Bern-Rotterdam Cohort Study

Newer generation everolimus-eluting stents eliminate the risk of very late stent thrombosis compared with early generation sirolimus-eluting and paclitaxel-eluting stents

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BR Cohort Study - Background I

- Stent thrombosis (ST) is a rare but potentially devastating complication following coronary stent implantation and is associated with death or myocardial infarction in up to 90% of cases.

- Whereas early and late ST occur with similar frequency among patients treated with early generation drug-eluting stents (DES) and bare metal stents (BMS), very late ST is more common with early generation DES with an annual risk of up to 0.6% per year during long-term follow-up.

BR Cohort Study - Background II

- The newer generation everolimus-eluting stent (EES) is a thin strut, cobalt chromium stent and releases everolimus, a semisynthetic sirolimus analogue from an acrylic and fluoropolymer mixture.

- Whether the newer generation EES reduces the risk of very late ST as compared to early generation DES has not been investigated in an adequately powered study with sufficient long-term follow-up.

BR Cohort Study - Objective

To compare the safety of the unrestricted use of EES (XIENCE/PROMUS™) compared with early generation sirolimus-eluting (CYPHER™) (SES) and paclitaxel-eluting stents (TAXUS Express™) (PES) for coronary revascularization in a large, consecutively enrolled patient population during long-term follow-up.

BR Cohort Study - Patient Population

Inclusion Criteria

- All consecutive patients treated with EES, SES, and PES at Bern University Hospital and the Thoraxcenter, Erasmus University Hospital in the setting of stable angina, silent ischemia, and acute coronary syndromes (UA, NSTEMI, STEMI)
- Diameter stenosis >50%
- Number of lesions: no limitation
- Number of vessels: no limitation
- Lesion length: no limitation

Exclusion Criteria

- Implantation of more than one stent type

BR Cohort Study - Endpoints

Primary Endpoint

- ARC definite ST

Secondary Endpoints

- ARC very late definite ST
- ARC definite or probable ST
- ARC very late definite or probable ST
- Cardiac Death
- Myocardial Infarction (MI)
- Cardiac Death or MI

BR Cohort Study - Statistical Analysis

- Propensity scores for receiving EES were estimated using a probit model including age, gender and pre-treatment variables associated with stent selection at $p<0.10$ and used to derive inverse probability of treatment weights (ITPW). Comparisons between stents were performed using a Cox proportional hazards model, crude and adjusted by weighting using ITPW.

- Landmark analyses according to a pre-specified landmark point at 1 year (360 days) were used and hazard ratios and cumulative incidence rates were estimated separately for events up to one year, and beyond.

- Clinical events are expressed as counts and cumulative incidence rates per 100 patient years.

BR Cohort Study - Clinical Trial Organization

Event Adjudication Committee

- Salvatore Brugaletta, MD, Barcelona, Spain
- Josep Lara Gomez, MD, Barcelona, Spain
- Gerrit Hellige, MD, Aarau, Switzerland
- Niklas Millauer, MD, Bern, Switzerland

Central Data Monitoring

- Clinical Trials Unit Bern, Switzerland

Independent Statistical Analysis

- Clinical Trials Unit Bern and Institute of Social and Preventive Medicine, P. Jüni, B. Kalesan

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BR Cohort Study - Patient Flow

12339 Patients Undergoing PCI

EES	SES	PES
4212 consecutive patients 11/2006 – 3/2009	3819 consecutive patients 3/2002-1/2006	4308 consecutive patients 3/2002-1/2006
Fup rate* 97.4% Mean fup duration 2.5 years (1.8-3.1)	Fup rate 97.5% Mean fup duration 4.0 years (3.1-4.0)	Fup rate 95.9% Mean fup duration 3.0 years (2.1-3.6)

*F/U rate at the time of latest follow-up

BR Cohort Study - Antithrombotic Drug Regimen

Pre or during procedure

Acetylsalicylic acid: ≥ 100 mg

Clopidogrel: 300-600 mg loading dose

Unfractionated heparin

– Bolus of at least 5000 IU i.v. or 70 IU/kg

Glycoprotein IIb/IIIa antagonists

– Operator discretion

Post procedure

Acetylsalicylic acid: 100 mg/d indefinitely

Clopidogrel 75 mg/d for 3-12 months

BR Cohort Study - Patient Characteristics

	EES	SES	PES	EES vs. SES	EES vs. PES
Total (n)	4212	3819	4308		
Age (%)	64±12	63±12	63±12	<0.0001	<0.0001
Sex (%)	73	75	74	0.11	0.35
BMI (%)	27±4	27±4	27±4	0.98	0.02
Hypertension (%)	57	52	41	<0.0001	<0.0001
Current smoking (%)	37	46	30	<0.0001	<0.0001
Dyslipidaemia (%)	54	55	46	0.54	<0.0001
Diabetes mellitus (%)	19	18	14	0.28	<0.0001
Renal failure (%)	11	12	12	0.46	0.81
LVEF <50%	34	27	25	<0.0001	<0.0001
ACS (%)	63	53	59	<0.0001	0.004
UA/NSTEMI (%)	42	57	45		
STEMI (%)	58	43	55		
Cardiogenic shock (%)	3	2	2	<0.0001	<0.0001

