

Angiographic complexity of coronary artery disease according to SYNTAX score and clinical outcomes after revascularisation with newer-generation drug-eluting stents: a substudy of the BIOSCIENCE trial



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KEYWORDS

- biodegradable polymer sirolimus-eluting stents
- coronary artery disease
- durable polymer everolimus-eluting stents
- SYNTAX score

Abstract

Aims: We sought to assess the performance of drug-eluting stents combining an ultrathin cobalt-chromium platform with a biodegradable polymer across categories of increasing SYNTAX score (SS).

Methods and results: Patients included in the BIOSCIENCE trial and randomly allocated to treatment with biodegradable polymer sirolimus-eluting stents (BP-SES) or durable polymer everolimus-eluting stents (DP-EES) were categorised according to SS tertiles (low <8, medium 8-15, high >15). The primary endpoint, target lesion failure (TLF), was defined as a composite of cardiac death, target vessel myocardial infarction and clinically indicated target lesion revascularisation. The patient-oriented endpoint (POCE) included death, myocardial infarction, or any repeat revascularisation. The SS was available in 2,041 out of 2,119 patients (96.3%). At two-year follow-up, patients with an SS >15 experienced higher rates of both TLF and POCE as compared to patients with medium and low SS (14.5% vs. 8.1% and vs. 5.9%, $p<0.001$; 22.7% vs. 14.9% and vs. 12.4%; $p<0.001$), respectively. Comparable rates of the composite endpoints were documented for both stent types in each category of SS.

Conclusions: Increasing lesion complexity as assessed by SS was associated with higher rates of TLF and POCE in a contemporary PCI population with minimal exclusion criteria. BP-SES and DP-EES showed comparable performance across the entire spectrum of CAD severity.

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Introduction

Originally conceived as a scoring system for angiographic extent and complexity of coronary artery disease (CAD)¹, the SYNTAX score (SS) has been correlated with the risk of adverse events after percutaneous coronary intervention (PCI) in patients receiving early- and new-generation drug-eluting stents (DES)²⁻⁴.

Refinements of the platform and the design of DES facilitated the treatment of increasingly complex CAD. Improved deliverability achieved by a reduction of strut thickness was paralleled by a decline of ischaemic events using biocompatible and biodegradable polymers⁵.

The randomised BIOSCIENCE trial (NCT01443104) showed the non-inferiority of the Orsiro stent (Biotronik AG, Bülach, Switzerland), featuring an ultrathin strut cobalt-chromium design in combination with a biodegradable sirolimus-eluting polymer (BP-SES), compared to the durable polymer everolimus-eluting stent (DP-EES) (XIENCE PRIME®/Xpedition®; Abbott Vascular, Santa Clara, CA, USA) with regard to a composite clinical outcome among patients with minimal exclusion criteria⁶.

The effect of an ultrathin strut stent design in combination with a biodegradable polymer on clinical outcome according to SS is unknown.

In the present substudy of the BIOSCIENCE trial, we sought to explore whether the predictability of the SS is confirmed in a contemporary PCI population and whether the complexity of CAD, as assessed by SS, differentially affects clinical outcomes up to two years after PCI with BP-SES or DP-EES. Furthermore, we evaluated the performance of the logistic clinical SS, which combines anatomical SS with clinical features⁷, to predict survival in a contemporary PCI population.

Methods

STUDY POPULATION AND PROCEDURES

The BIOSCIENCE trial was an investigator-initiated, multicentre, single-blind, randomised non-inferiority trial including patients with stable CAD and acute coronary syndromes (ACS) who were candidates for stenting. The trial design and criteria for inclusion and exclusion have previously been described⁸. The study complied with the Declaration of Helsinki. Written informed consent was mandatory for study inclusion. The study protocol was approved by the ethics committees of all participating centres. After diagnostic angiography, patients were randomly allocated (1:1) to treatment with BP-SES or DP-EES using a web-based system. All patients were clinically followed up at 30 days, 12 and 24 months.

STUDY ENDPOINTS

The primary endpoint of this sub-analysis was the occurrence of target lesion failure (TLF), defined as a composite of cardiac death, target vessel Q-wave or non-Q-wave myocardial infarction (MI) and clinically indicated target lesion revascularisation (TLR). Secondary endpoints were a patient-oriented composite endpoint (POCE), including death, MI, or any repeat revascularisation, the individual components of the composite primary endpoint, and

Academic Research Consortium (ARC)-defined stent thrombosis (ST). Endpoint definitions have been provided elsewhere⁶.

Calculation of SS, logistic clinical SS and statistical analysis are described in the **Appendix**.

Results

The SS was available in 2,041 out of 2,119 patients enrolled into the BIOSCIENCE trial (96.3%), and ranged from 0 to 63.5 with a mean±SD of 14±11.4 and a median of 11.0 (interquartile range 6 to 18). Patients randomly allocated to either one of the two treatment arms were categorised according to SS tertiles: low SS: <8 (BP-SES, n=346 and DP-EES, n=355), medium SS: 8-15 (BP-SES, n=317 and DP-EES, n=342), and high SS: >15 (BP-SES, n=346 and DP-EES, n=334).

BASELINE CLINICAL FEATURES

Baseline parameters were well balanced between the two treatment arms across SS tertiles, except for a significantly higher number of previous cerebrovascular events among patients with medium SS in the DP-EES arm as compared to the BP-SES arm (7.3% vs. 3.5%, p=0.04) (**Table 1**). Angiographic features and procedural data are reported in **Table 2**.

CLINICAL OUTCOMES ACCORDING TO CAD COMPLEXITY

Figure 1 shows cumulative survival curves for the primary endpoint TLF (**Figure 1A**) and the composite POCE (**Figure 1B**) in the overall population stratified according to SS tertile. Patients with SS >15 experienced significantly higher rates of adverse events as compared to patients in the lower SS categories. Rates of TLF were 14.5%, 8.1% and 5.9% in high, medium and low SS groups, respectively (p<0.001). Similarly, POCE occurred in 22.7% of high SS patients, 14.9% of medium SS patients, and 12.4% of low SS patients (p<0.001). These differences were driven by higher rates of cardiac death (high SS 5.3%, medium SS 2.2%, low SS 1.6%, p<0.001), target vessel MI (high SS 5.7%, medium SS 3.6%, low SS 2.1%, p=0.001) and clinically indicated TLR (high SS 7.4%, medium SS 3.6%, low SS 3.5%, p=0.001). Moreover, the occurrence of definite or probable ST was more frequent among high SS patients (5.9% compared with 3.4% and 2.2% in medium and low SS patients, respectively, p<0.001) (**Table 3**).

