Two-Year Outcome of a Randomized 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.

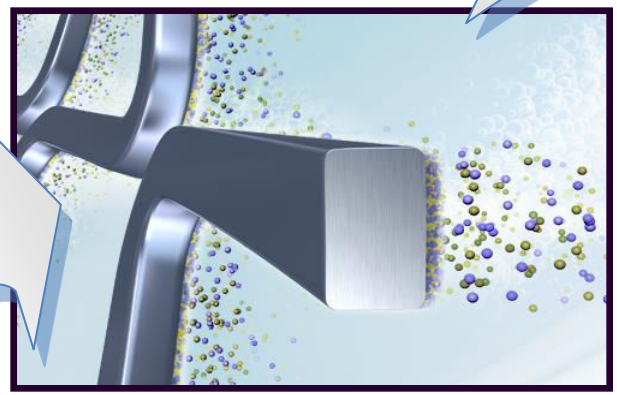
Study Sponsor of NEXT Trial

Terumo Japan

Nobori® Biodegradable Polymer Biolimus-eluting Stent Components

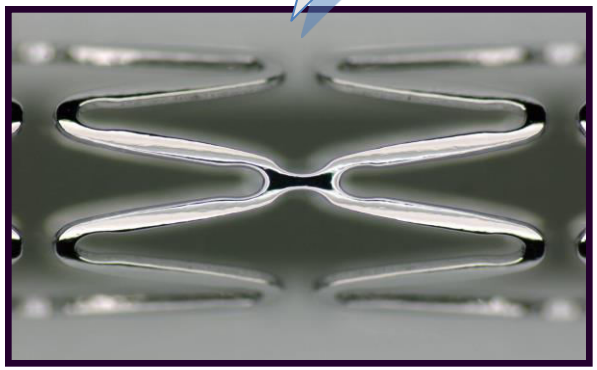
PLA Biodegradable Polymer

- Abluminal coating
- Controlled biodegradability
- Precise drug release kinetics
- Simultaneous release of drug and polymer degradation



Biolimus A9™

- Anti-proliferative, anti-inflammatory properties
- Highly lipophilic with optimal local tissue uptake