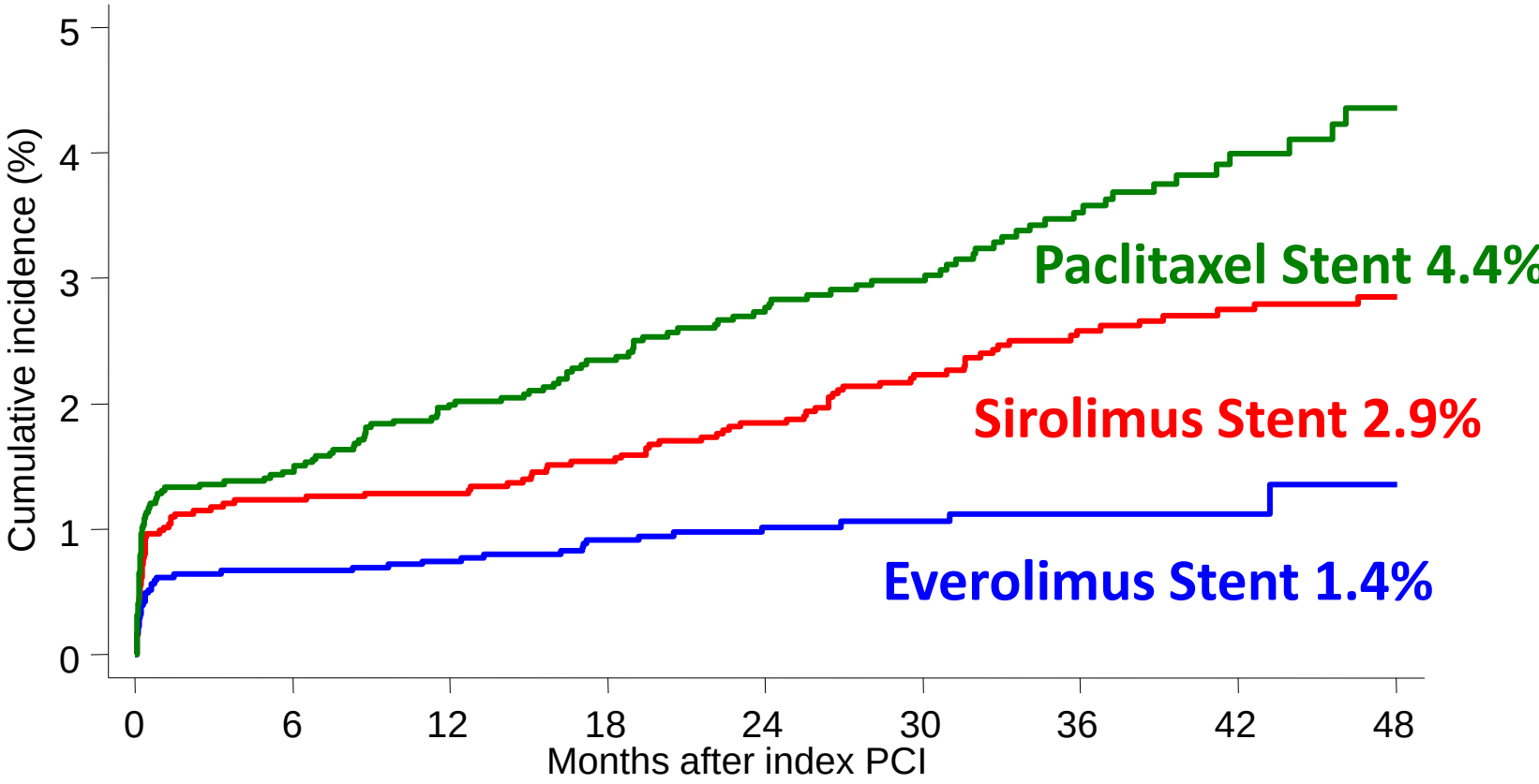
BR Cohort Study - Procedural Characteristics

	EES	SES	PES	EES vs. SES	EES vs. PES
Total (n)	4212	3819	4308		
Multivessel treatment (%)	16	17	19	0.29	0.003
No of vessels treated (n±SD)	1.2±0.4	1.2±0.4	1.2±0.4	0.21	0.66
No of lesions treated (n ±SD)	1.8±1	1.5±0.7	1.4±0.7	<0.0001	<0.0001
1 lesion (%)	51	64	65		
2 lesion (%)	29	27	28		
3 lesion (%)	13	7	6		
>4 lesions (%)	7	1	1		
Left main (%)	4	2	4	<0.0001	0.08
Saphenous vein graft (%)	3	3	1	0.41	<0.0001
No of stents per patient (n±SD)	1.9 ±1.2	1.9±1.1	2.0 ±1.3	0.01	<0.0001
Average stent diameter (n±SD)	3.0 ±0.4	2.9±0.5	3.0±0.4	<0.0001	0.03
Total stent length (n±SD)	33±23	34±23	39±28	0.27	<0.0001
GP IIb/IIIa antagonist (n%)	21	19	18	0.03	<0.0001