CLINICAL OUTCOMES ACCORDING TO STENT TYPE ACROSS SS TERTILES

Table 4 and **Figure 2** display clinical outcomes at two years stratified by stent type and SS tertile. Rates of TLF were not significantly different between treatment arms across SS tertiles: high SS, BP-SES 13.9% vs. DP-EES 15.1%, RR 0.91 (95% CI [0.61-1.37]), p=0.66; medium SS, BP-SES 6.6% vs. DP-EES 9.5%, RR 0.64 (95% CI [0.36-1.13]), p=0.12; low SS, BP-SES 5.7% vs. DP-EES 6.1%, RR 0.94 (95% CI [0.51-1.76]), p=0.85. Similarly, no significant differences were detected in the occurrence of POCE: high SS, BP-SES 23% vs. DP-EES 22.4%, RR 1.03 (95% CI [0.75-1.41]), p=0.87; medium SS, BP-SES 14.4% vs. DP-EES 15.4%,

Table 1. Baseline clinical characteristics of study population.

	Low SS		p-value	Medium SS		p-value	High SS		p-value
	BP-SES	DP-EES		BP-SES	DP-EES		BP-SES	DP-EES	
	n=346	n=355		n=317	n=342		n=346	n=334	
Age, years	64.2±12.1	63.5±11.0	0.45	65.0±11.6	65.6±11.4	0.50	69.0±10.5	68.6±10.9	0.71
Male gender	262 (75.7%)	272 (76.6%)	0.79	252 (79.5%)	255 (74.6%)	0.14	262 (75.7%)	267 (79.9%)	0.20
Body mass index, kg/m ²	27.7±4.6	27.6±4.8	0.74	27.8±4.4	27.7±4.6	0.81	27.8±4.5	27.4±4.1	0.25
Hypertension	231 (66.8%)	215 (60.7%)	0.10	214 (67.7%)	236 (69.0%)	0.74	245 (70.8%)	234 (70.1%)	0.87
Hypercholesterolaemia	222 (64.2%)	239 (67.3%)	0.38	210 (66.5%)	220 (64.3%)	0.62	242 (69.9%)	239 (71.6%)	0.67
Current smoker	123 (35.5%)	121 (34.1%)	0.69	98 (31.0%)	95 (27.8%)	0.39	77 (22.3%)	79 (23.8%)	0.65
Family history of CAD	90 (26.2%)	87 (24.6%)	0.66	89 (28.2%)	104 (30.4%)	0.55	96 (27.9%)	96 (28.7%)	0.87
Previous MI	59 (17.1%)	58 (16.3%)	0.84	63 (19.9%)	60 (17.5%)	0.48	86 (24.9%)	82 (24.6%)	0.93
Previous PCI	92 (26.6%)	81 (22.8%)	0.26	95 (30.0%)	91 (26.6%)	0.34	118 (34.1%)	110 (32.9%)	0.81
Previous CABG	2 (0.6%)	4 (1.1%)	0.69	4 (1.3%)	7 (2.0%)	0.55	95 (27.5%)	83 (24.9%)	0.49
Atrial fibrillation/atrial flutter	23 (6.6%)	24 (6.8%)	1.00	22 (6.9%)	25 (7.3%)	0.88	34 (9.8%)	29 (8.7%)	0.69
Previous stroke or TIA	8 (2.3%)	13 (3.7%)	0.38	11 (3.5%)	25 (7.3%)	0.04	19 (5.5%)	15 (4.5%)	0.60
Peripheral vascular disease	20 (5.8%)	25 (7.0%)	0.54	33 (10.4%)	26 (7.6%)	0.22	36 (10.4%)	25 (7.5%)	0.23
Renal failure (GFR <60 ml/min)	36 (11.2%)	29 (8.6%)	0.30	39 (12.8%)	44 (13.6%)	0.81	59 (17.9%)	55 (17.7%)	1.00
Unstable angina	24 (6.9%)	21 (5.9%)	0.65	26 (8.2%)	29 (8.5%)	1.00	23 (6.6%)	21 (6.3%)	0.88
NSTEMI	87 (25.1%)	100 (28.2%)	0.39	92 (29.0%)	97 (28.4%)	0.86	100 (28.9%)	83 (24.9%)	0.26
STEMI	79 (22.8%)	70 (19.7%)	0.36	65 (20.5%)	61 (17.8%)	0.43	60 (17.3%)	62 (18.6%)	0.69
Stable angina	120 (34.7%)	126 (35.5%)	0.87	100 (31.5%)	123 (36.0%)	0.25	129 (37.3%)	134 (40.1%)	0.48
Silent ischaemia	36 (10.4%)	38 (10.7%)	0.90	34 (10.7%)	32 (9.4%)	0.60	34 (9.8%)	34 (10.2%)	0.90
Acute MI within 72 hrs	59 (17.1%)	54 (15.2%)	0.54	50 (15.8%)	47 (13.7%)	0.51	51 (14.7%)	48 (14.4%)	0.91
Left ventricular ejection fraction	n=277	n=287	0.29	n=256	n=267	0.64	n=290	n=277	0.79
<30%	7 (2.5%)	13 (4.5%)	0.26	14 (5.5%)	12 (4.5%)	0.69	17 (5.9%)	16 (5.8%)	1.00
31%-50%	66 (23.8%)	58 (20.2%)	0.31	86 (33.6%)	82 (30.7%)	0.51	106 (36.6%)	109 (39.4%)	0.55
>50%	204 (73.6%)	216 (75.3%)	0.70	156 (60.9%)	173 (64.8%)	0.37	167 (57.6%)	152 (54.9%)	0.55
Multivessel treatment	24 (7.0%)	28 (7.9%)	0.67	77 (24.3%)	78 (22.8%)	0.71	93 (26.9%)	100 (29.9%)	0.40

Data expressed as n (%) or mean±standard deviation. P-values from Fisher's tests or chi-square tests (more than two categories) or unpaired t-tests, respectively. BP-SES: biodegradable polymer sirolimus-eluting stent; CABG: coronary artery bypass graft; CAD: coronary artery disease; DP-EES: durable polymer everolimus-eluting stent; MI: myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; TIA: transient ischaemic attack