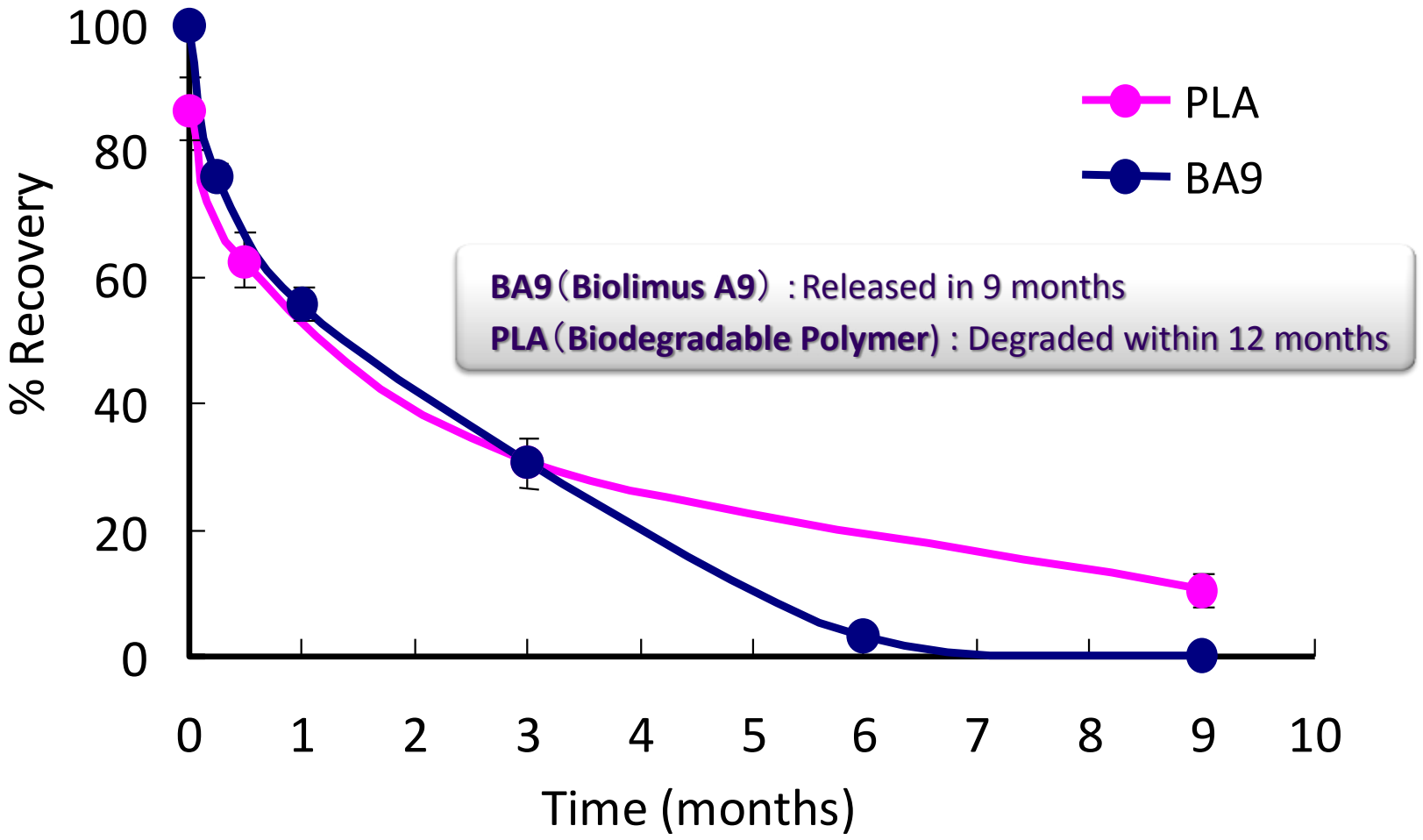


BMS Platform

- Stainless steel alloy stent
- Wide cell opening with optimal side branch access
- Innovative delivery system with hydrophilic M-coating

Nobori® Biolimus-eluting Stent

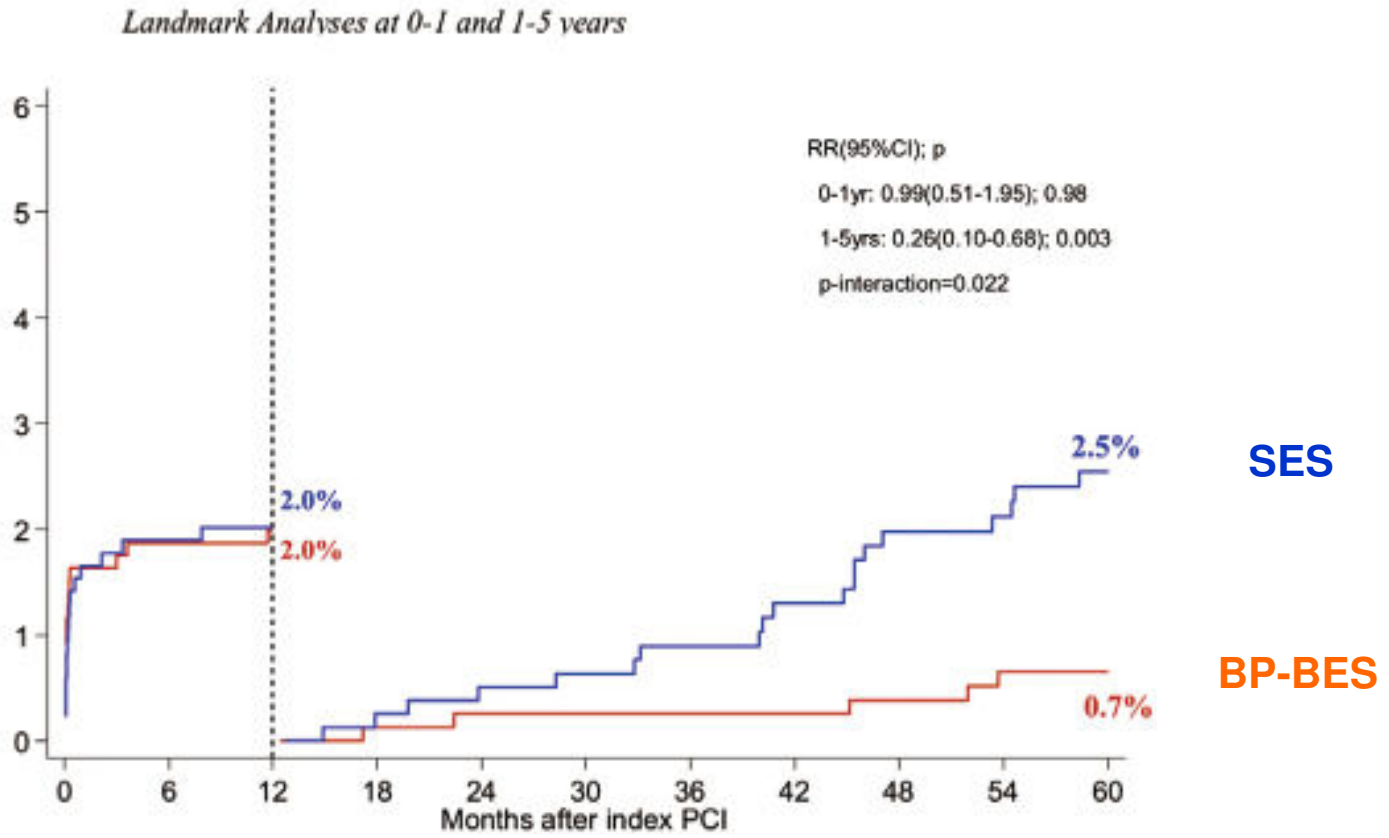
Biolimus A9 and PLA recovery over time on stents implanted in pig arteries



Background

In LEADERS trial, biodegradable polymer biolimus-eluting stent (BP-BES) significantly reduced the risk for very late stent thrombosis compared with durable polymer sirolimus-eluting stent (SES).

Very Late Stent Thrombosis: ***BP-BES vs SES RR 0.26 (0.1-0.68)***



Serruys PW, et al. JACC Intv. 2013;6: 777-789.