Primary Endpoint
ARC Definite ST @ 4 Years

EES vs. SES Hazard Ratio* = 0.41, 95% CI 0.27–0.62, P<0.0001

EES vs. PES Hazard Ratio* =0.33, 95% CI 0.23-0.48, P <0.0001

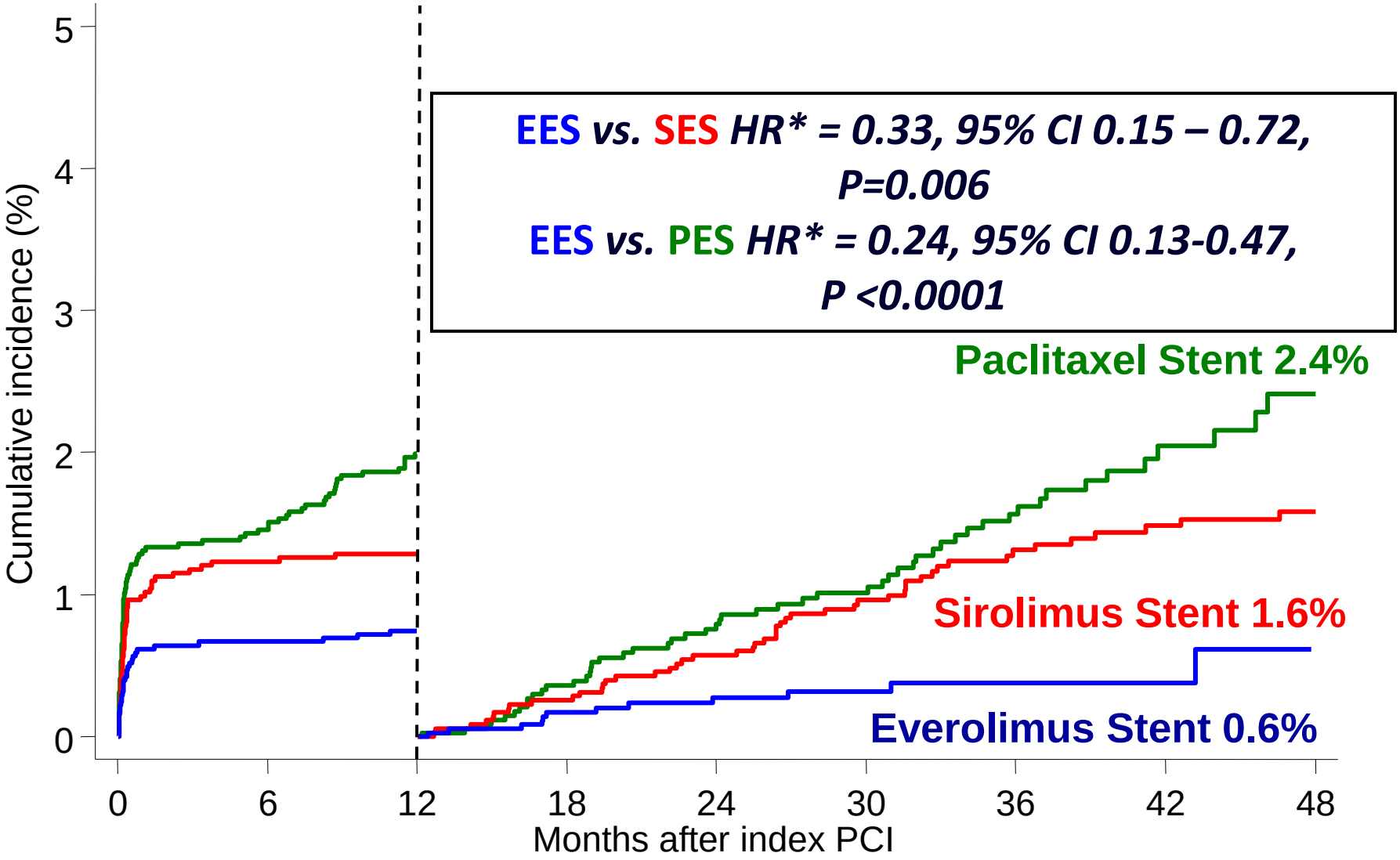


No. at risk

PES	4214	3916	3797	3176	2905	2344	1880	1077	686
SES	3784	3617	3569	3499	3404	3080	2521	2118	1734
EES	4135	3913	3793	3284	2604	1856	1041	514	208

*from Cox proportional hazards model

Very Late ST (1-4yrs)