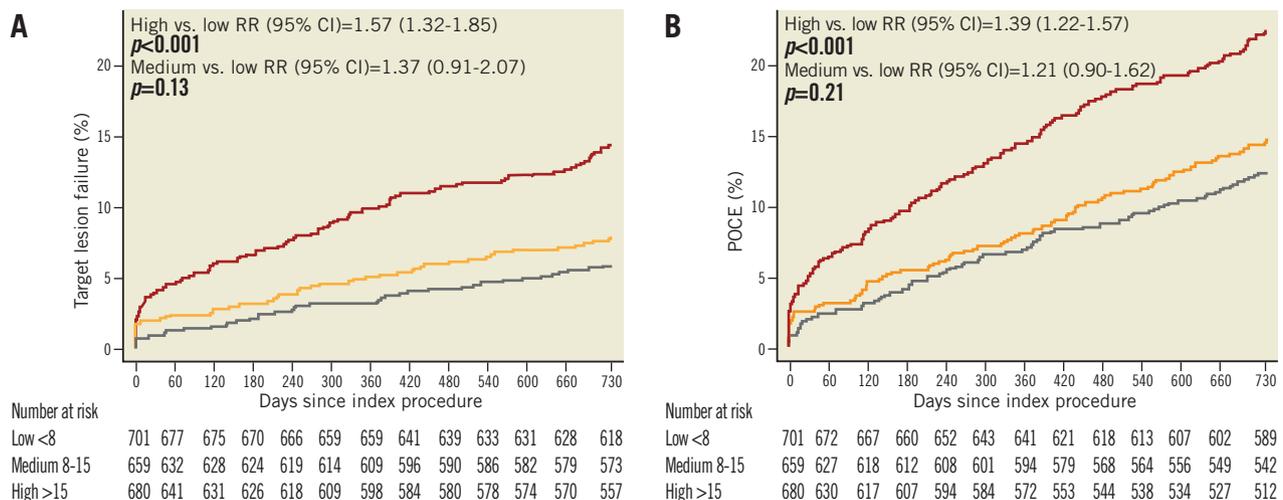


Figure 1. Kaplan-Meier estimates up to two years of follow-up. A) Target lesion failure (TLF). B) Patient-oriented composite endpoint (POCE). Grey lines indicate low SS (<8), orange lines indicate medium SS (8-15), red lines indicate high SS (>15).

Table 2. Baseline lesion characteristics stratified by SYNTAX tertile and treatment arm.

	Low SYNTAX score		p-value	Medium SYNTAX score		p-value	High SYNTAX score		p-value
	BP-SES	DP-EES		BP-SES	DP-EES		BP-SES	DP-EES	
No. of patients	n=346	n=355		n=317	n=342		n=346	n=334	
No. of lesions	413	423		507	508		606	579	
Target vessel location per lesion [‡]	n=413	n=423	0.51	n=507	n=508	0.49	n=606	n=579	0.12
Left main artery	0 (0.0%)	0 (0.0%)		3 (0.6%)	2 (0.4%)		23 (3.8%)	24 (4.1%)	
Left anterior descending artery	129 (31.2%)	132 (31.2%)		251 (49.5%)	269 (53.0%)		244 (40.3%)	271 (46.8%)	
Left circumflex artery	109 (26.4%)	125 (29.6%)		110 (21.7%)	92 (18.1%)		136 (22.4%)	111 (19.2%)	
Right coronary artery	175 (42.4%)	166 (39.2%)		143 (28.2%)	145 (28.5%)		170 (28.1%)	131 (22.6%)	
Bypass graft	Saphenous vein graft	0 (0.0%)		0 (0.0%)	0 (0.0%)		30 (5.0%)	37 (6.4%)	
	Arterial graft	0 (0.0%)		0 (0.0%)	0 (0.0%)		3 (0.5%)	5 (0.9%)	
No. of treated lesions per patient [¶]	1.19±0.46	1.19±0.48	0.98	1.60±0.78	1.49±0.68	0.24	1.75±0.95	1.73±0.88	0.86
No. of treated lesions per patient [‡]	n=346	n=355	0.98	n=317	n=342	0.24	n=346	n=334	0.86
One	287 (82.9%)	299 (84.2%)		173 (54.6%)	208 (60.8%)		178 (51.4%)	164 (49.1%)	
Two	52 (15.0%)	45 (12.7%)		108 (34.1%)	107 (31.3%)		100 (28.9%)	109 (32.6%)	
Three	6 (1.7%)	10 (2.8%)		28 (8.8%)	22 (6.4%)		49 (14.2%)	52 (15.6%)	
≥Four	1 (0.3%)	1 (0.3%)		8 (2.5%)	5 (1.5%)		19 (5.5%)	9 (2.7%)	
Type of intervention per lesion [*]	n=413	n=423	0.36	n=507	n=508	0.18	n=606	n=579	0.94
Stenting	399 (96.6%)	413 (97.6%)		479 (94.5%)	489 (96.3%)		573 (94.6%)	547 (94.5%)	
Balloonng	9 (2.2%)	10 (2.4%)		27 (5.3%)	18 (3.5%)		32 (5.3%)	31 (5.4%)	
CABG	2 (0.5%)	0 (0.0%)		0 (0.0%)	0 (0.0%)		0 (0.0%)	1 (0.2%)	
Failed PCI	3 (0.7%)	0 (0.0%)		1 (0.2%)	1 (0.2%)		1 (0.2%)	0 (0.0%)	
Baseline TIMI flow per lesion	n=398	n=414	0.76	n=497	n=501	0.97	n=601	n=573	0.28
0 or 1	92 (23.1%)	98 (23.7%)		85 (17.1%)	83 (16.6%)		129 (21.5%)	106 (18.5%)	
2	46 (11.6%)	41 (9.9%)		70 (14.1%)	72 (14.4%)		99 (16.5%)	111 (19.4%)	
3	260 (65.3%)	275 (66.4%)		342 (68.8%)	346 (69.1%)		373 (62.1%)	356 (62.1%)	
TIMI flow post PCI per lesion	n=404	n=421	0.61	n=504	n=506	0.34	n=601	n=578	0.94
0 or 1	1 (0.2%)	1 (0.2%)		0 (0.0%)	2 (0.4%)		3 (0.5%)	3 (0.5%)	
2	3 (0.7%)	1 (0.2%)		5 (1.0%)	1 (0.2%)		12 (2.0%)	10 (1.7%)	
3	400 (99.0%)	419 (99.5%)		499 (99.0%)	503 (99.4%)		586 (97.5%)	565 (97.8%)	
Restenotic lesion per lesion	30 (7.3%)	20 (4.7%)	0.13	29 (5.7%)	22 (4.3%)	0.32	44 (7.3%)	29 (5.0%)	0.09
Total occlusion per lesion	93 (22.6%)	88 (20.9%)	0.51	87 (17.2%)	74 (14.7%)	0.28	90 (14.9%)	86 (14.9%)	1.00
Thrombus aspiration per lesion	62 (15.1%)	48 (11.4%)	0.10	41 (8.1%)	40 (7.9%)	0.86	37 (6.1%)	37 (6.4%)	0.84
Number of stents per lesion	1.18±0.45	1.23±0.52	0.50	1.32±0.62	1.34±0.64	0.81	1.38±0.68	1.41±0.70	0.63
Total stent length per lesion (mm)	22.00±11.06	23.18±11.55	0.13	26.06±14.94	27.42±16.70	0.18	28.80±17.99	30.82±19.23	0.10
Maximum stent diameter per lesion (mm)	3.04±0.50	3.01±0.52	0.33	3.06±0.48	3.05±0.47	0.91	3.04±0.48	3.02±0.49	0.47
Maximum pressure per lesion (atm)	13.76±3.46	13.32±3.15	0.06	13.54±3.56	13.79±3.32	0.50	13.94±3.49	14.03±3.50	0.55
Overlapping stents per lesion	56 (14.0%)	71 (17.2%)	0.22	103 (21.5%)	120 (24.5%)	0.26	140 (24.4%)	150 (27.4%)	0.27
Direct stenting per lesion	130 (32.6%)	136 (32.9%)	0.79	141 (29.4%)	154 (31.5%)	0.48	131 (22.9%)	139 (25.4%)	0.29
Long lesion per lesion (>20 mm)	164 (41.1%)	194 (47.0%)	0.10	273 (57.0%)	282 (57.7%)	0.83	355 (62.0%)	348 (63.6%)	0.66
Small vessel per lesion (<2.75 mm)	149 (37.3%)	186 (45.0%)	0.02	189 (39.5%)	204 (41.7%)	0.44	259 (45.2%)	267 (48.8%)	0.26
Bifurcation treatment per lesion	36 (8.8%)	28 (6.6%)	0.69	95 (18.8%)	99 (19.5%)	0.75	121 (20.0%)	123 (21.3%)	0.76
Type of stent per lesion			0.16			0.49			0.44
Study stent BP-SES	393 (98.5%)	1 (0.2%)		472 (98.5%)	3 (0.6%)		571 (99.7%)	5 (0.9%)	
Study stent DP-EES	3 (0.8%)	412 (99.8%)		7 (1.5%)	485 (99.2%)		2 (0.3%)	543 (99.3%)	
Other drug-eluting stent	1 (0.3%)	0 (0.0%)		0 (0.0%)	0 (0.0%)		1 (0.2%)	0 (0.0%)	
Bare metal stent	3 (0.8%)	1 (0.2%)		0 (0.0%)	1 (0.2%)		0 (0.0%)	0 (0.0%)	
IABP per patient	1 (0.3%)	1 (0.3%)	0.99	1 (0.3%)	0 (0.0%)	0.48	1 (0.3%)	1 (0.3%)	1.00
Vasopressors per patient	3 (0.9%)	1 (0.3%)	0.33	0 (0.0%)	1 (0.3%)	1.00	6 (1.7%)	0 (0.0%)	0.03

