One-Year Outcome of a Trial Comparing Second Generation Drug-eluting Stents Using Either Biodegradable Polymer or Durable Polymer

The NOBORI Biolimus-Eluting versus XIENCE/PROMUS Everolimus-eluting Stent Trial (NEXT)

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On behalf of the NEXT Investigators

Disclosures

Masahiro Natsuaki, MD

None.

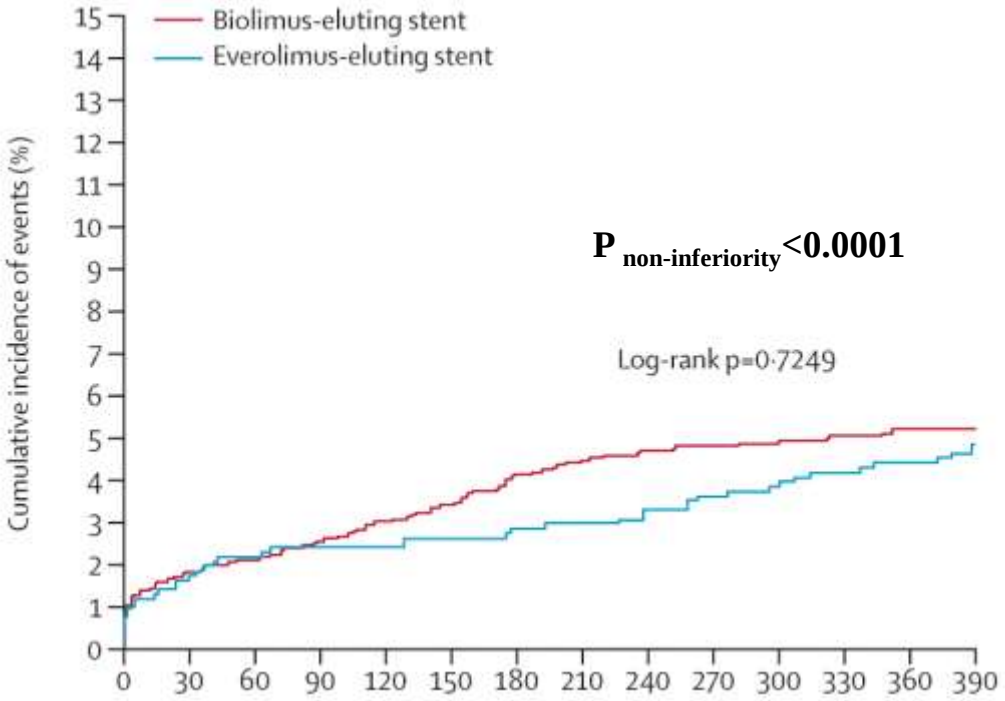
Study Sponsor of the NEXT Trial

Terumo Japan

Background

The COMPARE II trial demonstrated non-inferiority of biolimus-eluting stent (BES) relative to everolimus-eluting stent (EES) in terms of a composite of cardiac death, non-fatal myocardial infarction (MI) and clinically-driven target-vessel revascularization (TVR) at 1 year.

Kaplan-Meier Cumulative Event Curves for the Primary Endpoint at 1 year

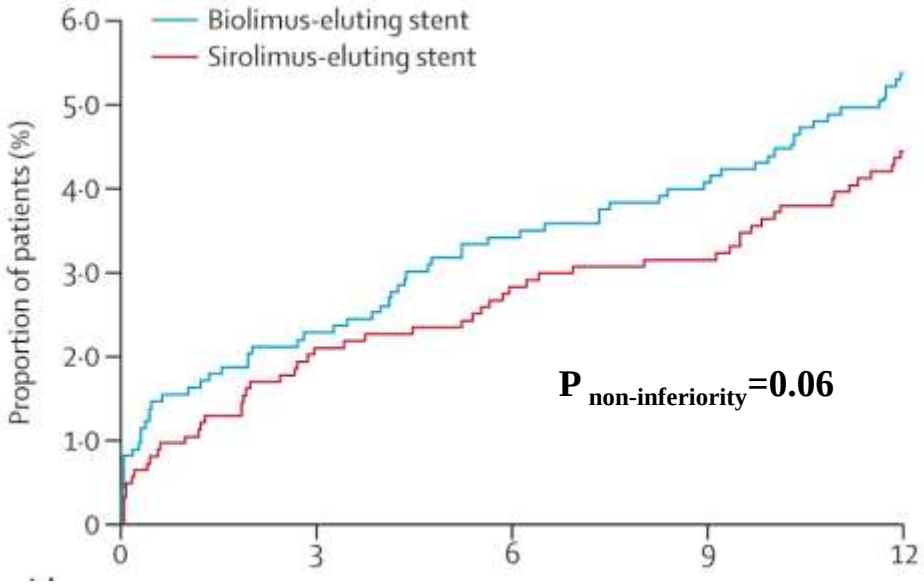


Smits PC, et al. Lancet. 2013. Jan 29. Epub ahead of print.

Background

On the other hand, non-inferiority of BES relative to sirolimus-eluting stent was not demonstrated in the SORT-OUT V trial in terms of a composite of cardiac death, MI, definite stent thrombosis and TVR at 9 months.

The results of these trials were inconsistent and it is still unknown whether the biodegradable polymer BES has the efficacy- and safety-profile equivalent to or even better than the durable polymer EES.



Christiansen EH, et al. Lancet. 2013. Jan 29. Epub ahead of print.

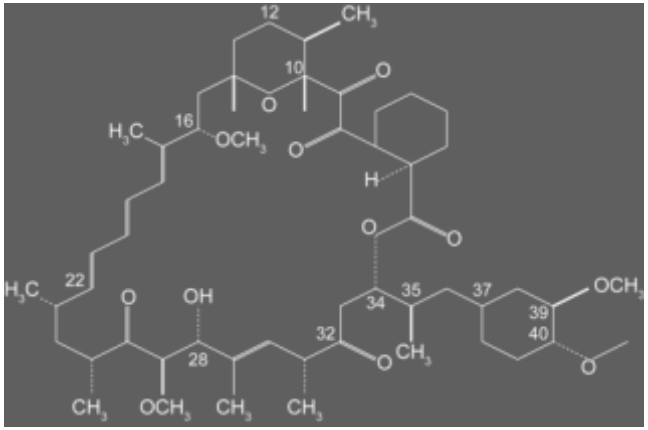
Nobori® Biolimus-eluting Stent

Stent

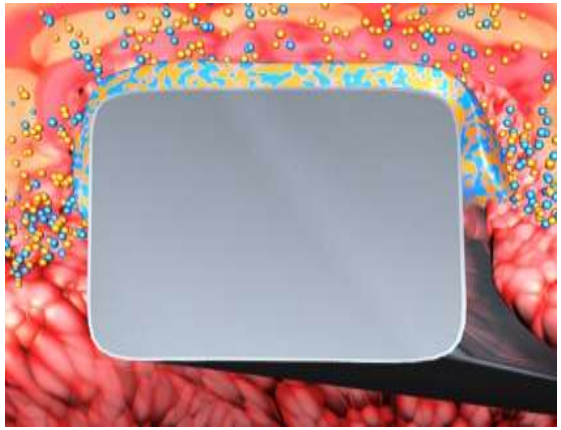
Nobori® biolimus-eluting stent is a stainless steel alloy stent with relatively thick strut (120μm).

Drug and polymer

Biolimus A9, a highly lipophilic analogue of sirolimus, and biodegradable polymer (poly-lactic acid) are coated only on the abluminal side.