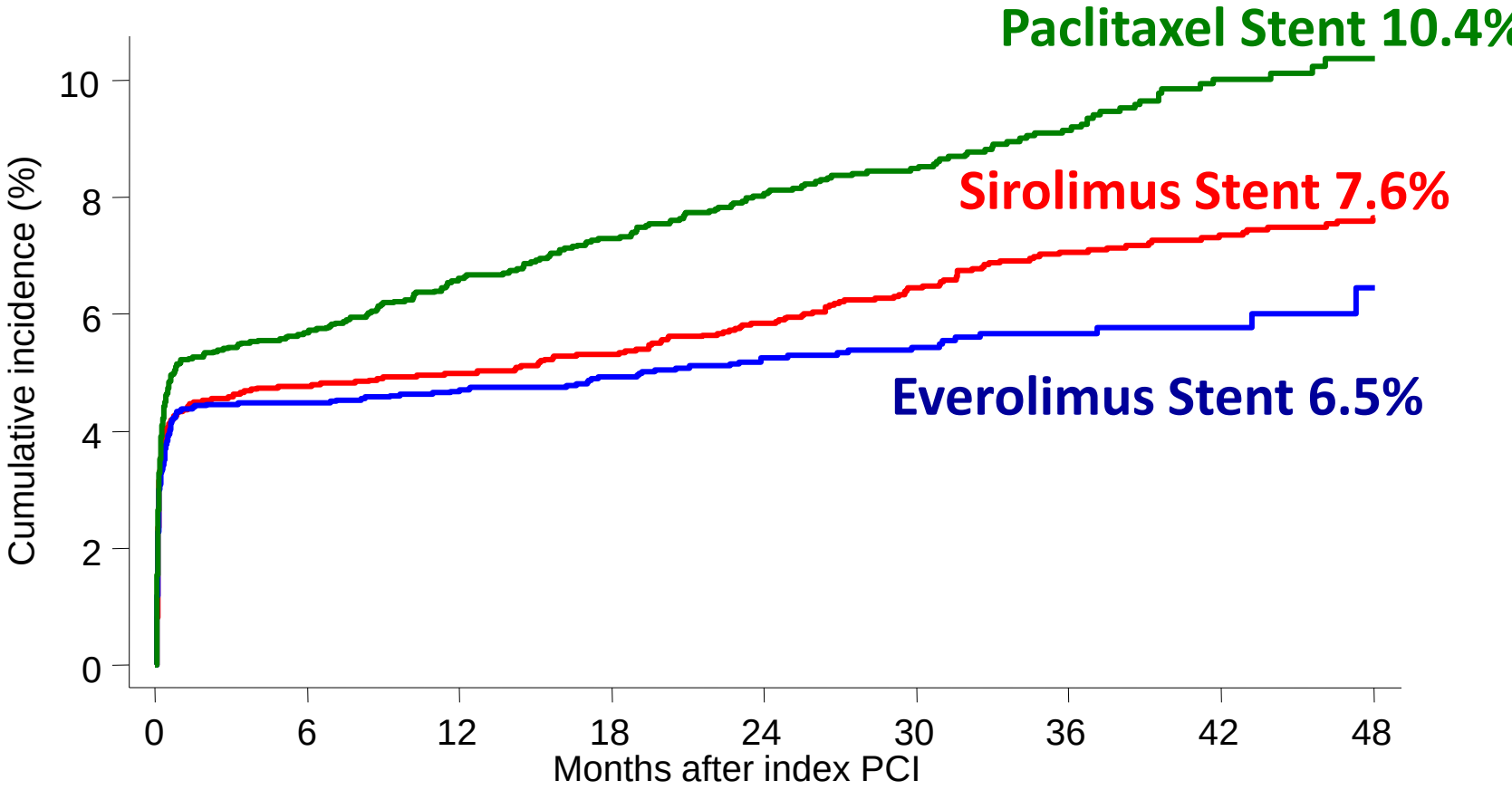


*from Cox proportional hazards model

ARC Definite or Probable ST @ 4yrs

EES vs. SES HR* = 0.41, 95% CI 0.27–0.62, P<0.0001

EES vs. PES HR* =0.33, 95% CI 0.23-0.48, P <0.0001

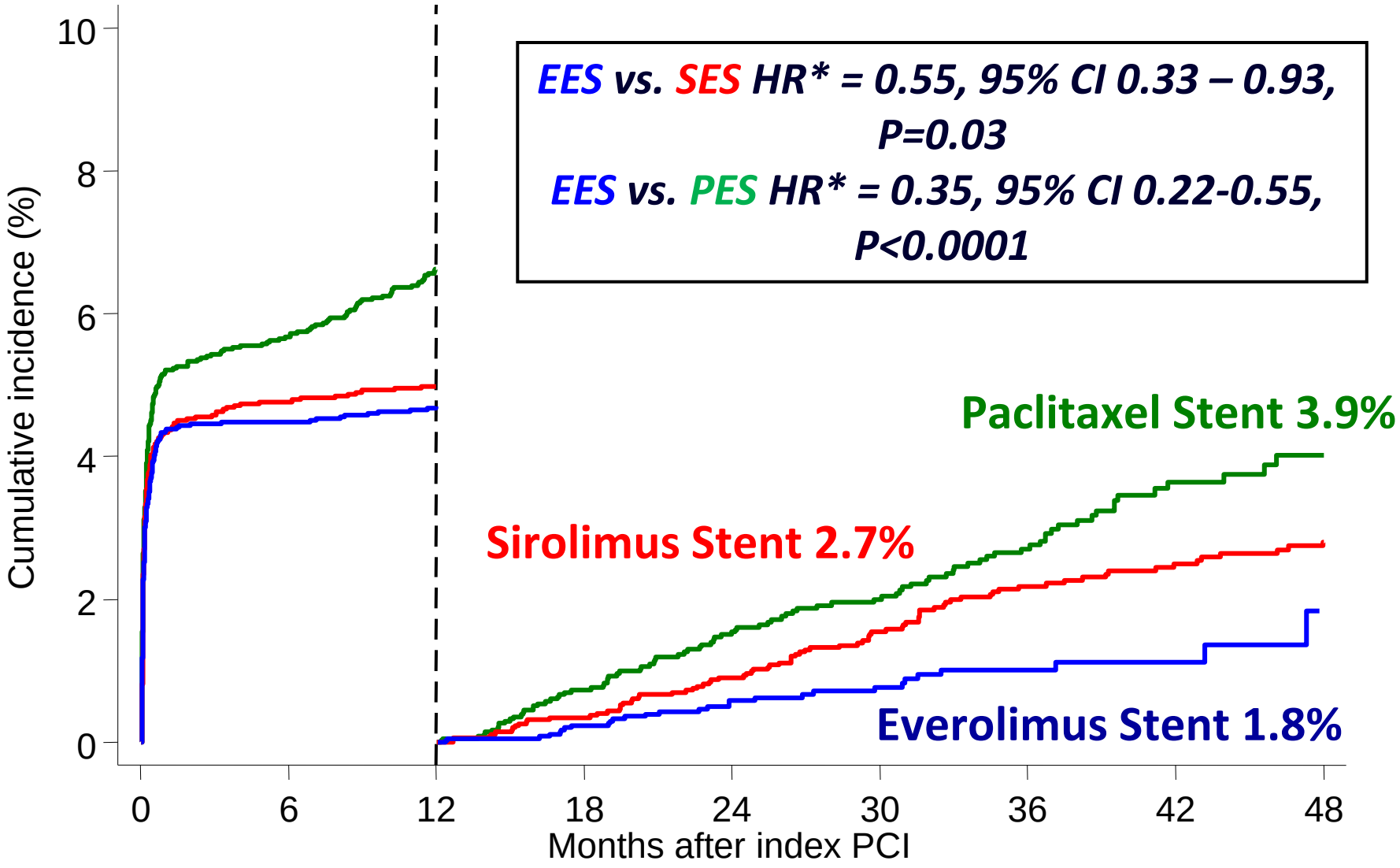


No. at risk