Data expressed as n (%) or mean±standard deviation. P-values from [¶]Poisson regression and [‡]chi-square tests or Fisher's test; otherwise p-values from mixed models for the per-lesion analyses, accounting for lesions nested within patients: general linear mixed models for continuous variables, generalised linear mixed models for counts no. *p-value for stenting vs. non-stenting per patient. Long lesion: total stent length >20 mm; Small vessel: minimum stent diameter <2.75 mm. BP-SES: biodegradable polymer sirolimus-eluting stent; CABG: coronary artery bypass graft; DP-EES: durable polymer everolimus-eluting stent; IABP: intra-aortic balloon pump; PCI: percutaneous coronary intervention

Table 3. Clinical outcomes according to CAD complexity.

		SYNTAX score			p-value	interaction p-value [†]
		Low (<8) n=701	Medium (8-15) n=659	High (>15) n=680		
Target lesion failure	Overall	40 (5.9)	51 (8.1)	96 (14.5)	<0.001	<0.001
	0-1 year	22 (3.2)	33 (5.1)	67 (10.0)	<0.001	
	1 year-2 years	18 (2.8)	18 (3.2)	29 (5.1)	0.048	
Cardiac death	Overall	11 (1.6)	14 (2.2)	35 (5.3)	<0.001	<0.001
	0-1 year	6 (0.9)	9 (1.4)	25 (3.7)	<0.001	
	1 year-2 years	5 (0.8)	5 (0.8)	10 (1.6)	0.146	
TV myocardial infarction (any)	Overall	14 (2.1)	23 (3.6)	37 (5.7)	0.001	0.002
	0-1 year	8 (1.2)	18 (2.8)	26 (3.9)	0.002	
	1 year-2 years	6 (0.9)	5 (0.8)	11 (1.9)	0.146	
Clinically indicated TLR	Overall	23 (3.5)	22 (3.6)	47 (7.4)	0.001	0.001
	0-1 year	10 (1.5)	9 (1.4)	28 (4.2)	0.001	
	1 year-2 years	13 (2.0)	13 (2.3)	19 (3.3)	0.190	
POCE	Overall	85 (12.4)	95 (14.9)	151 (22.7)	<0.001	<0.001
	0-1 year	49 (7.1)	53 (8.1)	98 (14.5)	<0.001	
	1 year-2 years	36 (5.8)	42 (7.3)	53 (9.6)	0.016	
Definite stent thrombosis	Overall	3 (0.5)	4 (0.6)	8 (1.2)	0.100	0.229 [‡]
	0-1 year	0 (0.0)	2 (0.3)	7 (1.1)	0.013	
	1 year-2 years	3 (0.5)	2 (0.3)	1 (0.2)	0.646	
Definite or probable stent thrombosis	Overall	15 (2.2)	22 (3.4)	39 (5.9)	<0.001	0.001
	0-1 year	9 (1.3)	18 (2.8)	28 (4.2)	0.001	
	1 year-2 years	6 (0.9)	4 (0.7)	11 (1.9)	0.143	

