one of the significant factors affecting TLR, was significantly greater in the DP-DES group than in the BP-SES group. Second, the stent material and structure, other than the polymer, are markedly different in the two stent types tested. The CYPHER DP-SES has a closed cell design and is made of stainless steel, and the stent strut thickness is 140 µm thick, whereas the Orsiro BP-SES has an open cell design and is made of cobalt-chromium L-605, and the stent strut is thinner (60 or 80 µm). The coating thickness of the stent is 7 µm for the CYPHER stent and 3.5 or 7.5 µm for the Orsiro stent depending on the strut thickness. These structural differences may have influenced the study results. However, as was shown in the BMS era, when the strut was as thick as that in the DP-SES

used in this study, late failure was seldom seen[25,26]. Moreover, it should be borne in mind that PSS and very late stent malapposition **(Figure 3)** were very rare after BMS implantation. Third, although the drug dose of both stents is 1.4 μg/mm², the drug elution from the two stents is different: the CYPHER releases 80% of the drug within 30 days of implantation while the Orsiro releases about 50% of the drug within 30 days. This difference in drug release may influence the inflammation of the vessel wall. Fourth, the separate enrolment periods for patients treated with DP-SES and BP-SES may have influenced the study results. For example, recent increases in the use of fractional flow reserve-based PCI could have affected the results.

Most of the technical advances have occurred in the field of stent technology, in dedicated devices for chronic occlusion and in antiplatelet agents as well as in breakthroughs for procedural success and rescue. We have shown no difference in the lesion complexity or in the proportion of chronic occlusions between the two groups. Stents were successfully implanted and the final TIMI flow was grade 3 in almost all cases. We do not believe that the potent antiplatelet agents affect our results because the BP-SES was superior without any newer-generation antiplatelet agents as shown.

Finally, the relatively low two-year clinical follow-up rate compared to those in other trials[21,27] might have affected the results, especially those related to clinically driven TLR in the BP-SES group. Despite these limitations, this is the first study to compare different polymers in stents with the same antiproliferative drug, thus allowing a conclusion regarding the reason for the late failures associated with CYPHER stents.

Conclusions

In conclusion, the Orsiro BP-SES was superior to the CYPHER DP-SES with respect to the clinical outcomes at two years post PCI. Incidences of adverse clinical outcomes in the Orsiro BP-SES were significantly lower than those in the CYPHER DP-SES. What clinicians should learn from the so-called "CYPHER failure" is that the failure is mainly attributable to the use of an inappropriate DP, indicating the need for thorough investigation of stent polymers. Regardless, sirolimus is still a useful antiproliferative drug for coronary stents.

Impact on daily practice

Sirolimus is a potent antiproliferative drug which is still used for newer-generation drug-eluting coronary stents. Earlier CYPHER stent failure left some concerns that these newer-generation stents could adversely affect vascular wall and clinical outcomes. The present study has shown that sirolimus-eluting stents are quite safe and effective when they are embedded in another kind of polymer. It is expected that the currently used sirolimus-eluting stents will demonstrate markedly improved long-term outcomes whether the polymers are biodegradable or newly durable.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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