PES	4214	3859	3726	3106	2831	2274	1821	1034	660
SES	3784	3549	3499	3428	3332	3010	2456	2061	1687
EES	4138	3878	3753	3241	2566	1831	1025	505	203

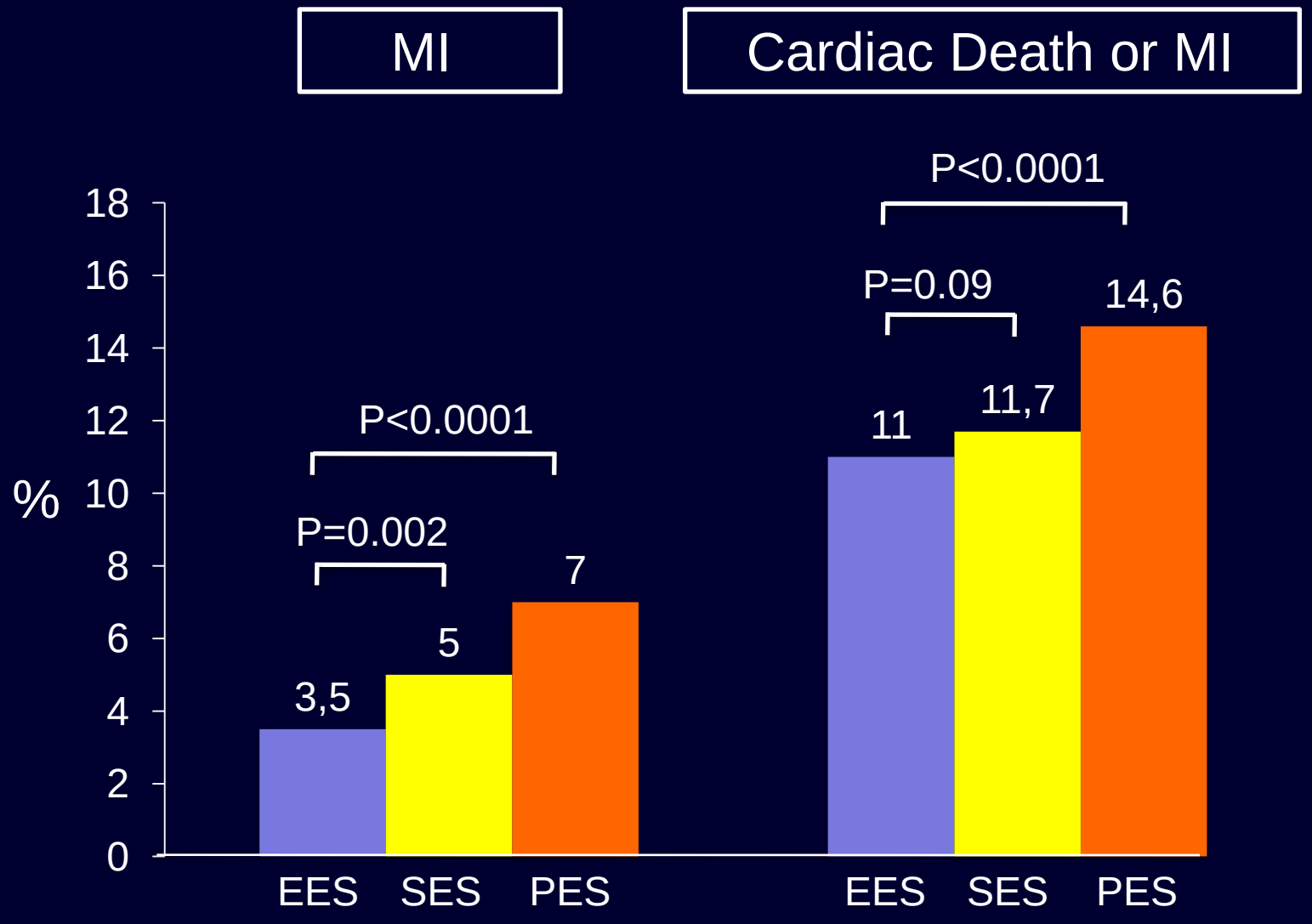
*from Cox proportional hazards model

ARC Definite or Probable Very Late ST (1-4yrs)