Number of first events and percentages are reported. Mantel-Cox regression with two-sided p-values from a log-rank test. [†]Approximate chi-square test for effect modification of the overall difference between SYNTAX tertiles due to the period (0-30 days vs. 31-365 days). [‡]Approximate Z-test for risk modification comparing the two follow-up periods. POCE: patient-oriented composite endpoint; TLR: target lesion revascularisation; TV: target vessel

RR 0.89 (95% CI [0.60-1.34]), p=0.58; low SS, BP-SES 13% vs. DP-EES 11.9%, RR 1.12 (95% CI [0.73-1.71]) p=0.62. However, among patients in the medium SS tertile, there was an increase in the rates of target vessel MI and definite or probable ST with

DP-EES as compared to BP-SES (target vessel MI, BP-SES: 1.6% vs. DP-EES 5.3%, RR 0.30 (95% CI [0.11-0.81]), p=0.01; definite or probable ST, BP-SES: 1.6% vs. DP-EES 5.0%, RR 0.31 (95% CI [0.12-0.86]), p=0.02). The interaction p-value between

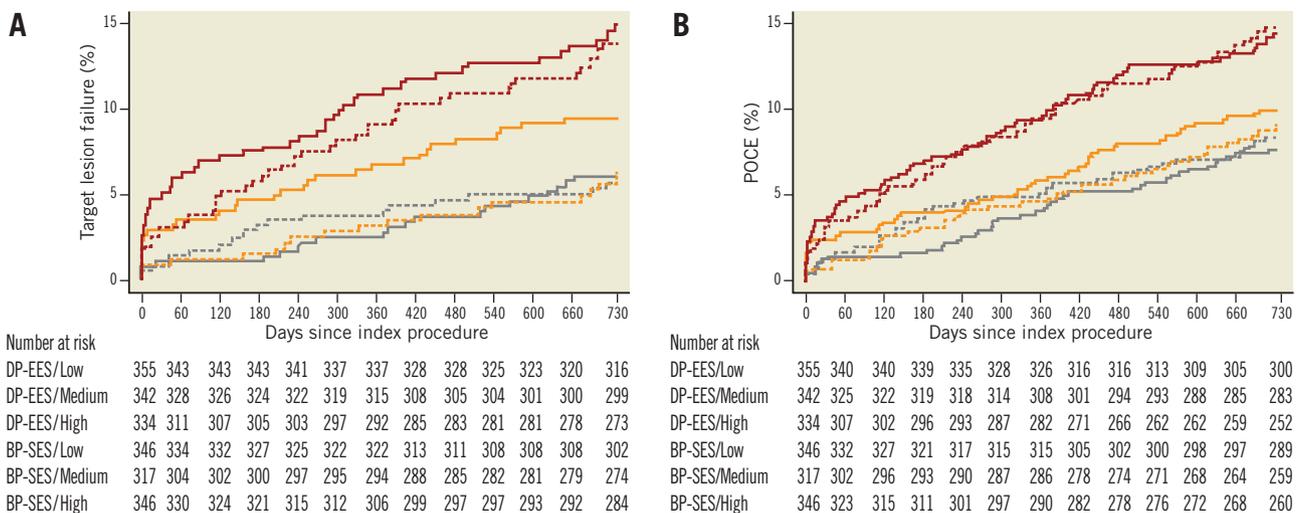


Figure 2. Kaplan-Meier estimates according to stent type up to two years of follow-up. A) Target lesion failure (TLF). B) Patient-oriented composite endpoint (POCE). Grey lines indicate low SS (<8), orange lines indicate medium SS (8-15), red lines indicate high SS (>15). BP-SES=solid lines; DP-EES=dashed lines.

Table 4. Two-year clinical outcomes according to stent type across tertiles of SS.

		BP-SES n=1,009	DP-EES n=1,031	Risk difference (95% CI)	Risk ratio (95% CI)	p-value	interaction p-value [†]
Target lesion failure	High SYNTAX score	47 (13.9)	49 (15.1)	-1.09 (-6.32 to 4.15)	0.91 (0.61-1.37)	0.66	0.55
	Medium SYNTAX score	19 (6.6)	32 (9.5)	-3.36 (-7.41 to 0.68)	0.64 (0.36-1.13)	0.12	
	Low SYNTAX score	19 (5.7)	21 (6.1)	-0.42 (-3.86 to 3.01)	0.94 (0.51-1.76)	0.85	
Cardiac death	High SYNTAX score	12 (3.6)	23 (7.0)	-3.42 (-6.75 to -0.09)	0.50 (0.25-1.00)	0.04	0.040
	Medium SYNTAX score	9 (3.0)	5 (1.5)	1.38 (-0.85 to 3.60)	2.01 (0.68-5.99)	0.20	
	Low SYNTAX score	7 (2.1)	4 (1.2)	0.90 (-0.95 to 2.74)	1.83 (0.53-6.27)	0.33	
Target vessel MI (any)	High SYNTAX score	21 (6.3)	16 (5.0)	1.28 (-2.12 to 4.68)	1.25 (0.65-2.41)	0.50	0.045
	Medium SYNTAX score	5 (1.6)	18 (5.3)	-3.69 (-6.42 to -0.95)	0.30 (0.11-0.81)	0.01	
	Low SYNTAX score	5 (1.5)	9 (2.6)	-1.0 (-3.15 to 0.97)	0.58 (0.19-1.72)	0.32	
Clinically indicated TLR	High SYNTAX score	29 (8.7)	18 (6.0)	2.99 (-0.80 to 6.79)	1.56 (0.87-2.81)	0.14	0.10
	Medium SYNTAX score	7 (2.7)	15 (4.5)	-2.18 (-4.88 to 0.53)	0.52 (0.21-1.26)	0.14	
	Low SYNTAX score	10 (3.1)	13 (3.8)	-0.77 (-3.40 to 1.86)	0.81 (0.35-1.84)	0.61	
POCE	High SYNTAX score	78 (23.0)	73 (22.4)	0.69 (-5.56 to 6.93)	1.03 (0.75-1.41)	0.87	0.75
	Medium SYNTAX score	43 (14.4)	52 (15.4)	-1.64 (-7.00 to 3.72)	0.89 (0.60-1.34)	0.58	
	Low SYNTAX score	44 (13.0)	41 (11.9)	1.17 (-3.67 to 6.00)	1.12 (0.73-1.71)	0.62	
Definite stent thrombosis	High SYNTAX score	5 (1.5)	3 (0.9)	0.55 (-1.07 to 2.16)	1.60 (0.38-6.71)	0.52	0.48
	Medium SYNTAX score	1 (0.3)	3 (0.9)	-0.56 (-1.73 to 0.60)	0.37 (0.04-3.57)	0.37	
	Low SYNTAX score	1 (0.3)	2 (0.6)	-0.27 (-1.24 to 0.69)	0.53 (0.05-5.84)	0.60	
Definite or probable stent thrombosis	High SYNTAX score	18 (5.4)	21 (6.5)	-1.09 (-4.59 to 2.42)	0.81 (0.43-1.53)	0.52	0.27
	Medium SYNTAX score	5 (1.6)	17 (5.0)	-3.39 (-6.07 to -0.71)	0.31 (0.12-0.86)	0.02	
	Low SYNTAX score	6 (1.8)	9 (2.6)	-0.80 (-2.94 to 1.34)	0.69 (0.24-1.95)	0.48	