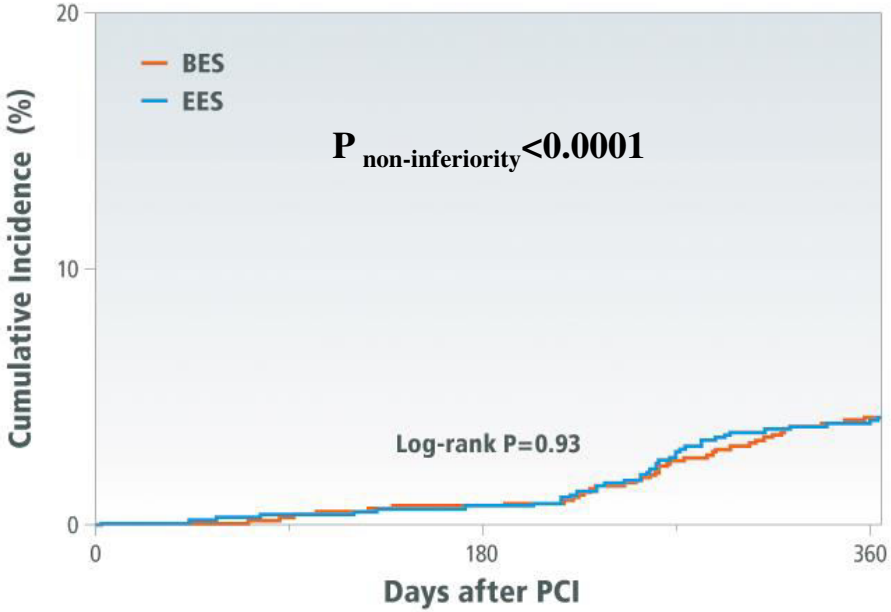
Background

However, SES is no longer used in the current clinical practice, and second-generation biocompatible durable polymer drug-eluting stent (DES) would be the more clinically relevant comparator stent for the biodegradable polymer DES (BP-DES).

NEXT and COMPARE II trial demonstrated non-inferiority of BP-BES relative to biocompatible durable polymer everolimus-eluting stent (DP-EES) in terms of the safety and efficacy endpoint at 1-year.

NEXT

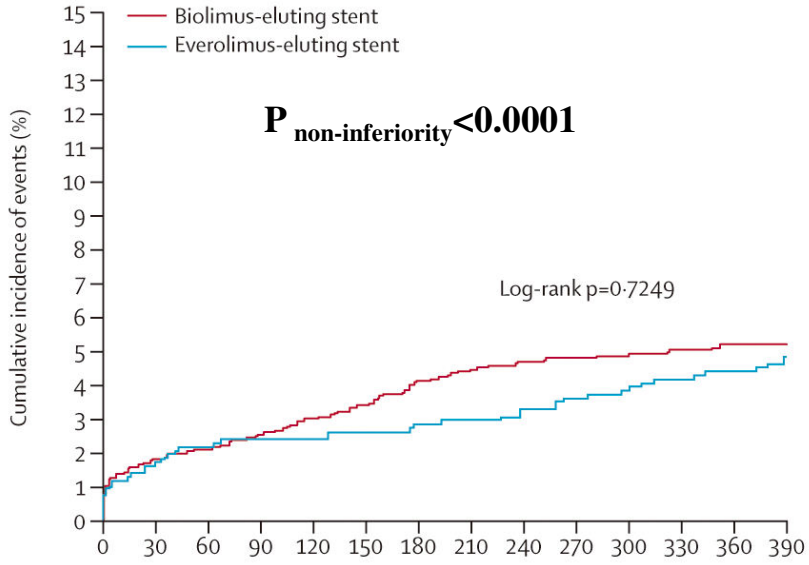
Target-Lesion Revascularization



Natsuaki M, et al. JACC. 2013. 62 (3): 181-190.

COMPARE II

Cardiac death, MI , TVR



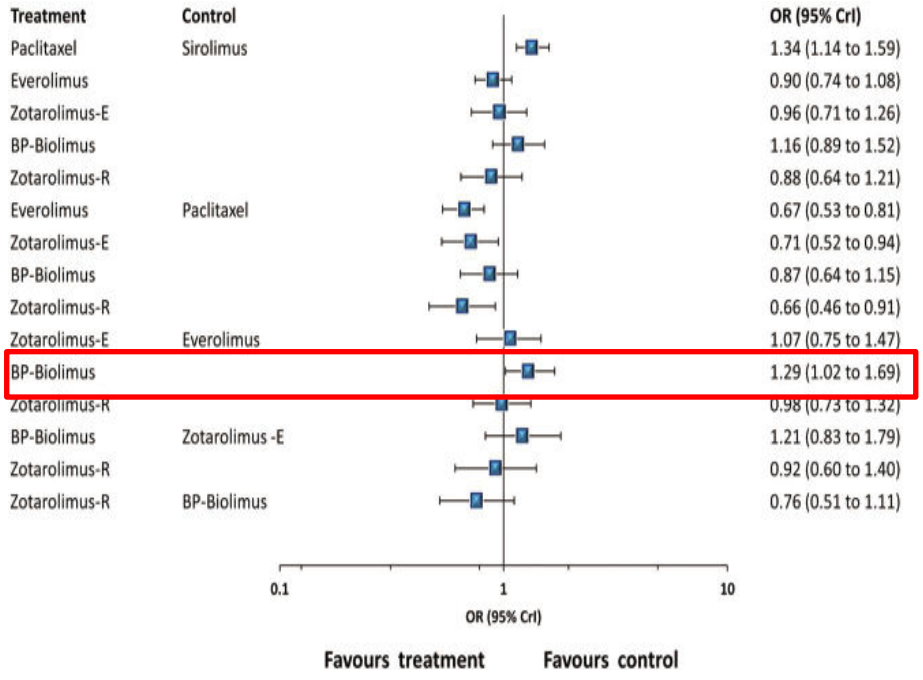
Smits PC, et al. Lancet. 2013. 381 (9867): 651-660.