*from Cox proportional hazards model

BR Cohort Study - Clinical Safety Outcome *@4yrs*



P-values from Cox proportional hazards model

Association of Cardiac Death or MI With ARC Definite ST

Cardiac Death or MI associated with ST

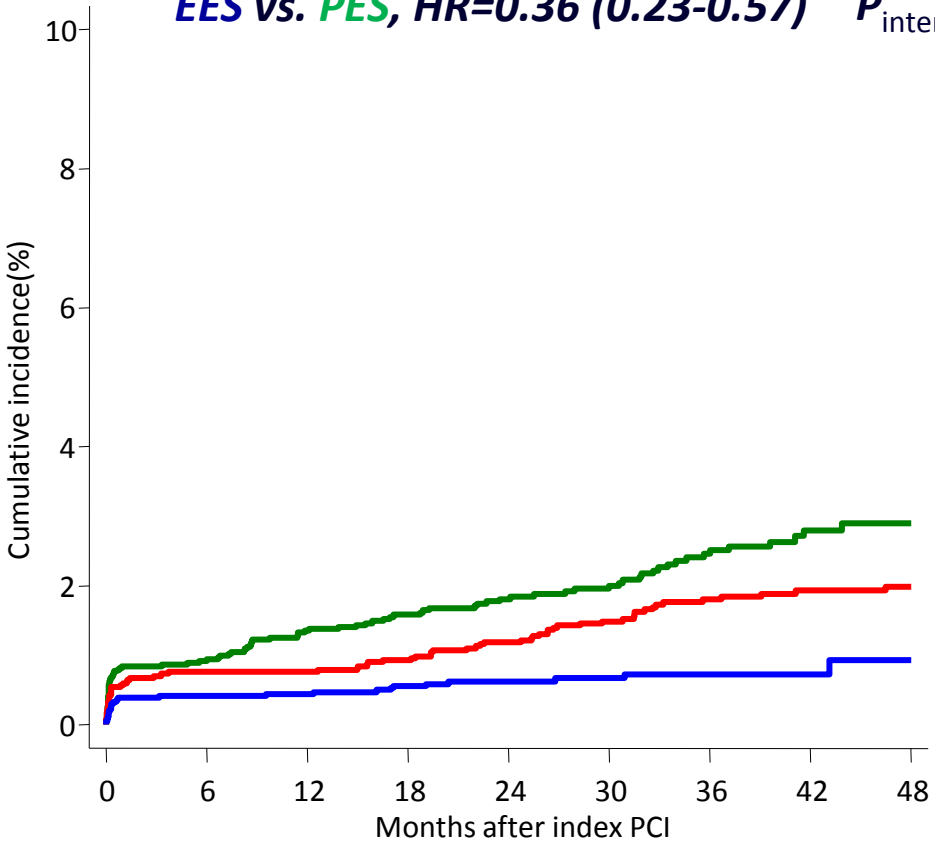
Cardiac Death or MI not associated with ST

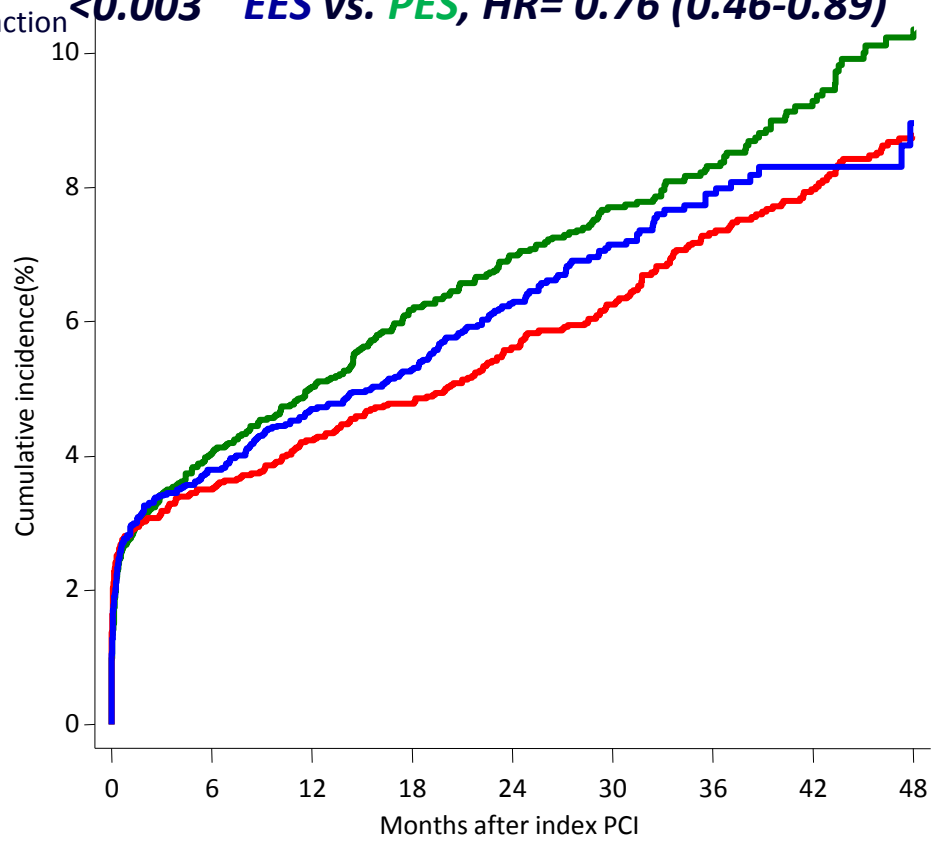
EES vs. SES HR = 0.46 (0.26-0.81) $P_{interaction}$***=0.01***