Number of first events and percentages are reported. Rate ratios (RR [95% CI]) are estimated using the Mantel-Cox method with two-sided p-values from log-rank test. [†]Approximate chi-square test for unequal RRs testing for effect modification of the difference between the stents due to the tertile groups. Approximate Z-test in case of zero events. MI: myocardial infarction; POCE: patient-oriented composite endpoint; TLR: target lesion revascularisation

treatment arms and SS tertiles for these endpoints was 0.045 and 0.27, respectively, meriting caution when interpreting the final results. Furthermore, in the high SS tertile, the rate of cardiac death was significantly higher in patients receiving DP-EES as compared to BP-SES (7.0% vs. 3.6%, RR 0.50 [95% CI (0.25-1.00)], p=0.04). One-year outcomes according to stent type and stratified by SS tertile are reported in **Table 5**.

PERFORMANCE OF THE LOGISTIC CLINICAL SYNTAX SCORE

Figure 3 shows Kaplan-Meier mortality curves for tertiles of logistic clinical SYNTAX score (low: 0-5; medium: 6-10; high: 11-22). Increasing categories of scores were associated with higher risk of death at two-year follow-up: high vs. low, RR 7.21 (95% CI [3.78-13.75]), p<0.001; medium vs. low, RR 2.15 (95% CI [1.07-4.30]), p=0.03. As displayed in **Figure 4A** and **Figure 4B**, the score showed fair discrimination (Harrell’s c-index 0.73, 95% CI: 0.68-0.78) and good calibration.

Discussion

The main findings of the present study are the following:

1. The predictive value of the SS is confirmed among patients undergoing PCI with new-generation DES.
2. BP-SES and DP-EES perform similarly across the entire spectrum of CAD complexity throughout two years of follow-up

with regard to a lesion-oriented and a patient-oriented composite endpoint. Differences in individual endpoints across SS categories need to be evaluated in larger studies.

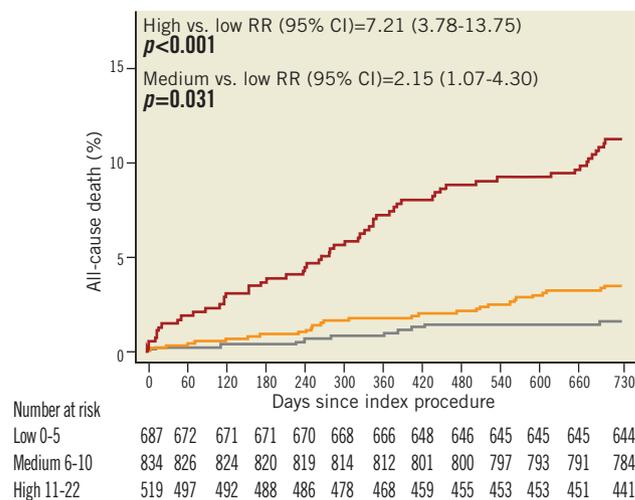


Figure 3. Kaplan-Meier estimates of all-cause death at two years of follow-up for low, medium and high tertiles of logistic clinical SS. Grey line indicates low logistic clinical SS (0-5), orange line indicates medium logistic clinical SS (6-10), red line indicates high logistic clinical SS (11-22).

Table 5. One-year clinical outcomes according to stent type across tertiles of SS.