Biolimus

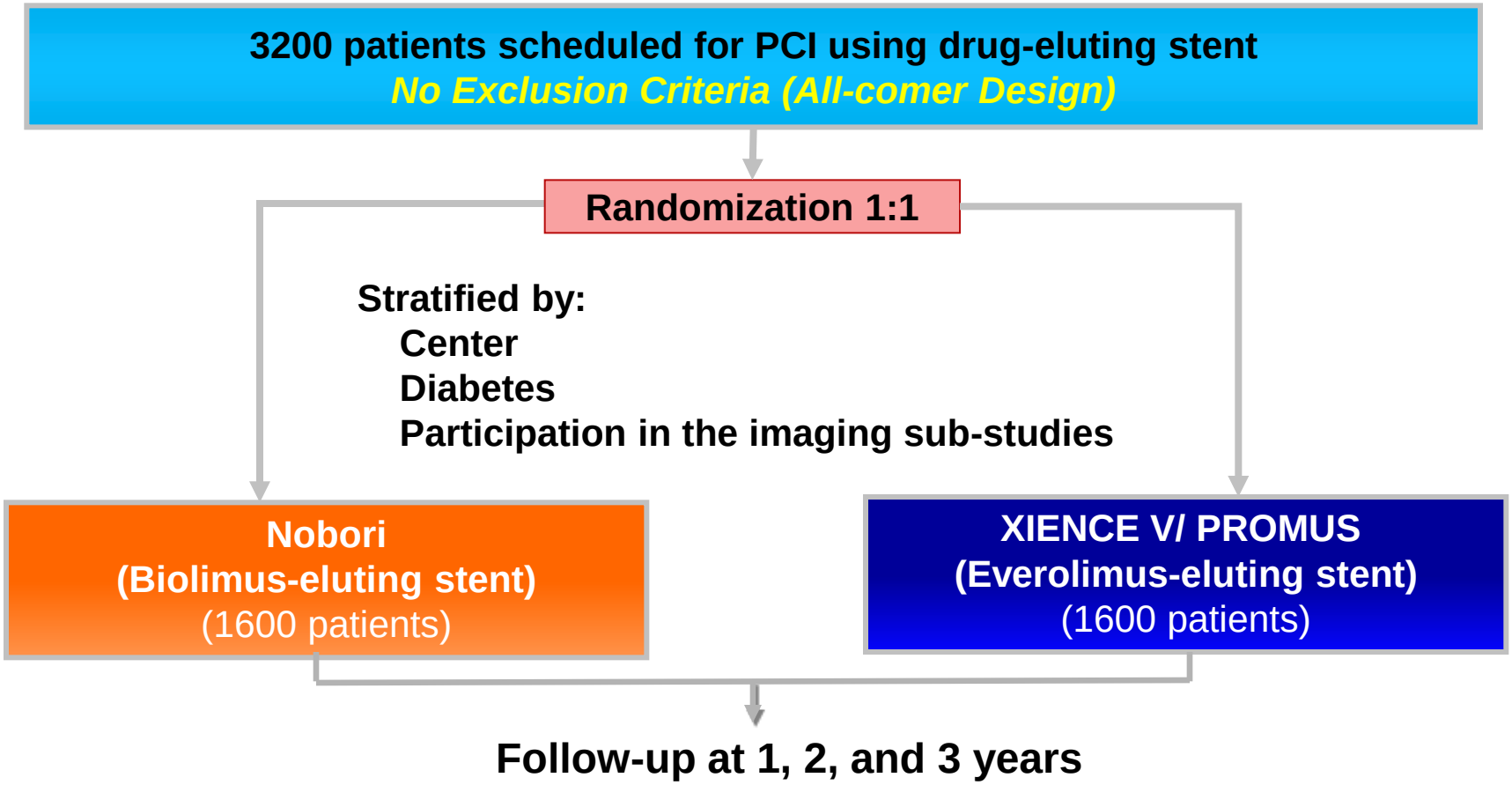


Poly-lactic acid

NEXT Trial

(NOBORI Biolimus-Eluting versus XIENCE/PROMUS Everolimus-eluting stent Trial)

Multicenter, randomized, non-inferiority trial comparing BES with EES



Imaging Sub-studies at 8-12 months:

Angiography (500 patients), IVUS/OCT (120 patients), Endothelial function (100 patients)

(Scheduled follow-up angiography by local site protocol was allowed beyond 240 days.)

Primary Endpoints and Sample Size Calculation

- **Primary Efficacy Endpoint:**
  Any Target-lesion Revascularization (TLR) at 1 year

- **Primary Safety Endpoint:**

  Death or Myocardial Infarction at 3 years

- **Sample size calculation:**
  Estimated TLR rate at 1 year in the EES group: 6.9%
  Non-inferiority margin of 3.4% and one-sided type I error of 0.025
  3000 patients would yield > 95% power to detect non-inferiority.

- A total of 3200 patients were to be enrolled considering possible drop-out during follow-up.

Angiographic Primary Endpoint and Sample Size Calculation

- **Primary Angiographic Endpoint:**

  In-segment Late Loss at 8-12 Months

- **Sample size calculation:**

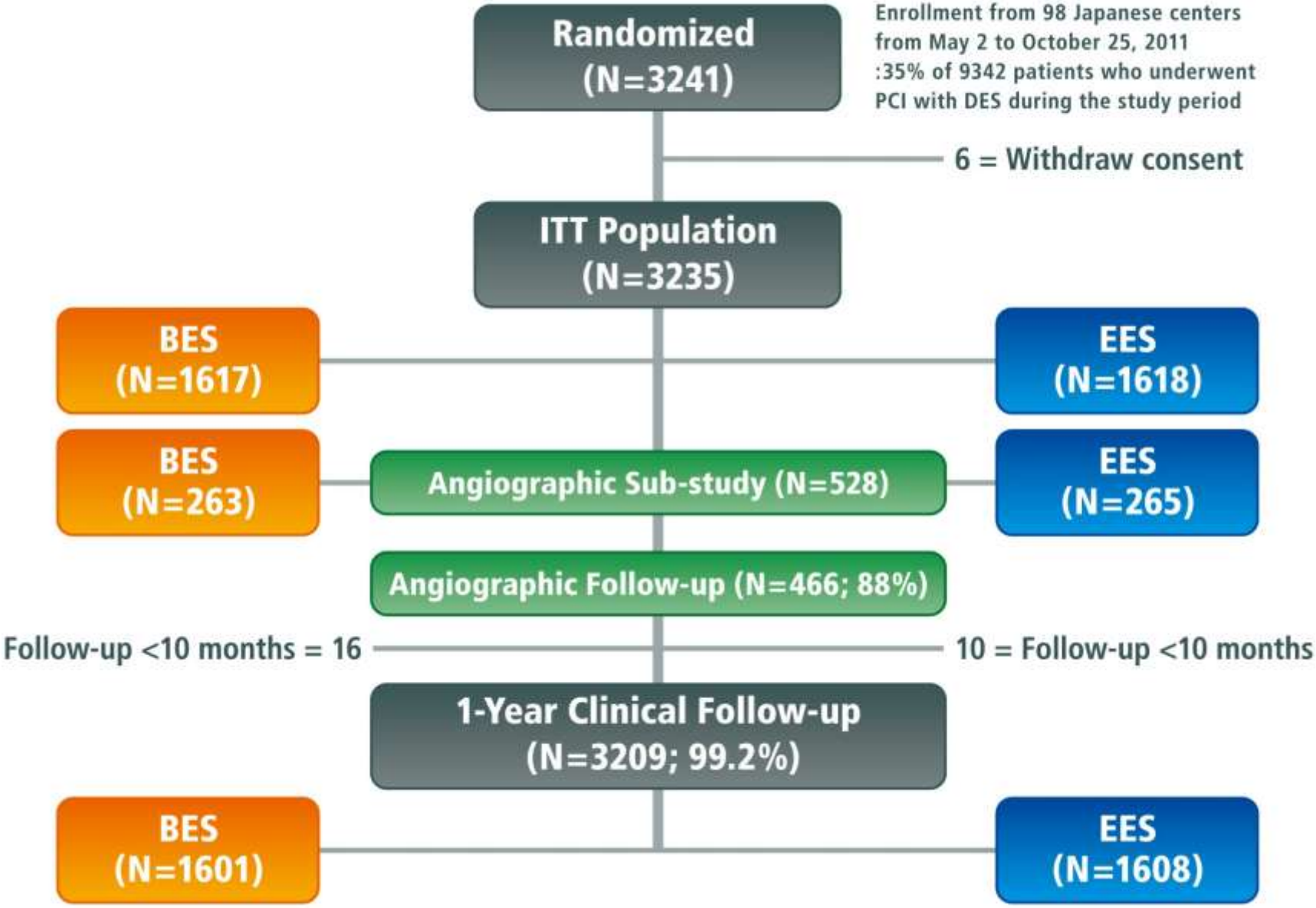
  Estimated in-segment late loss in the EES group:
  0.04 ± 0.49 mm (Cypher PMS Japan)

  Non-inferiority margin of 0.195 mm (SPIRIT III trial) and one-sided type I error of 0.025

  400 patients would yield 97% power to detect non-inferiority.