Background

On the other hand, recent network meta-analyses have raised concerns on the safety of BP-BES compared with DP-EES.

Myocardial Infarction

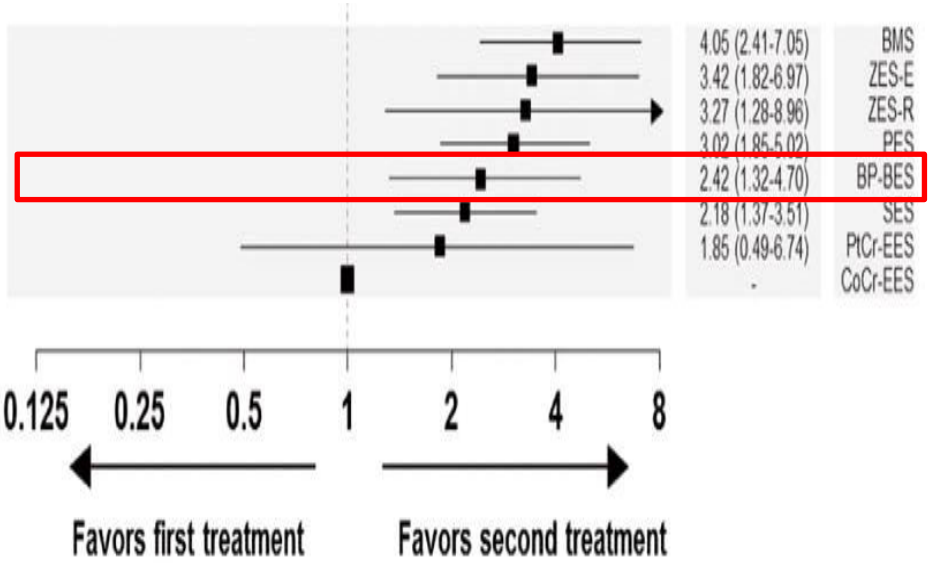
BP-BES vs. DP-EES OR 1.29 (1.02-1.69)



Navarese EP, et al. BMJ 2013; 347:f6530.

Definite Stent Thrombosis

BP-BES vs. DP-EES OR 2.42 (1.32-4.7)



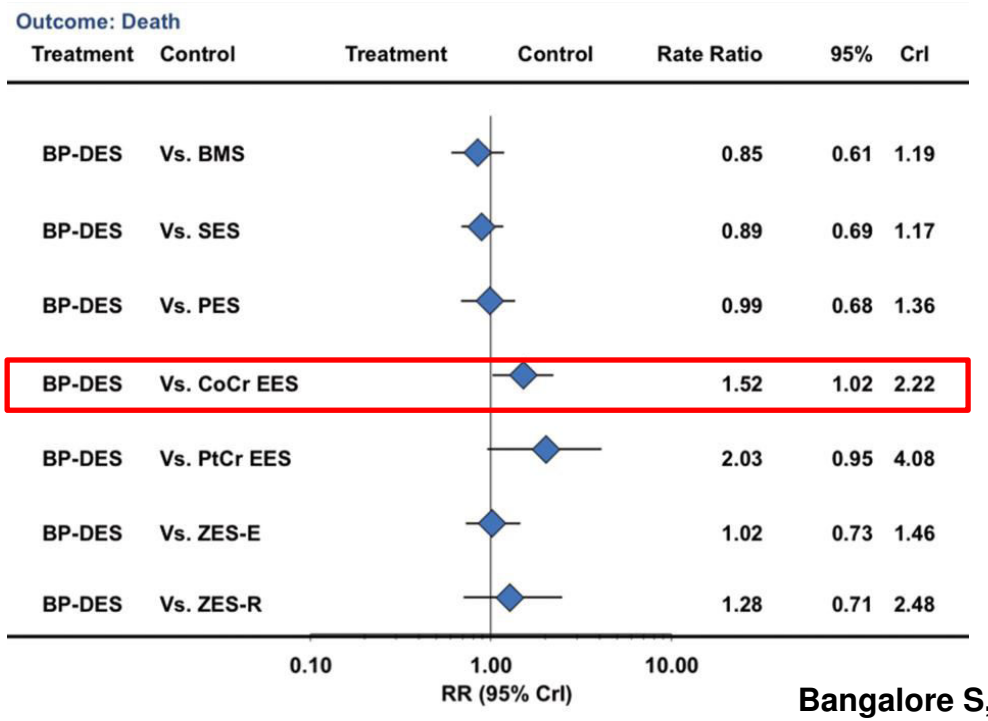
Kang SH, et al. Eur Heart J 2014; Jan 23.