		BP-SES n=1,010	DP-EES n=1,031	Risk difference (95% CI)	Risk ratio (95% CI)	p-value	interaction p-value [†]
Target lesion failure**	High SYNTAX score	31 (9.1)	35 (10.6)	-1.52 (-5.97 to 2.94)	0.85 (0.52-1.37)	0.50	0.18
	Medium SYNTAX score	10 (3.3)	21 (6.2)	-2.99 (-6.18 to 0.20)	0.52 (0.24-1.10)	0.08	
	Low SYNTAX score	13 (3.8)	9 (2.6)	1.21 (-1.37 to 3.79)	1.49 (0.64-3.50)	0.35	
Cardiac death	High SYNTAX score	8 (2.4)	17 (5.2)	-2.78 (-5.62 to 0.06)	0.45 (0.19-1.04)	0.06	0.04
	Medium SYNTAX score	5 (1.7)	4 (1.2)	0.41 (-1.38 to 2.19)	1.41 (0.38-5.23)	0.61	
	Low SYNTAX score	5 (1.5)	1 (0.3)	1.16 (-0.21 to 2.53)	5.17 (0.60-44.50)	0.09	
Target vessel MI (any)	High SYNTAX score	13 (3.8)	12 (3.7)	0.16 (-2.66 to 2.99)	1.04 (0.47-2.28)	0.93	0.53
	Medium SYNTAX score	5 (1.6)	11 (3.2)	-1.64 (-3.96 to 0.68)	0.49 (0.17-1.42)	0.18	
	Low SYNTAX score	4 (1.2)	5 (1.4)	-0.26 (-1.92 to 1.41)	0.82 (0.22-3.08)	0.77	
Clinically indicated TLR	High SYNTAX score	19 (5.7)	9 (2.8)	2.80 (-0.17 to 5.76)	2.04 (0.92-4.51)	0.07	0.07
	Medium SYNTAX score	2 (0.7)	7 (2.1)	-1.42 (-3.15 to 0.32)	0.32 (0.07-1.54)	0.13	
	Low SYNTAX score	4 (1.2)	5 (1.4)	-0.26 (-1.92 to 1.41)	0.83 (0.22-3.09)	0.78	
POCE***	High SYNTAX score	50 (14.6)	47 (14.2)	0.38 (-4.88 to 5.64)	1.03 (0.69-1.53)	0.90	0.56
	Medium SYNTAX score	22 (7.2)	29 (8.5)	-1.54 (-5.61 to 2.53)	0.83 (0.48-1.45)	0.51	
	Low SYNTAX score	26 (7.7)	21 (6.0)	1.58 (-2.12 to 5.28)	1.29 (0.72-2.29)	0.39	
Definite stent thrombosis	High SYNTAX score	4 (1.2)	3 (0.9)	0.26 (-1.26 to 1.77)	1.28 (0.29-5.74)	0.74	0.93
	Medium SYNTAX score	1 (0.3)	1 (0.3)	0.02 (-0.82 to 0.86)	1.11 (0.07-17.36)	0.94	
	Low SYNTAX score	0 (0.0)	0 (0.0)				
Definite or probable stent thrombosis	High SYNTAX score	11 (3.2)	16 (4.8)	-1.61 (-4.55 to 1.33)	0.66 (0.30-1.42)	0.28	0.67
	Medium SYNTAX score	5 (1.6)	11 (3.2)	-1.64 (-3.96 to 0.68)	0.49 (0.17-1.42)	0.18	
	Low SYNTAX score	5 (1.5)	5 (1.4)	0.03 (-1.72 to 1.79)	1.03 (0.30-3.57)	0.96	

Number of first events and percentages are reported. Rate ratios (RR [95% CI]) are estimated using the Mantel-Cox method with two-sided p-values from log-rank test. All events were censored beyond 365 days. Continuity corrected RR with Fisher's exact test for zero outcomes. **Primary endpoint, defined as the composite of cardiac death, target vessel Q-wave or non-Q-wave MI, clinically indicated TLR. ***Patient-oriented composite endpoint which is death, MI, or any repeat revascularisation. [†]Approximate chi-square test for unequal RRs testing for effect modification of the difference between the stents due to the tertile groups. Approximate Z-test in case of zero events. High SYNTAX: >15; Medium SYNTAX: 8-15; Low SYNTAX: <8. MI: myocardial infarction; TLR: target lesion revascularisation

After its introduction as an angiographic instrument to grade the extent and severity of CAD¹, the SS proved to be an effective predictor of clinical outcomes in several settings. Specifically, the paradigm relating high anatomic complexity (higher SS) with higher rates of adverse ischaemic events has been validated in

patients undergoing PCI with early- and newer-generation DES⁹⁻¹¹. In an *ad hoc* analysis of the RESOLUTE All Comers trial, the SS was identified as an independent predictor of adverse ischaemic events, with patients in the highest SS tertile experiencing higher rates of POCE, TLF, MI, repeat revascularisation and ST³.

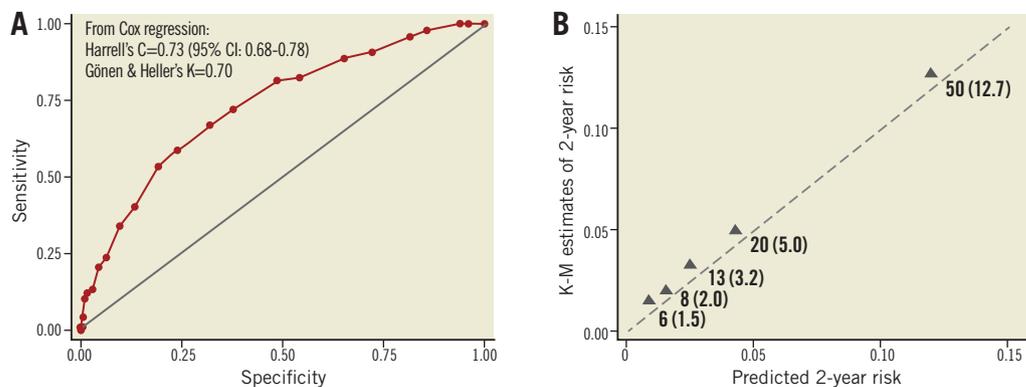


Figure 4. Performance of the logistic clinical SS. A) Area under the curve and discrimination measures. B) Calibration plots. The triangles indicate the observed frequencies by quintile of predicted probabilities.

Similarly, major cardiac event-free survival was lower for patients in the LEADERS trial in the highest tertile of SS². The present study confirms the prognostic value of the SS by documenting higher mortality and higher risk of adverse events among patients with SS >15. The validation of such a predictive role in a real-world population mirroring the currently increasing gradient of complexity for lesions and patients receiving DES supports the utility of implementing its use in current clinical practice.

To date, this study is among the first to assess the role of the SS in a large population treated with biodegradable polymer stents. While a sub-analysis of the LEADERS trial investigated clinical outcomes according to SS tertiles in patients treated with thick strut stainless steel biodegradable polymer DES^{2,12}, we analysed patients treated with ultrathin strut cobalt-chromium biodegradable polymer DES in comparison with the best in class DP-EES.

In a recent pooled analysis of more than 6,000 patients from four all-comers trials (including the BIOSCIENCE trial), new-generation DES were associated with improved clinical outcomes compared with early-generation DES across the entire spectrum of coronary disease complexity¹³. Our study further expands this observation by showing comparable performance of two new-generation DES, irrespective of the extent and severity of coronary disease.