- A total of 500 patients were to be enrolled considering possible drop-out from the follow-up angiography.

NEXT Patient Flow



Baseline Patient Characteristics

	Biolimus-eluting stent	*Everolimus-eluting stent*	*P*
No. of patients	**1617**	**1618**	
Age (years)	69.1 ± 9.8	69.3 ± 9.8	0.49
Age>= 75 years	31 %	34 %	0.052
Male gender	77 %	77 %	0.76
Body mass Index (kg/m^2)	24.1 ± 3.7	24.2 ± 3.5	0.55
Diabetes	46 %	46 %	0.85
Insulin-treated	10 %	11 %	0.73
Hypertension	81 %	82 %	0.81
Current smoker	19 %	18 %	0.71
Statin use	77 %	75 %	0.47
Prior PCI	50 %	51 %	0.9
Prior CABG	5.3 %	4.8 %	0.52

Baseline Patient Characteristics

	Biolimus-eluting stent	*Everolimus-eluting stent*	*P*
No. of patients	**1617**	**1618**	
Clinical diagnosis			0.62
Acute myocardial infarction	5.1 %	4.5 %	
Unstable angina	12 %	11 %	
Stable coronary artery disease	83 %	84 %	
Prior myocardial infarction	28 %	28 %	0.81
Prior stroke	10 %	11 %	0.43
Heart failure	13 %	11 %	0.13
Hemodialysis	6.5 %	5.2 %	0.11
Peripheral vascular disease	9.7 %	11 %	0.1
Multivessel disease	51 %	51 %	0.9
SYNTAX score	10 (6-17) (N=1494)	10 (6-16) (N=1506)	0.17

Baseline Lesion Characteristics

	Biolimus-eluting stent	*Everolimus-eluting stent*	*P*
No. of lesions	**2059**	**2010**	
Target vessel location			0.42
LMCA	2.4 %	2.3 %	
LAD	42 %	42 %	
LCx	22 %	24 %	
RCA	33 %	31 %	
Graft	0.7 %	0.9 %	
STEMI culprit lesions	3.0 %	2.9 %	0.88
Chronic total occlusion	8.6 %	7.9 %	0.39
In-stent restenosis	11 %	11 %	0.94
Bifurcation lesions	43 %	45 %	0.36
Reference vessel size <= 2.75 mm	60%	62%	0.25
Lesion length > 18 mm	43%	42%	0.51

Procedural Characteristics

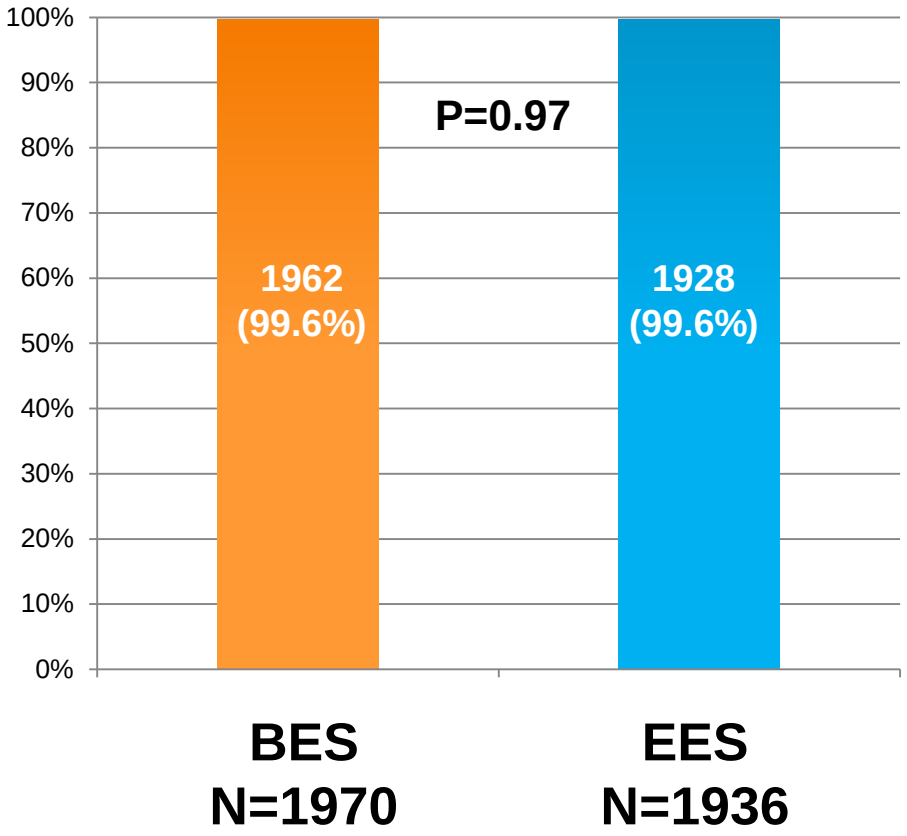
	Biolimus-eluting stent	*Everolimus-eluting stent*	*P*
No. of lesions treated per patient	1.27 ± 0.56	1.24 ± 0.51	0.1
No. of stents			
Per patient	1.59 ± 0.84	1.6 ± 0.83	0.74
Per lesion	1.29 ± 0.56	1.32 ± 0.6	0.13
Total stent length (mm)			
Per patient	33.0± 20.3	32.9 ± 20.7	0.87
Per lesion	26.9 ± 15.1	27.2 ± 16.5	0.52
Stent diameter (mm)	2.88 ± 0.67	2.87 ± 0.64	0.7
Direct stenting	23 %	23 %	0.93
Maximum inflation pressure (atm)	17.2 ± 4.5	16.9 ± 4.4	0.03
Bifurcation 2-stent	1.2 %	1.0 %	0.41
IVUS use	88%	87%	0.21
Multivessel treatment	13%	11%	0.21
Staged procedures	27%	27%	0.77

Baseline QCA Data

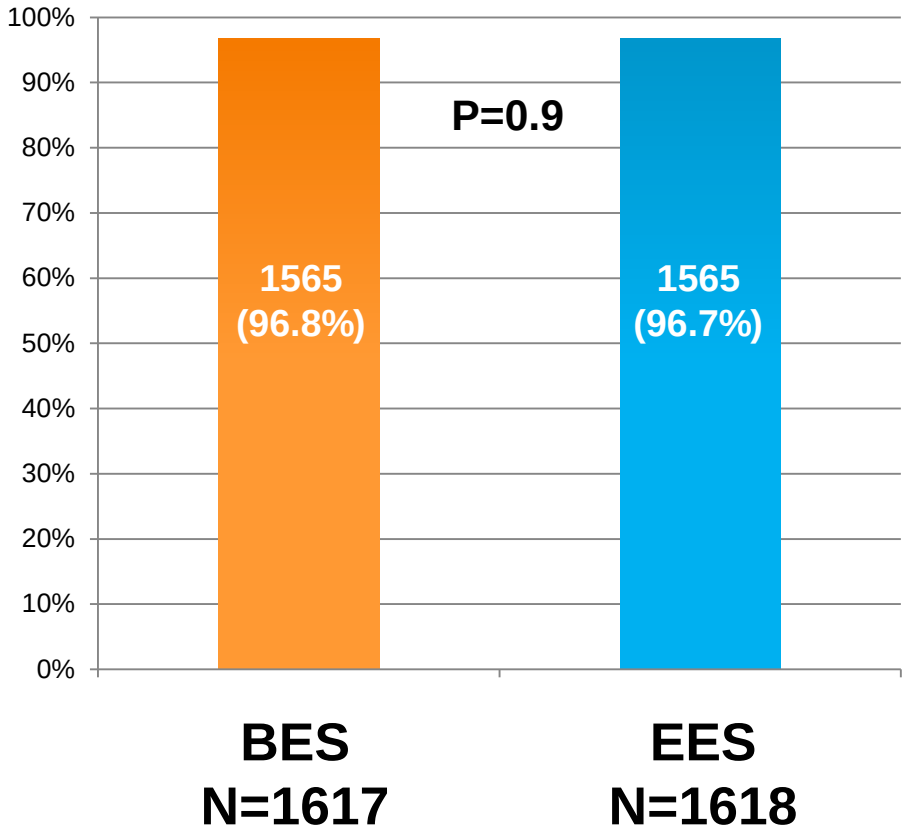
Variables — no. (%)	BES (1960 lesions)	EES (1930 lesions)	p-value
Before procedure			
Lesion length — mm	19.5±12.8	19.3±13.1	0.7
Reference vessel diameter — mm	2.62±0.6	2.61±0.57	0.49
Minimal luminal diameter (MLD)— mm	0.77±0.44	0.75±0.42	0.11
Diameter stenosis (DS)— %	71.0±14.6	71.4±14.6	0.4
After procedure			
Minimal luminal diameter (MLD) — mm			
In stent	2.51±0.48	2.47±0.46	0.006
In segment	2.08±0.56	2.07±0.53	0.7
Diameter stenosis (DS) — %			
In stent	9.7±7.9	10.0±7.9	0.26
In segment	22.2±12.3	21.1±11.2	0.005
Acute gain — mm			
In stent	1.73±0.5	1.71±0.51	0.21
In segment	1.3±0.53	1.32±0.54	0.41