EES vs. SES, HR = 1.00 (0.84-1.20)

EES vs. PES, HR=0.36 (0.23-0.57) $P_{interaction}$***<0.003***

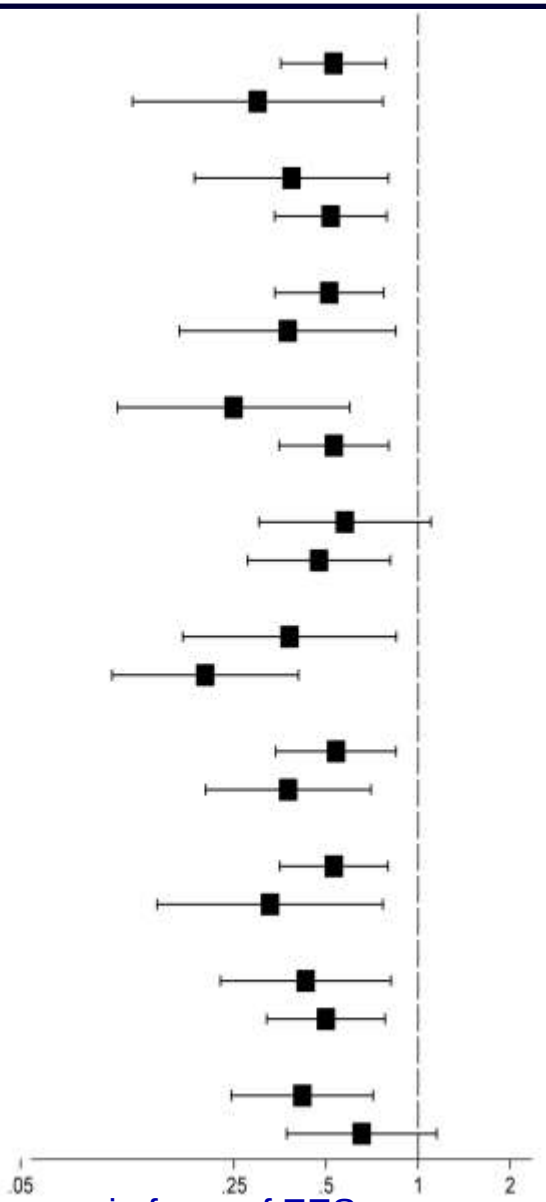
EES vs. PES, HR= 0.76 (0.46-0.89)