Background

Network meta-analyses also showed that BP-DES was associated with increased mortality compared with DP-EES beyond 1-year after stent implantation. However, there is no head-to-head randomized trial of BP-DES compared with DP-EES reporting the clinical outcomes beyond 1-year after stent implantation when the advantage of BP-DES could emerge after complete polymer degradation.

Therefore, we report the interim 2-year outcome evaluating non-inferiority of BP-BES relative to DP-EES.

All-cause Death beyond 1-year: ***BP-DES vs DP-EES RR 1.52 (1.02-2.22)***

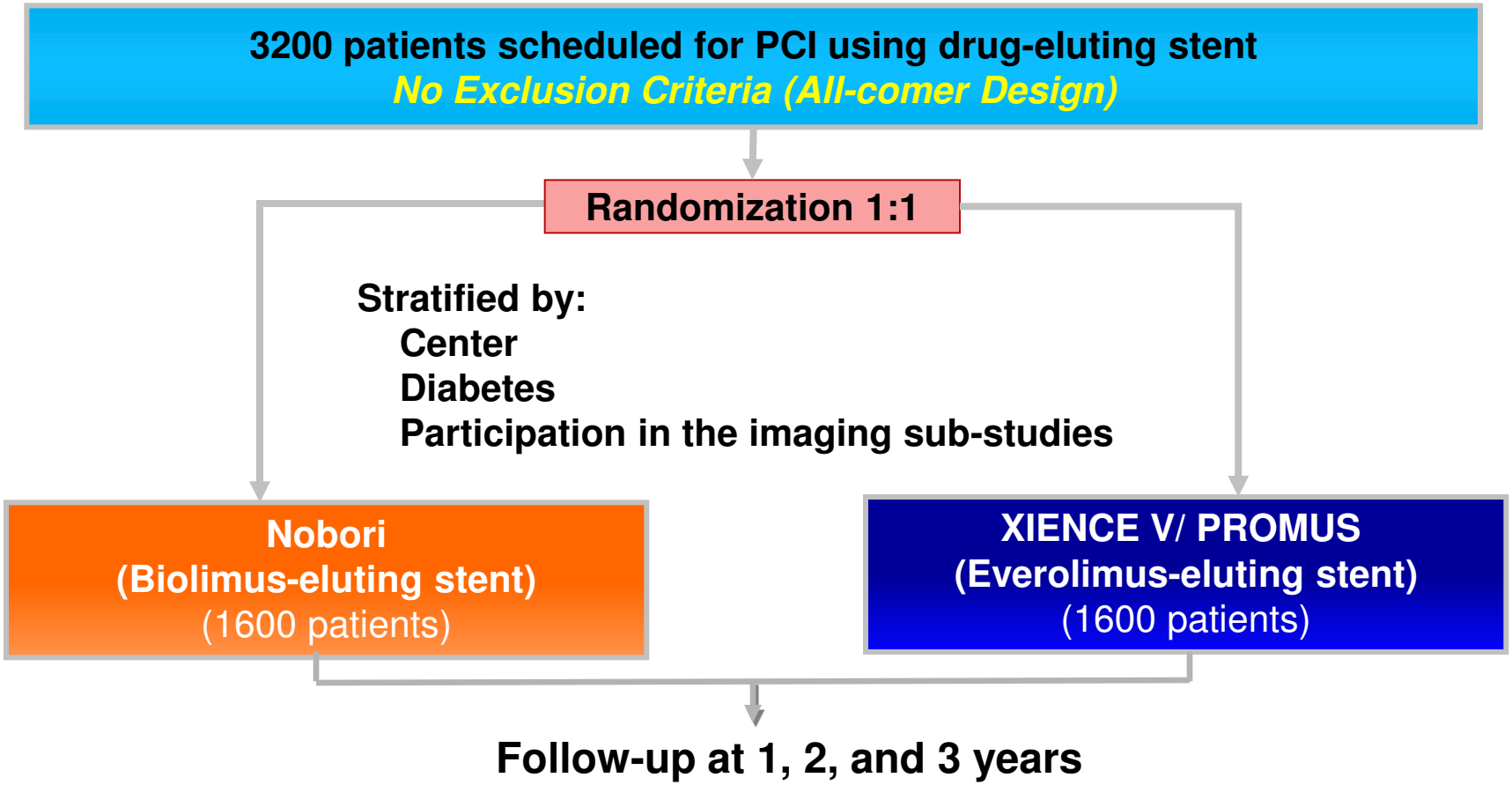


Bangalore S, et al. BMJ 2013; 347:f6625.

NEXT Trial

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

Multicenter, randomized, non-inferiority trial comparing BP-BES with DP-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.)

NEXT Trial

Primary Endpoints and Sample Size Calculation

- **Primary Endpoints:**

  Efficacy: Any Target-lesion Revascularization at 1 year

- **Estimated TLR rate at 1 year:**

  Everolimus-eluting stent 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.