Procedural Results

Acute Device Success



Patient Success

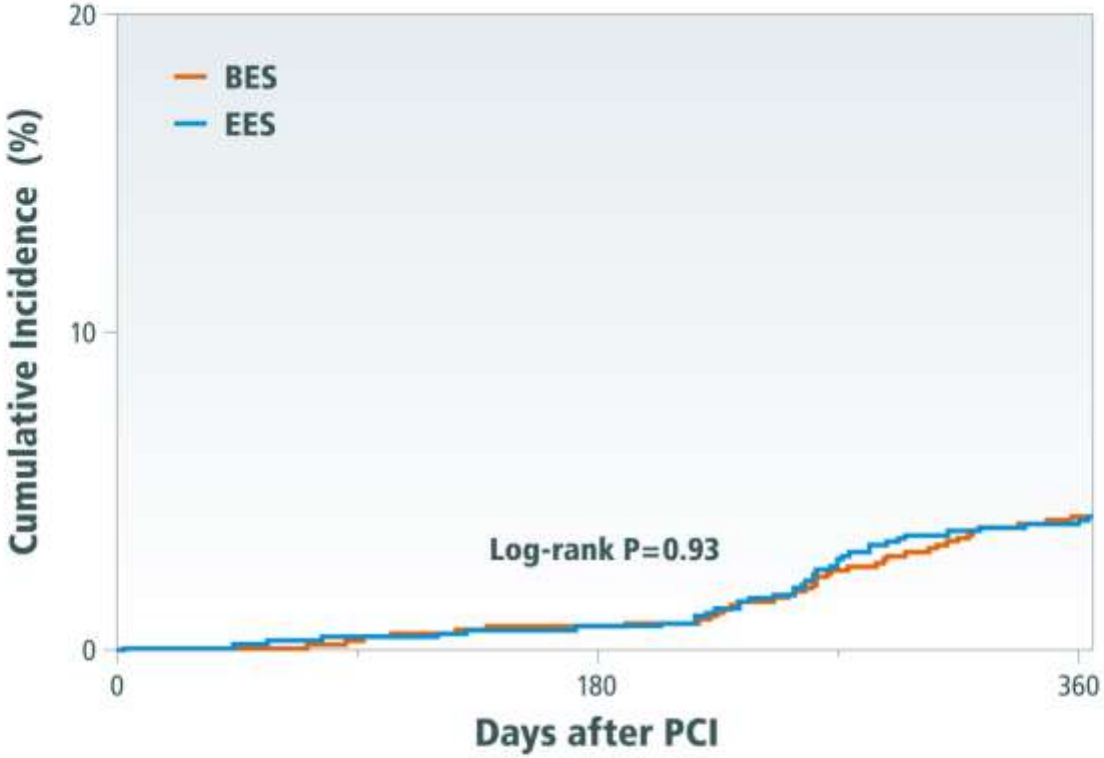


Acute device success: Successful implantation of all the study stents attempted
Patient success: Successful procedure without any major in-hospital complications

Procedural duration (min) : 72.6 ± 43.5 vs. 71.3 ± 43.4 (BES vs. EES, P=0.38)

Clinical Outcomes at 1-year

Target-Lesion Revascularization



Interval	0 day	30 days	180 days	240 days	365 days
BES group					
No. of patients with event		2	13	24	67
No. of patients at risk	1617	1607	1579	1556	1491
Cumulative Incidence		0.1%	0.8%	1.5%	4.2%
EES group					
No. of patients with event		2	12	26	66
No. of patients at risk	1618	1612	1578	1556	1497
Cumulative Incidence		0.1%	0.8%	1.6%	4.2%

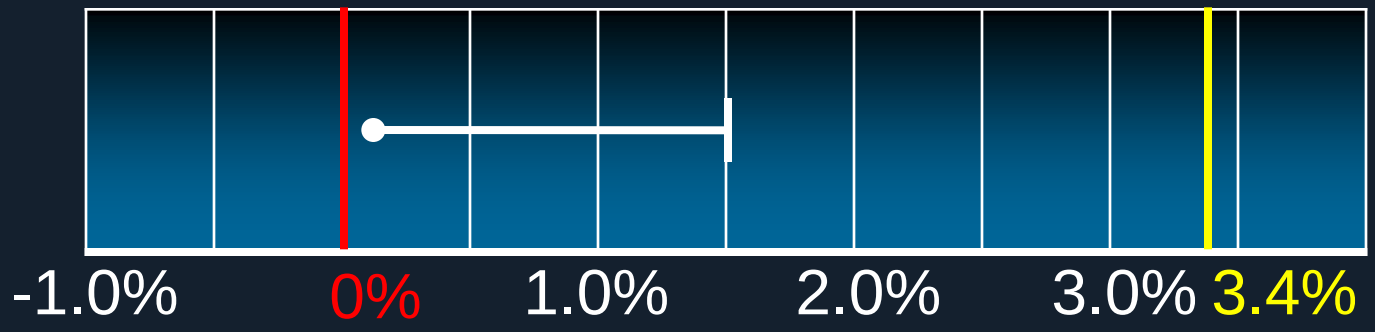
Non-inferiority Assessment for the Primary Efficacy Endpoint

Target-Lesion Revascularization (TLR)