Nevertheless, differences in the occurrence of the individual components of the primary endpoint have been detected within medium and high SS tertiles. We acknowledge that this subgroup analysis is underpowered and the observed results could be a play of chance, requiring a cautious interpretation. Indeed, the higher rates of target vessel MI and ST in patients with medium SS receiving DP-EES were not accompanied by a significantly increased rate of cardiac death. Moreover, there is no obvious explanation for higher rates of cardiac death among patients in the high SS tertile receiving DP-EES. A similar variability in the ability of SS to predict individual major outcomes has previously been pointed out^{3,12}. It could be a consequence of the fact that the score includes several angiographic variables differentially affecting specific clinical endpoints. For example, the lesion length can be related to the occurrence of TVR whilst the disease of proximal vessels could be associated with sudden cardiac death¹⁴. On the other hand, it could be speculated that the peculiar features of the devices are responsible for the diverging outcomes. In this regard, the Orsiro stent represents the latest iteration of stent technology, featuring an ultrathin strut design with a biodegradable polymer aiming to overcome the safety issues of second-generation DES. Its safety and efficacy profile was reassuringly preserved in high-risk groups such as diabetic patients¹⁵. Moreover, a beneficial effect of BP-SES over DP-EES has been advocated in patients presenting with STEMI¹⁶. However, the limited numbers of patients included in the previous and current analyses prevent us from establishing definitely the effect of the refined stent design and biodegradable polymer on prognosis.

Although this study was mainly focused on the performance of BP-SES and DP-EES across the spectrum of coronary anatomy complexity, we additionally assessed the ability of the logistic clinical SS to predict two-year mortality after PCI. To the best of our knowledge, this analysis represents the first external validation of this score. We found a good performance in terms of discrimination and calibration. Notably, the Harrell's C-statistic observed in our study (0.73) perfectly matched with the c-index in the derivation cohort (0.73), further corroborating the clinical utility of the logistic clinical SS.

Limitations

The present analysis has several limitations. First, the sub-analysis was not pre-specified, and numbers are modest, compromising particularly the robustness of individual endpoint analyses. Second, the SS was evaluated retrospectively. However, assessors were blinded to the treatment arm and clinical outcomes, and inter- and intra-rater variability of calculated SS was low. Third, adherence to dual antiplatelet therapy was high in the present cohort and may have further obliterated potential differences across groups.

Conclusions

Increasing lesion complexity as assessed by SS was associated with higher rates of TLF and POCE in a contemporary PCI population. BP-SES and DP-EES performed similarly across the entire spectrum of CAD severity in terms of composite endpoints up to two years of follow-up. The observed differences in the occurrence of individual outcomes and the potential of the SS to discriminate stent performance are only hypothesis-generating and deserve further evaluation. The external validation of the logistic clinical SS confirmed the utility of combining clinical and anatomic variables for predicting long-term mortality after PCI.

Impact on daily practice

Our findings support the use of the SS as a valuable tool to predict the risk of adverse ischaemic events after PCI even in a contemporary scenario in which the complexity of patients receiving coronary stenting is rising apace. In addition, by confirming a comparable safety and efficacy profile as compared with the best performing durable polymer DES across the SS tertiles, they provide further insights concerning our knowledge of the newer-generation biodegradable polymer DES.

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Conflict of interest statement

T. Pilgrim has received travel expenses and payment for lectures from Biotronik. M. Roffi has received grants from Boston Scientific, Abbott Vascular, Medtronic, and Biosensors; and payment for lectures from Lilly-Daiichi Sankyo. D. Tüller has received travel expenses from Biotronik, Biosensors, Terumo, and Medtronic. S. Cook has received grants and personal fees from Boston Scientific, grants from Medtronic and Cordis, and personal fees from St Jude Medical. C. Kaiser has received grants from B. Braun, Biotronik, Abbott Vascular, Terumo, Daiichi Sankyo, and Eli Lilly, and received personal fees from Eli Lilly, AstraZeneca, Abbott Vascular, General Electric Healthcare, Eli Lilly, and Daiichi Sankyo. P. Jüni is an unpaid steering committee or statistical executive committee member of trials funded by Abbott Vascular, Biosensors, Medtronic, and Johnson & Johnson. S. Windecker has received research contracts to the institution from Biotronik and St Jude. The other authors have no conflicts of interest to declare.

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Appendix. Methods

SYNTAX SCORE CALCULATION

Angiographic analyses were performed by two independent invasive cardiologists (M. Tanawaki, F. Rigamonti) at the Core Angiographic Laboratory of the Department of Cardiology of Bern University Hospital, Bern, Switzerland.

The operators were trained for score calculation and blinded to randomisation and clinical data. They scored each coronary lesion with a diameter stenosis $\geq 50\%$ from the baseline angiogram according to the instructions available at the SS algorithm website (www.syntaxscore.com). The SS of 30 randomly selected cases were reassessed by the same readers four weeks later, with evidence of high similarity between score ratings within a patient, and high reliability of individual patient ratings of the SS: intraclass

correlation coefficients (ICC)=0.90 (95% CI: 0.80-0.95). Cases of disagreement were referred to the judgement of a third analyst and the final decision was reached by consensus. For patients with prior coronary artery bypass surgery (CABG), the CABG SS was applied. In-stent restenosis lesions were scored as *de novo* lesions.

LOGISTIC CLINICAL SYNTAX SCORE

Logistic clinical SS was calculated according to the extended model proposed by Iqbal et al⁷. The anatomic SS was combined with the following clinical variables: age (years), creatinine clearance (ml/min), left ventricular ejection fraction (%), SYNTAX-like patients (as fulfilling the enrolment criteria for the SYNTAX trial, i.e., left main stem or three-vessel disease), body mass index, diabetes mellitus, peripheral vascular disease.

STATISTICAL ANALYSIS

All patients with available SS were included in the analyses. Baseline characteristics and clinical outcomes were stratified according to SS tertile (low <8, medium 8-15, high >15) and study arm (BP-SES or DP-EES). Continuous variables were expressed as mean \pm standard deviation (SD); categorical variables were summarised as frequencies (%). Cox regressions were used to compare the outcomes between stent types across SS tertiles. In case of zero events in one comparator group, we reported continuity-corrected risk ratios with p-values from Fisher's exact tests. Survival curves up to two-year follow-up were constructed for time-to-event variables with Kaplan-Meier estimates and compared by the log-rank test. We assessed performance of the logistic clinical SS using measures of calibration and discrimination. The calibration (how well the predicted event rate agrees with the observed event rate over a range of scores) was graphically assessed with plots of predicted vs. observed mortality rates by quintiles of logistic clinical SS. The discrimination of the logistic clinical SS was assessed with the Harrell's C-index for survival data, which measures the ability to distinguish patients who experience an adverse event from those who do not. Larger values indicate better discrimination. A p-value of <0.05 was considered significant, and all tests were two-tailed. All analyses were carried out with Stata Statistical Software: Release 13 (StataCorp LP., College Station, TX, USA).