NEXT Trial

Primary Endpoints and Sample Size Calculation

- **Primary Endpoint:**

  Safety: Death or Myocardial Infarction at 3-year

- **Estimated event rate at 3-year:**

  Everolimus-eluting stent group: 12.2%

  Non-inferiority margin of 4.3% and one-sided type I error of 0.025

  3000 patients would yield 91% power to detect non-inferiority.

NEXT Trial: 2-Year Interim Analysis

Main Outcome Measures and Power Calculation

- ***Safety: Death or Myocardial Infarction (MI) at 2-year***

  Statistical Power for Death or MI:

  Actual event rate at 2-year: 7.8%

  Non-inferiority margin of 2.9% (2/3 of 4.3% at 3-y) and one-sided type I error of 0.006

  3235 patients had 71% power to detect non-inferiority.

- ***Efficacy: Any Target-lesion Revascularization at 2-year***

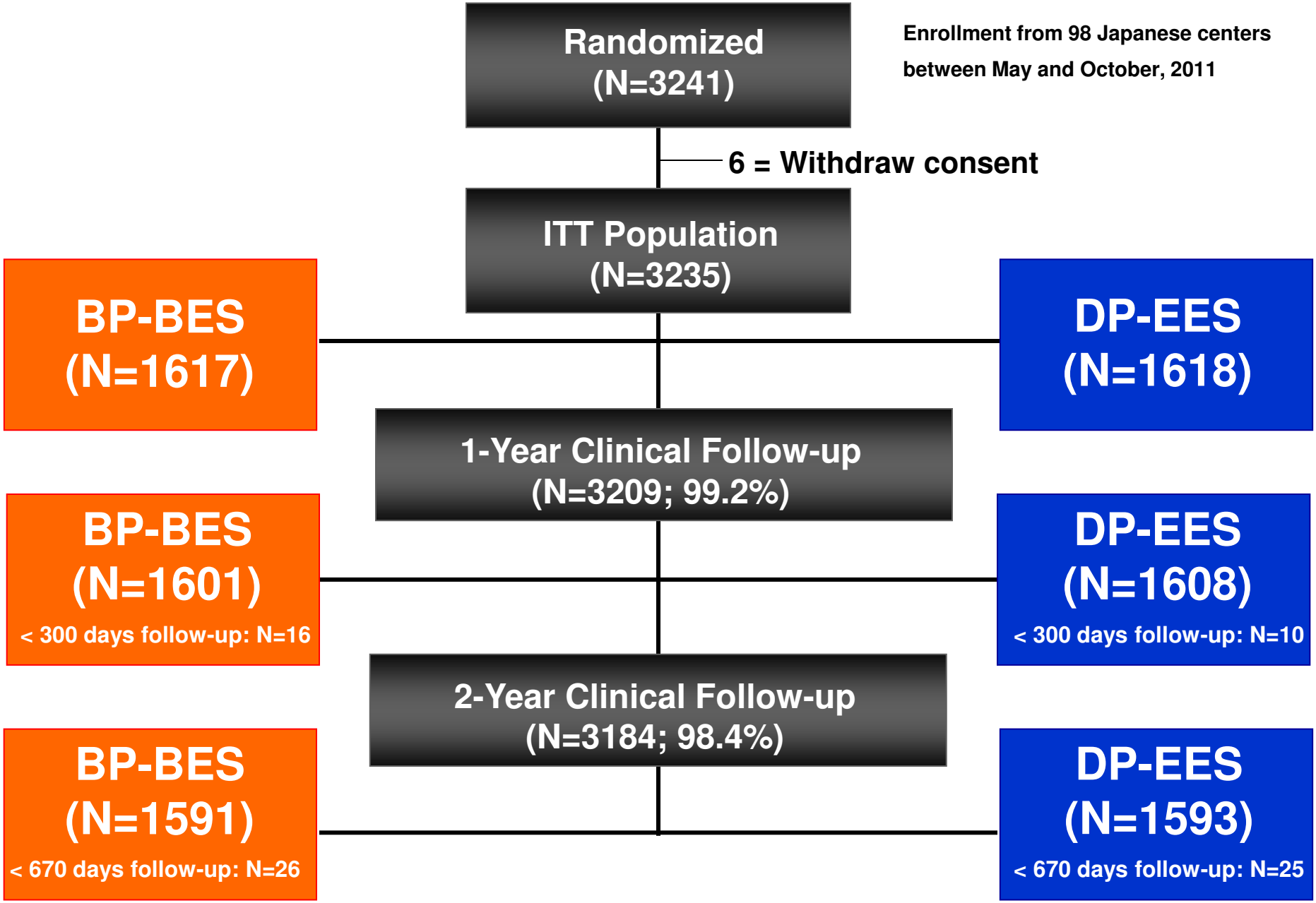
  Statistical Power for TLR:

  Actual event rate at 2-year: 6.1%

  Non-inferiority margin of 3.4% (the same at 1-y) and one-sided type I error of 0.025

  3235 patients had 98% power to detect non-inferiority.