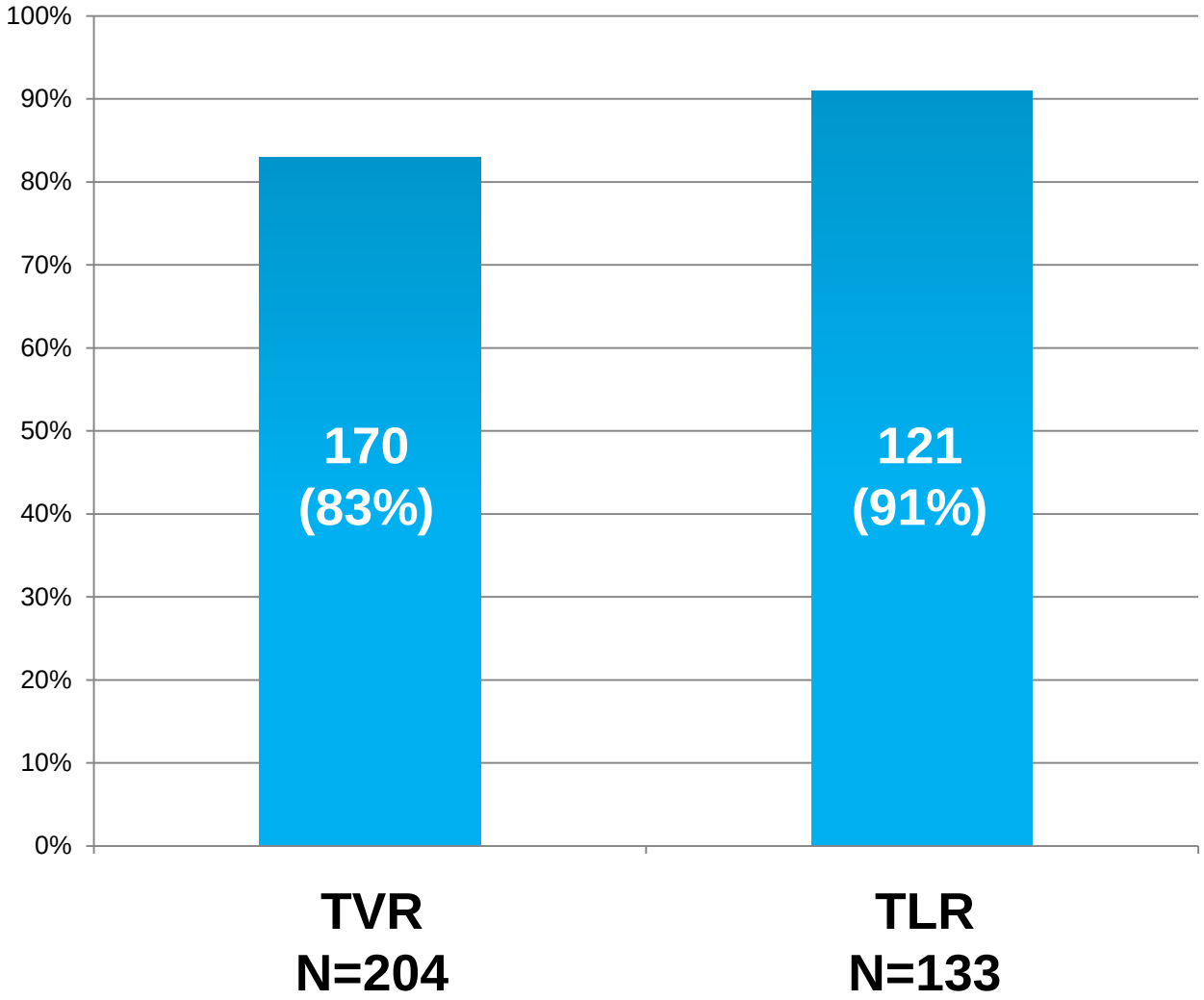
BES 4.2% vs. EES 4.2%

$P_{non\text{-}inferiority} < 0.0001$

Difference:	0.07%
Upper one-sided 95% CI:	1.5%

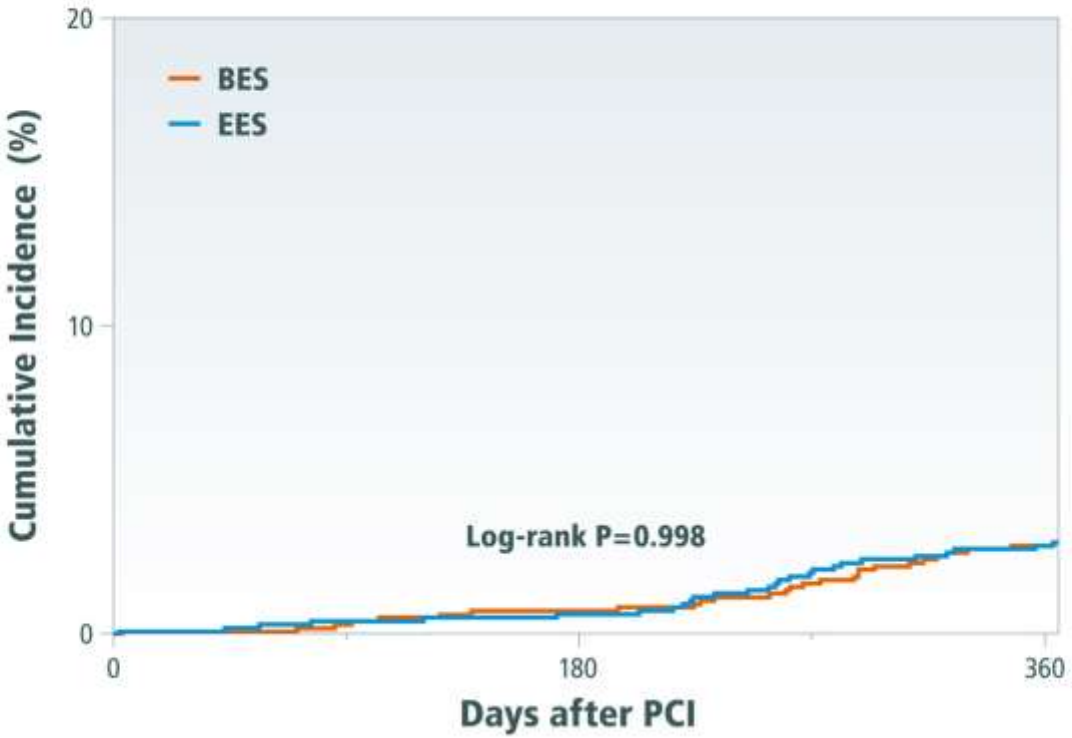


Proportion of Events Adjudicated by the Angiographic Core Laboratory



All the angiograms of patients with TVR were to be analyzed by the angiographic core laboratory in an attempt to discriminate TLR from non-TLR TVR and to identify clinically-driven TLR.

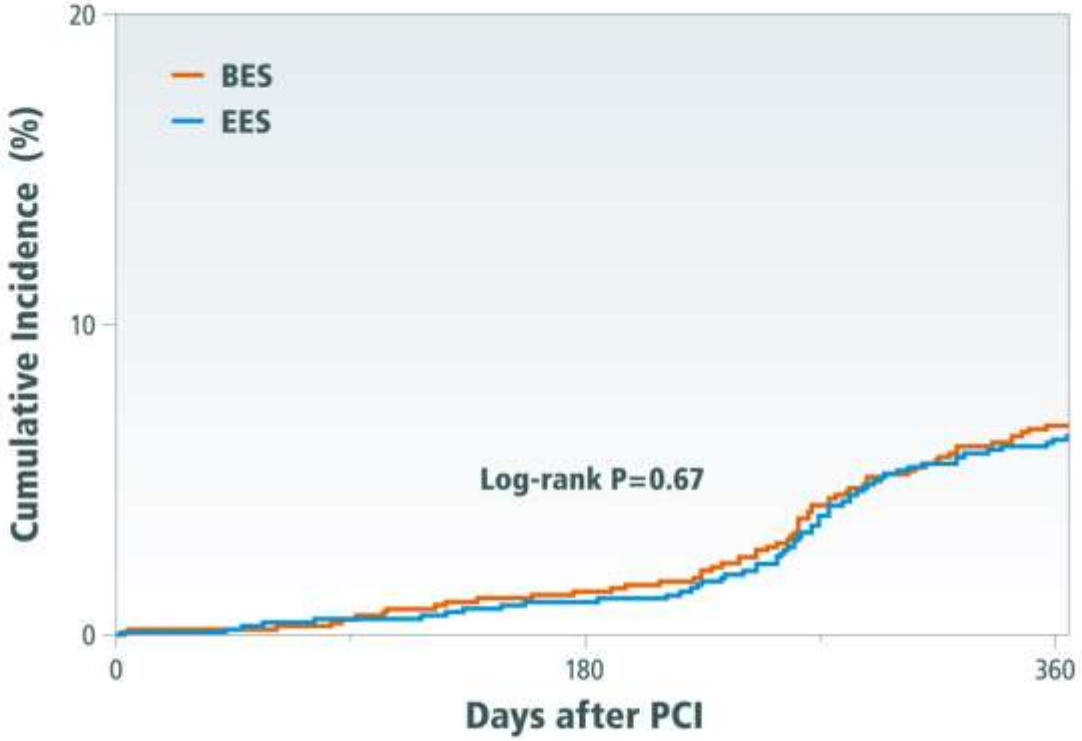
Clinically-driven TLR



Interval	0 day	30 days	180 days	240 days	365 days
BES group					
No. of patients with event		2	13	19	47
No. of patients at risk	1617	1607	1579	1556	1491
Cumulative Incidence		0.1%	0.8%	1.2%	3.0%
EES group					
No. of patients with event		2	10	22	47
No. of patients at risk	1618	1612	1578	1556	1497
Cumulative Incidence		0.1%	0.6%	1.4%	3.0%