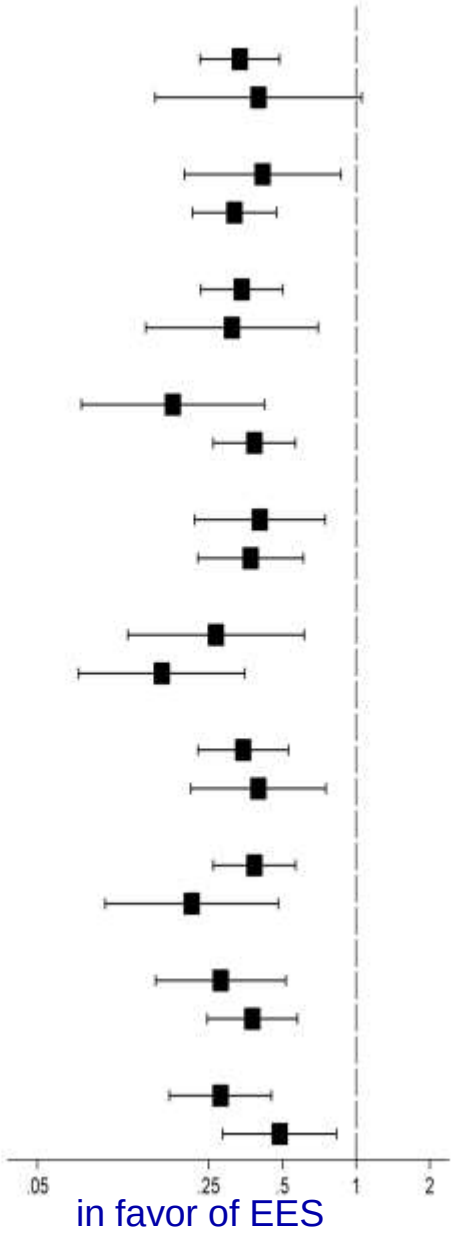
Stratified Analysis of Primary Endpoint

	EES	SES	HR 95% CI	P Value
Age (n [%])				0.32
<75 years	36 (1.5)	81 (2.8)	0.53 (0.36-0.79)	
>=75	6 (0.7)	16 (3.0)	0.30 (0.12-0.77)	
Gender (n [%])				0.45
Women	10 (1.1)	28 (3.3)	0.39 (0.19-0.80)	
Men	32 (1.5)	69 (2.7)	0.52 (0.34-0.79)	
Diabetes mellitus (n [%])				0.45
No	34 (1.2)	74 (2.6)	0.51 (0.34-0.77)	
Yes	8 (2.1)	23 (3.8)	0.37 (0.17-0.85)	
Acute coronary syndrome (n [%])				0.13
No	6 (0.9)	33 (2.0)	0.25 (0.10-0.60)	
Yes	36 (1.6)	64 (3.7)	0.53 (0.35-0.80)	
Acute coronary syndrome: type (n [%])				0.62
Unstable angina/ Non-ST-elevation MI	14 (1.4)	28 (3.0)	0.58 (0.30-1.10)	
ST-elevation MI	22 (1.7)	36 (4.5)	0.47 (0.28-0.81)	
Left ventricular ejection fraction*(n [%])				0.27
>=50%	7 (0.7)	43 (2.4)	0.38 (0.17-0.85)	
<50%	11 (0.8)	27 (4.2)	0.20 (0.10-0.41)	
Glycoprotein IIb/IIIa antagonist (n [%])				0.43
No	28 (1.3)	61 (2.2)	0.54 (0.34-0.85)	
Yes	14 (1.7)	35 (5.4)	0.38 (0.20-0.70)	
Total stent length per patient (n [%])				0.34
>20mm	35 (1.8)	72 (3.3)	0.53 (0.35-0.80)	
<=20mm	7 (0.5)	24 (2.0)	0.33 (0.14-0.77)	
Number of stents per patient (n [%])				0.71
1	13 (0.8)	35 (2.1)	0.43 (0.23-0.81)	
>1	29 (1.8)	62 (3.6)	0.50 (0.32-0.78)	
Stent diameter (n [%])				0.24
>2.75mm	22 (0.9)	36 (2.6)	0.42 (0.24-0.71)	
<=2.75mm	20 (2.3)	32 (3.0)	0.65 (0.37-1.15)	



Stratified Analysis EES vs. PES

	EES	PES	HR 95% CI	P Value
Age (n [%])				0.72
<75 years	36 (1.5)	121 (4.8)	0.34 (0.23-0.49)	
>=75	6 (0.7)	13 (2.3)	0.40 (0.15-1.06)	
Gender (n [%])				0.54
Women	10 (1.1)	25 (3.2)	0.42 (0.20-0.87)	
Men	32 (1.5)	109 (4.8)	0.32 (0.21-0.47)	
Diabetes mellitus (n [%])				0.69
No	34 (1.2)	111 (4.1)	0.34 (0.23-0.50)	
Yes	8 (2.1)	23 (6.2)	0.31 (0.14-0.70)	
Acute coronary syndrome (n [%])				0.11
No	6 (0.9)	40 (3.0)	0.18 (0.08-0.42)	
Yes	36 (1.6)	94 (5.4)	0.38 (0.26-0.57)	
Acute coronary syndrome: type (n [%])				0.64
Unstable angina/ Non-ST-elevation MI	14 (1.4)	38 (4.7)	0.40 (0.22-0.75)	
ST-elevation MI	22 (1.7)	55 (6.0)	0.37 (0.23-0.61)	
Left ventricular ejection fraction*(n [%])				0.51
>=50%	7 (0.7)	32 (3.4)	0.27 (0.12-0.61)	
<50%	11 (0.8)	15 (4.9)	0.16 (0.07-0.35)	
Glycoprotein IIb/IIIa antagonist (n [%])				0.57
No	28 (1.3)	92 (3.9)	0.35 (0.23-0.53)	
Yes	14 (1.7)	30 (4.4)	0.40 (0.21-0.75)	
Total stent length per patient (n [%])				0.18
>20mm	35 (1.8)	96 (4.7)	0.38 (0.26-0.57)	
<=20mm	7 (0.5)	37 (3.5)	0.21 (0.09-0.48)	
Number of stents per patient (n [%])				0.41
1	13 (0.8)	51 (3.7)	0.28 (0.15-0.52)	
>1	29 (1.8)	82 (4.8)	0.38 (0.25-0.58)	
Stent diameter (n [%])				0.16
>2.75mm	22 (0.9)	70 (4.0)	0.28 (0.17-0.45)	
<=2.75mm	20 (2.3)	42 (5.2)	0.49 (0.29-0.83)	



BR Cohort Study - Antiplatelet Therapy

	EES	SES	PES	EES vs. SES	EES vs. PES
At Discharge*	4212	3819	4308		
ASA	98.7	98.9	98.3	0.36	0.10
Clopidogrel	99.2	99.8	99.4	<0.001	0.17
DAPT	97.2	97.9	98.6	0.15	0.006
At Follow-up**					
Mean follow-up duration (yrs)	2.4	3.6	4.0		
Aspirin, %	93.2	87.1	86.9		
Clopidogrel, %	28.5	21.7	18.6		
DAPT, %	24.1	16.4	13.7		

*all patients, **only Bern data available

BR Cohort Study - Limitations

- Non-randomized observational study
  - *analyses were adjusted for differences using inverse probability of treatment weighting (ITPW)*
  - *differences in favour of EES were large and consistent among subgroups*
- Patients were enrolled sequentially and advances in implantation technique and prolongation of DAPT to one year may have favored EES
  - *Study focused on very late ST*
  - *DAPT duration during last follow-up was comparable among all groups*
  - *Sequential enrollment reduces the risk of selection bias*
  - *EES patients were at higher risk*

BR Cohort Study - Conclusions

- In this observational, prospective cohort study, the unrestricted use of a EES was associated with a lower risk of overall ARC definite and ARC definite or probable ST up to four years of follow-up.
- The benefit in favor of a EES was most pronounced during the very late period with a 71% and 77% reduced risk of definite ST compared with SES and PES, respectively, resulting in a nearby elimination of very late ST.
- The reduced risk of VLST with the unrestricted use of EES overcomes the principal limitation of early generation DES and constitutes an important advance in DES safety.