Patient Flow Chart



Baseline Patient Characteristics

	BP-BES	*DP-EES*	*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

	BP-BES	*DP-EES*	*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

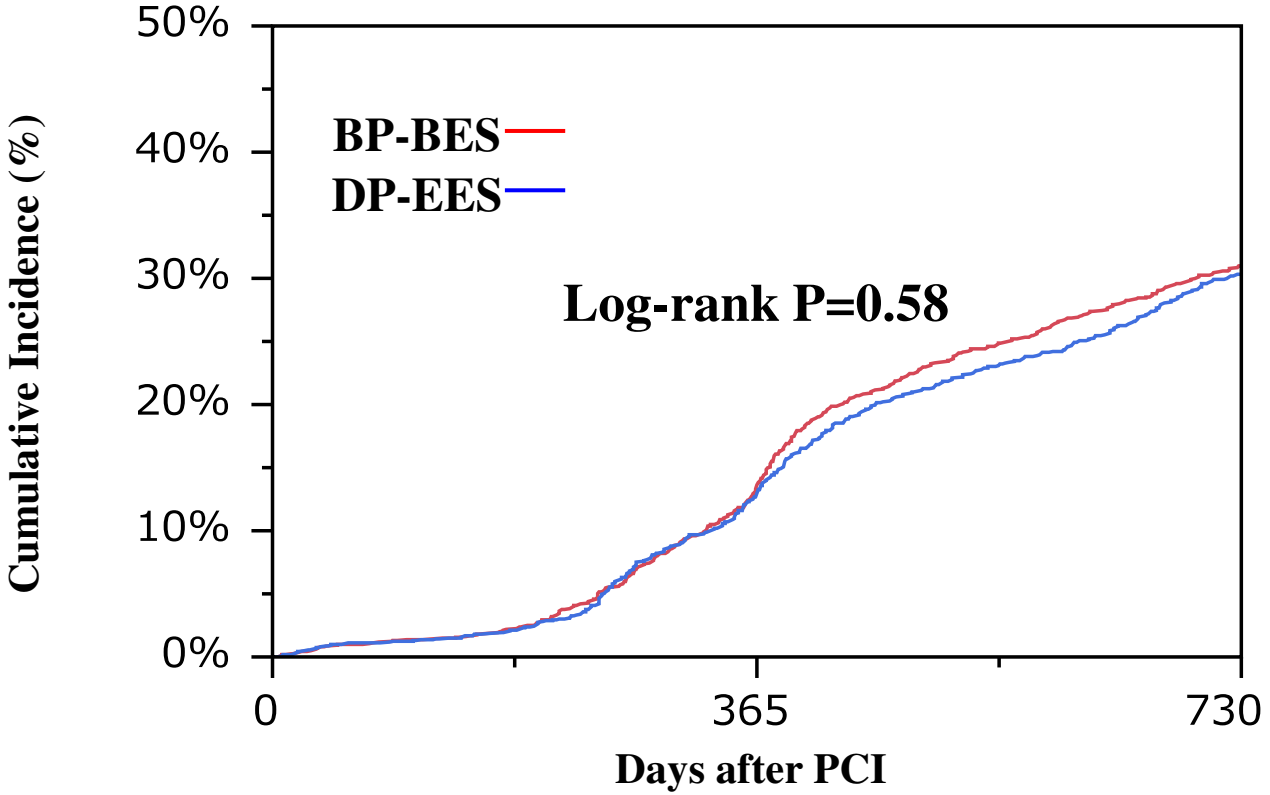
	BP-BES	*DP-EES*	*P*
No. of lesions	**2059**	**2010**	
Target vessel location			0.42
LMCA	2.4 %	2.3 %	
LAD	42 %	42 %	
LCx	22 %	24 %	
RCA	33 %	31 %	
Graft	0.7 %	0.9 %	
STEMI culprit lesions	3.0 %	2.9 %	0.88
Chronic total occlusion	8.6 %	7.9 %	0.39
In-stent restenosis	11 %	11 %	0.94
Bifurcation lesions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

Procedural Characteristics

	BP-BES	DP-EES	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

Clinical Outcomes at 2-year

Persistent Discontinuation of Dual Antiplatelet Therapy (DAPT)



BP-BES:31%

DP-EES:30%

Interval	0 day	30 days	365 days	730 days
BP-BES group				
N of patients with discontinuation		10	215	483
N of patients at risk	1617	1598	1347	1026
Cumulative Incidence		0.6%	13.6%	31.1%
DP-EES group				
N of patients with discontinuation		11	202	471
N of patients at risk	1618	1601	1365	1033
Cumulative Incidence		0.7%	12.8%	30.4%