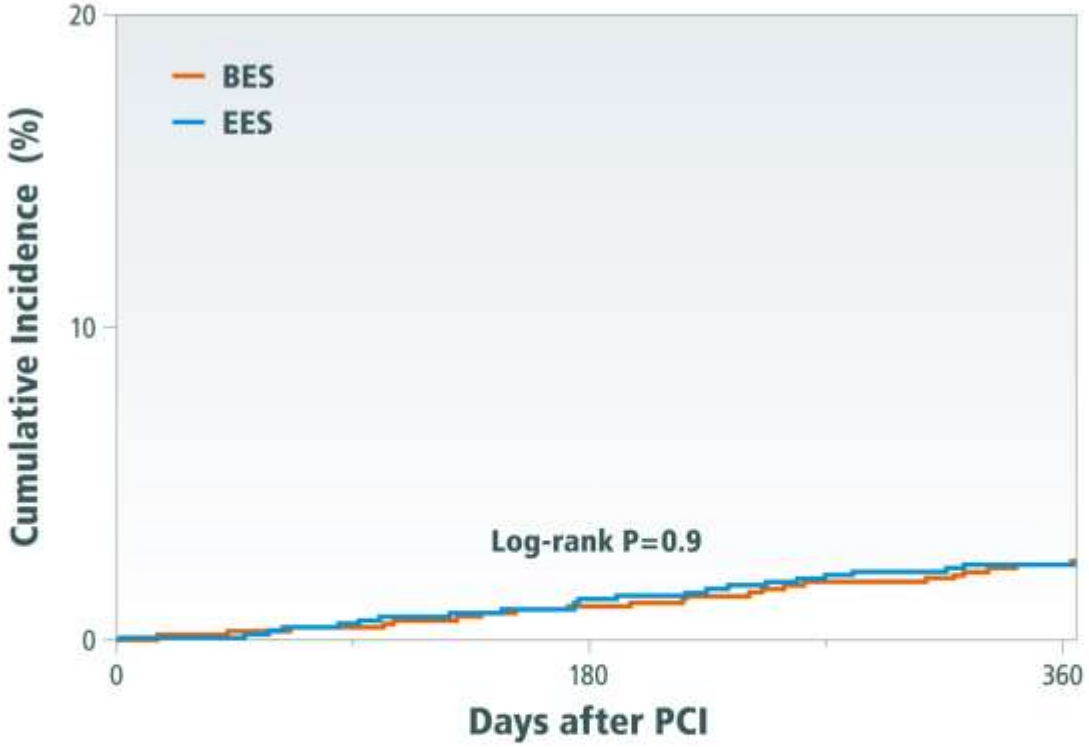
Follow-up angiography was performed in 2103 patients (65%) within 1-year.

Target-Vessel Revascularization



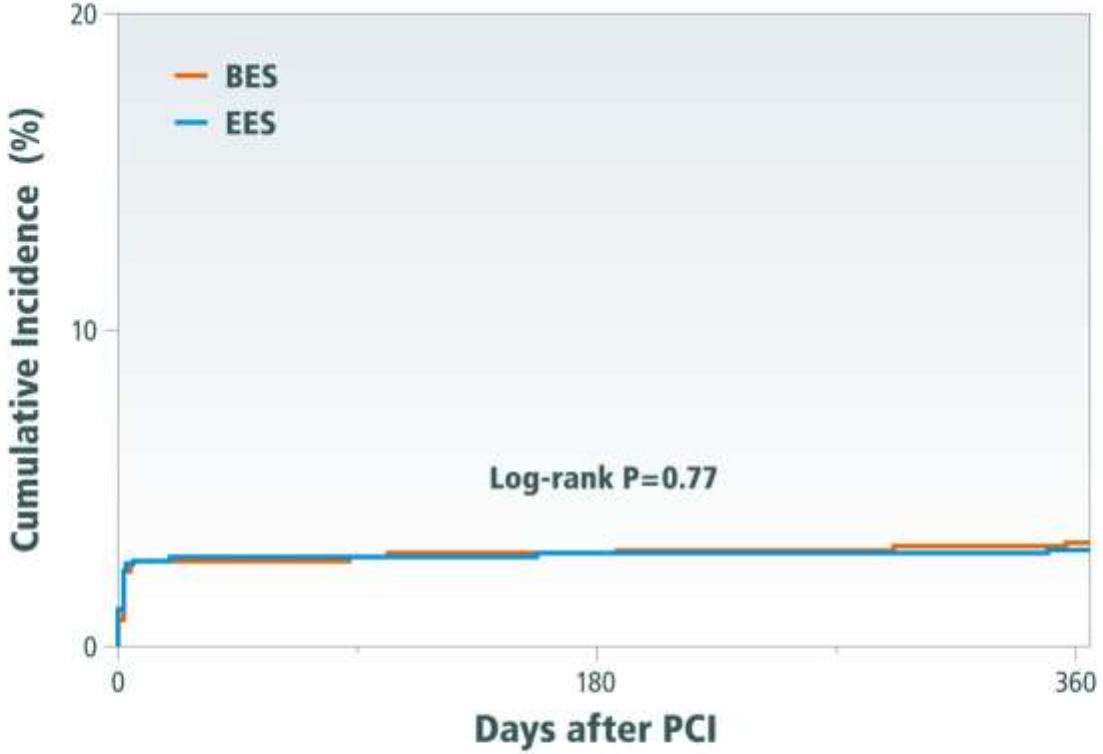
Interval	0 day	30 days	180 days	240 days	365 days
BES group					
No. of patients with event		4	23	40	105
No. of patients at risk	1617	1603	1553	1515	1368
Cumulative Incidence		0.3%	1.4%	2.5%	6.8%
EES group					
No. of patients with event		2	18	33	99
No. of patients at risk	1618	1608	1553	1518	1368
Cumulative Incidence		0.1%	1.1%	2.1%	6.5%

All-cause Death



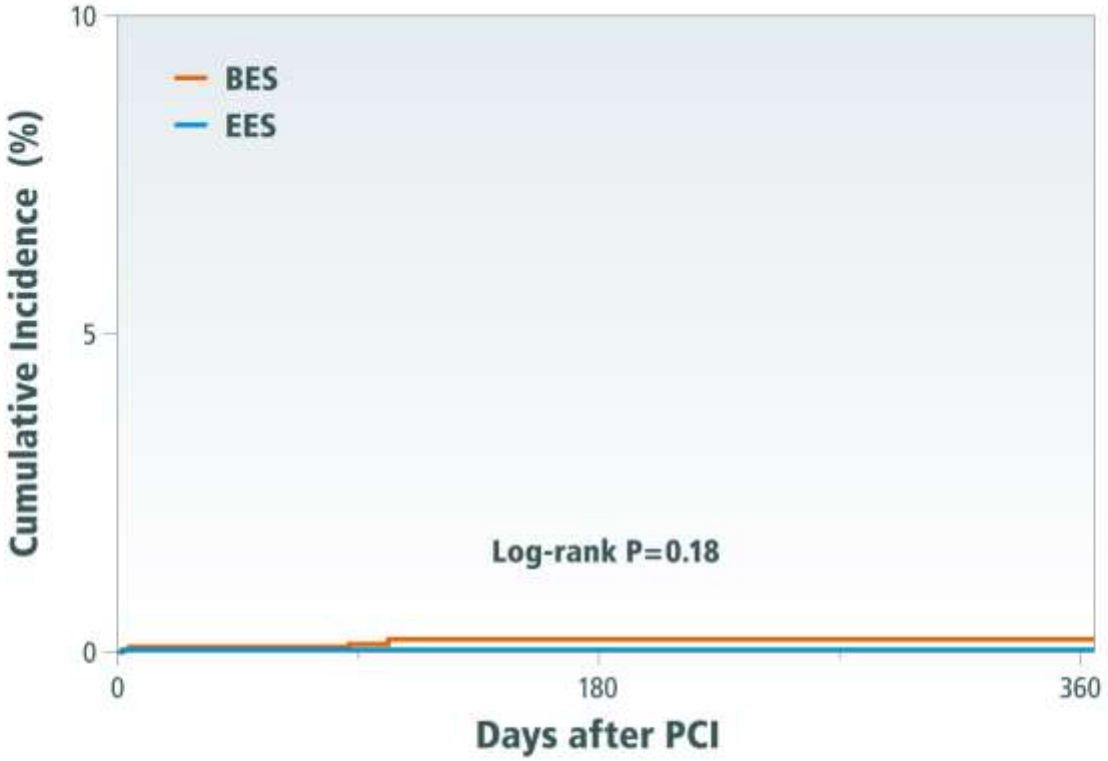
Interval	0 day	30 days	180 days	240 days	365 days
BES group					
No. of patients with event		3	17	25	41
No. of patients at risk	1617	1608	1589	1577	1557
Cumulative Incidence		0.2%	1.1%	1.6%	2.6%
EES group					
No. of patients with event		2	21	29	40
No. of patients at risk	1618	1614	1590	1581	1563
Cumulative Incidence		0.1%	1.3%	1.8%	2.5%

Myocardial Infarction



Interval	0 day	30 days	180 days	240 days	365 days
BES group					
No. of patients with event		45	49	51	53
No. of patients at risk	1617	1564	1544	1531	1508
Cumulative Incidence		2.8%	3.0%	3.2%	3.3%
EES group					
No. of patients with event		46	49	49	50
No. of patients at risk	1618	1570	1543	1535	1515
Cumulative Incidence		2.8%	3.0%	3.0%	3.1%

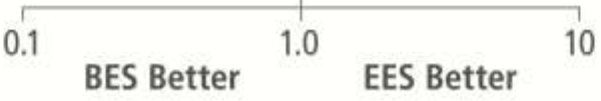
Definite Stent Thrombosis



Interval	0 day	30 days	180 days	240 days	365 days
BES group					
No. of patients with event		2	4	4	4
No. of patients at risk	1617	1607	1588	1576	1553
Cumulative Incidence		0.12%	0.25%	0.25%	0.25%
EES group					
No. of patients with event		1	1	1	1
No. of patients at risk	1618	1614	1589	1580	1561
Cumulative Incidence		0.06%	0.06%	0.06%	0.06%

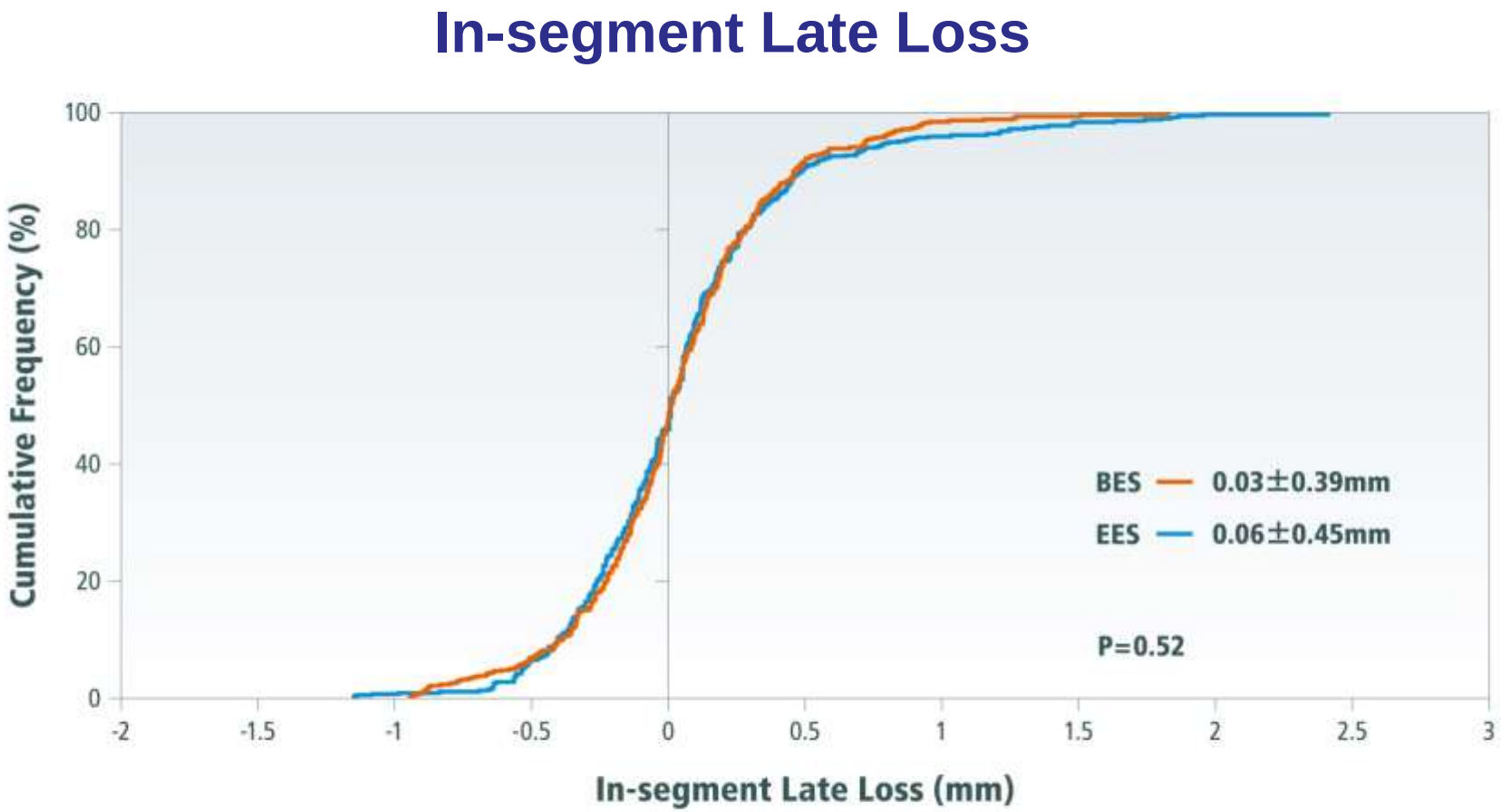
Pre-specified Subgroup Analysis for TLR
BES versus EES

Subgroups	N (BES/EES)	H.R. 95% CI.	P	Interaction P
Diabetic Status				
Diabetes	(745/740)	0.89 (0.57-1.38)	0.59	0.36
Non-diabetes	(872/878)	1.23 (0.72-2.12)	0.46	
Insulin use				
DM insulin	(166/172)	0.61 (0.27-1.33)	0.22	0.26
DM non-insulin	(579/568)	1.05 (0.62-1.81)	0.85	
Elderly				
Age >= 75 years	(496/548)	1.11 (0.57-2.14)	0.76	0.74
Age < 75 years	(1121/1070)	0.97 (0.65-1.45)	0.89	
Hemodialysis				
Yes	(105/84)	0.6 (0.28-1.28)	0.19	0.16
No	(1512/1534)	1.1 (0.75-1.61)	0.64	
Multivessel PCI				
Yes	(207/184)	1.08 (0.5-2.39)	0.84	0.84
No	(1410/1434)	0.99 (0.68-1.45)	0.96	



Angiographic Outcomes at 8-12 months

Cumulative Distribution Function Curves of Late Loss



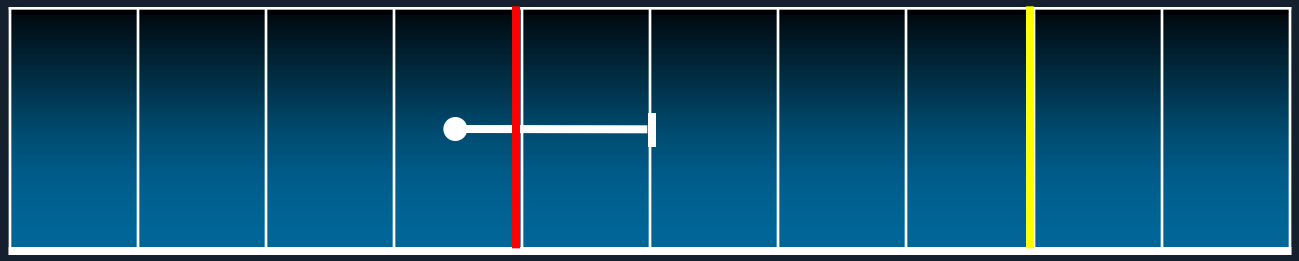
Non-inferiority Assessment for the Primary Angiographic Endpoint

In-segment Late Loss

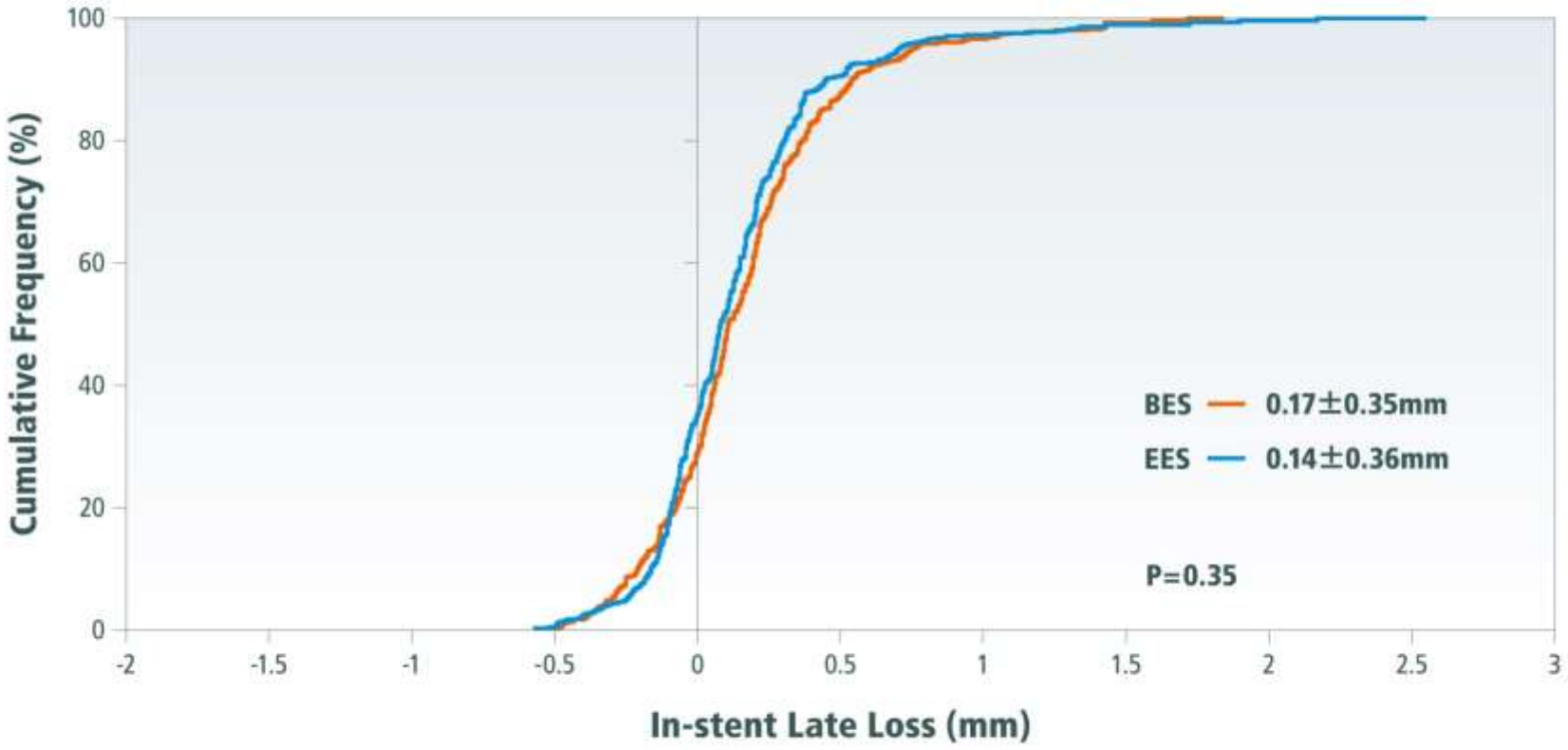
BES 0.03 mm vs. EES 0.06 mm

$P_{non\text{-}inferiority} < 0.0001$

Difference:	-0.03 mm
Upper one-sided 95% CI:	0.05 mm



Cumulative Distribution Function Curves of Late Loss



Follow-up QCA Data in Angiographic Sub-study

Variables — no. (%)	BES (295 lesions)	EES (293 lesions)	p-value
Follow-up at 8-12 months			
Binary restenosis — n (%)			
In segment	21 (7.1%)	22 (7.5%)	0.86
Location of restenosis— n (%)			0.17
Stent body	10 (48%)	6 (27%)	
Both edges	5 (24%)	5 (23%)	
Proximal edge	2 (9.5%)	4 (18%)	
Distal edge	4 (19%)	7 (32%)	
Restenosis pattern — n (%)			0.23
Focal	12 (57%)	17 (77%)	
Diffuse	6 (29%)	3 (14%)	
Total occlusion	3 (14%)	1 (4.6%)	
Proliferative	0	1 (4.6%)	
Stent fracture — n (%)	9 (3.1%)	0	0.004
Peri-stent contrast staining — n (%)	8 (2.7%)	4 (1.4%)	0.24

Limitations

- *Despite the all-comers trial design, the actual study population mostly included patients with stable coronary artery disease.*

- *Actual 1-year rate of TLR was lower than expected due to less complex coronary anatomy, leading to a relatively large non-inferiority margin.*

- *High prevalence of follow-up angiography based either on the current study protocol or on the local site-protocols certainly inflated the rate of TLR.*

Conclusions

- *In this large scale randomized controlled trial, BES was demonstrated to be non-inferior to EES with respect to 1 year TLR rate and 8-12 months angiographic in-segment late loss.*

- *One-year clinical outcome after both BES- and EES-use was excellent with low rate of TLR and very low rate of stent thrombosis.*

- *Long-term follow-up of the biodegradable polymer BES compared with the durable polymer EES will provide crucial implications for the future development of metallic drug-eluting stents.*

Participating Centers

Caress Sappro Tokeidai Memorial Hospital

Oji General Hospital

Cardio-vascular Center Hokkaido Ohno Hospital

Caress Sappro Hokko Memorial Hospital

Hokkaido Social Insurance Hospital

Hokkaido Junkanki Hospital

Teine Keijinkai Hospital

Aomori Prefectural Central Hospital

Iwate Prefectural Central Hospital

Iwate Medical University Hospital

Tohoku Kousei Nenkin Hospital

Sendai Open Hospital

Iwaki Kyoritsu General Hospital

Fukushima Medical University Hospital

Saiseikai Kurihashi Hospital

Saitama Cardiovascular and Respiratory Center

Dokkyo Medical University Koshigaya Hospital

New Tokyo Hospital

Juntendo University Hospital

Sakakibara Memorial Hospital

NTT Medical Center Tokyo

The Cardiovascular Institute Hospital

Mitsui Memorial Hospital

Tokyo Medical University Hospital

Teikyo University Hospital

Tokyo Women's Medical University Hospital

Juntendo University Nerima Hospital

Itabashi Chuo General Hospital

Saiseikai Yokohama-city Eastern Hospital

Kanto Rosai Hospital

Yokohama Rosai Hospital

Tokai University Hospital

Yokohama City University Medical Center

Kitasato University Hospital

Kanazawa Cardiovascular Hospital

University of Fukui Hospital

Fukui Cardiovascular Center

Ogaki Municipal Hospital

Juntendo University Shizuoka Hospital

Shizuoka General Hospital

Okamura Memorial Hospital

Seirei Hamamatsu General Hospital

Hamamatsu Medical Center

Aichi Medical University Hospital

Tosei General Hospital

Toyota Memorial Hospital

Fujita Health University Hospital

Japanese Red Cross Nagoya Daini Hospital

Chubu Rosai Hospital

Nagai Hospital

Mie University Hospital

Mie Heart Center

Yokkaichi Social Insurance Hospital

Koto Memorial Hospital

Shiga University of Medical Science Hospital

Kyoto University Hospital

Mitsubishi Kyoto Hospital

National Hospital Organization Kyoto Medical Center

Kyoto Second Red Cross Hospital

Osaka University Hospital

Sakurabashi Waranabe Hospital

Osaka City General Hospital

Osaka Saiseikai Noe Hospital

Osaka City University Hospital

Osaka Red Cross Hospital

National Cerebral and Cardiovascular Center

Sumitomo Hospital

Higashisumiyoshi Morimoto Hospital

Bell Land General Hospital

Kobe City Medical Center General Hospital

Kobe University Hospital

Kansai Rosai Hospital

Hyogo Prefectural Amagasaki Hospital

Hyogo College of Medicine Hospital

Tenri Hospital

Japanese Red Cross Society Wakayama Medical Center

Wakayama Medical University Hospital

Tottori University Hospital

Matsue Red Cross Hospital

The Sakakibara Heart Institute of Okayama

Kurashiki Central Hospital

Kawasaki Medical School Hospital

Hiroshima City Hospital

Fukuyama Cardiovascular Hospital

Tsuchiya General Hospital

Iwakuni Clinical Center

Chikamori Hospital

Unversity Of Occupational and Environmental Health Japan

Fukuoka Wajiro Hospital

Kurume University Hospital

Kokura Memorial Hospital

Kouseikai Hospital

Saiseikai Kumamoto Hospital

National Hospital Organization Kumamoto Medical Center

Kumamoto Rousai Hospital

Miyazaki Medical Association Hospital

Tenyokai Central Hospital

National Hospital Organization Kagoshima Medical Center