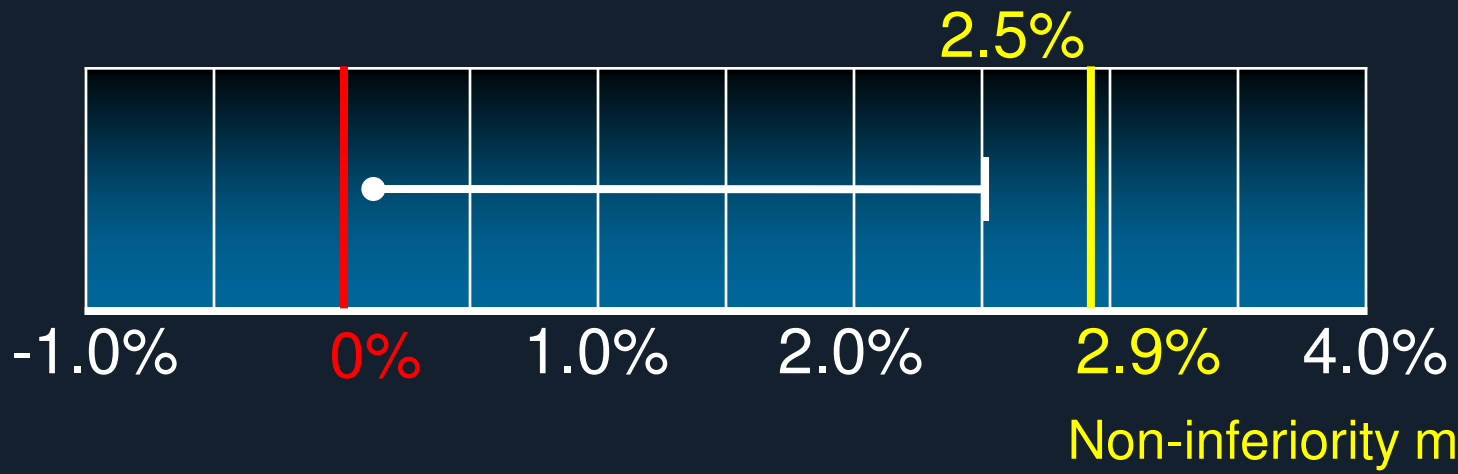
Non-inferiority Assessment for the Primary Safety Endpoint

Death or Myocardial Infarction

BP-BES 7.83% vs. DP-EES 7.69%

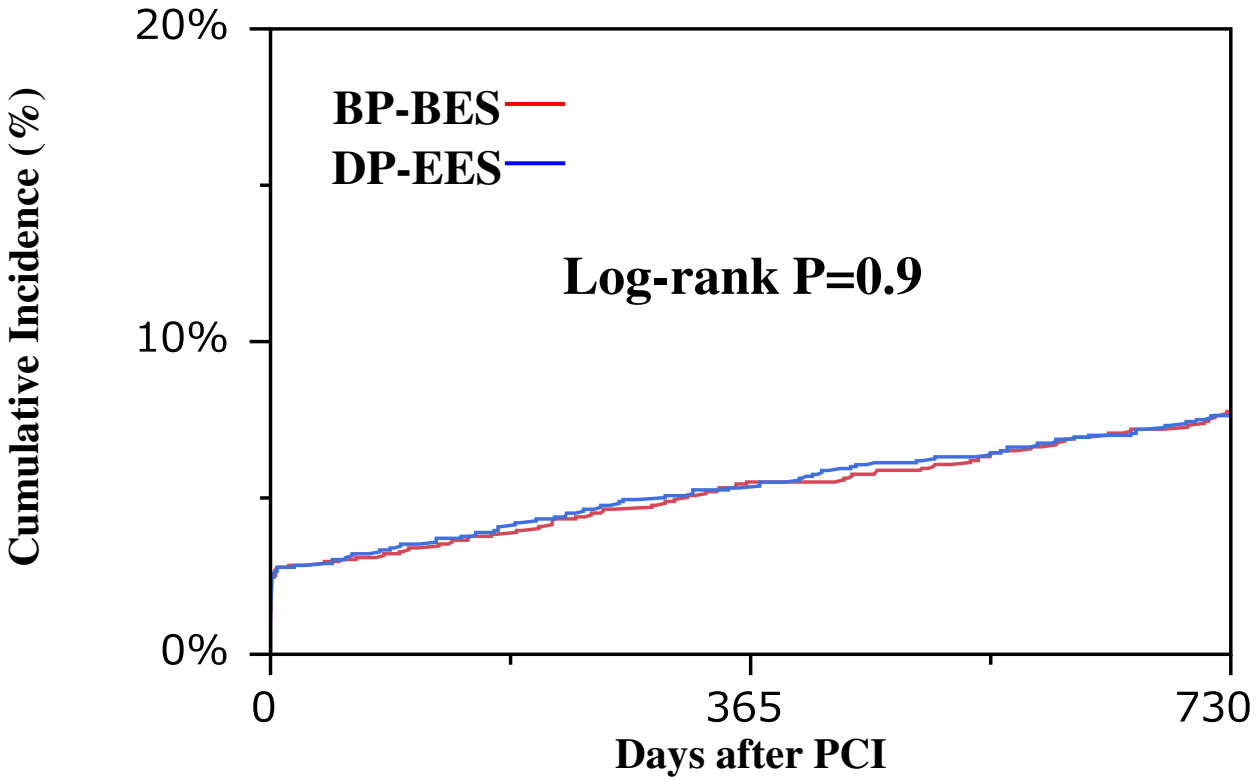
$P_{non\text{-}inferiority} = 0.003$

Difference:	0.14%
Upper one-sided 99.4% CI:	2.5%



Safety Endpoint

Death or Myocardial Infarction

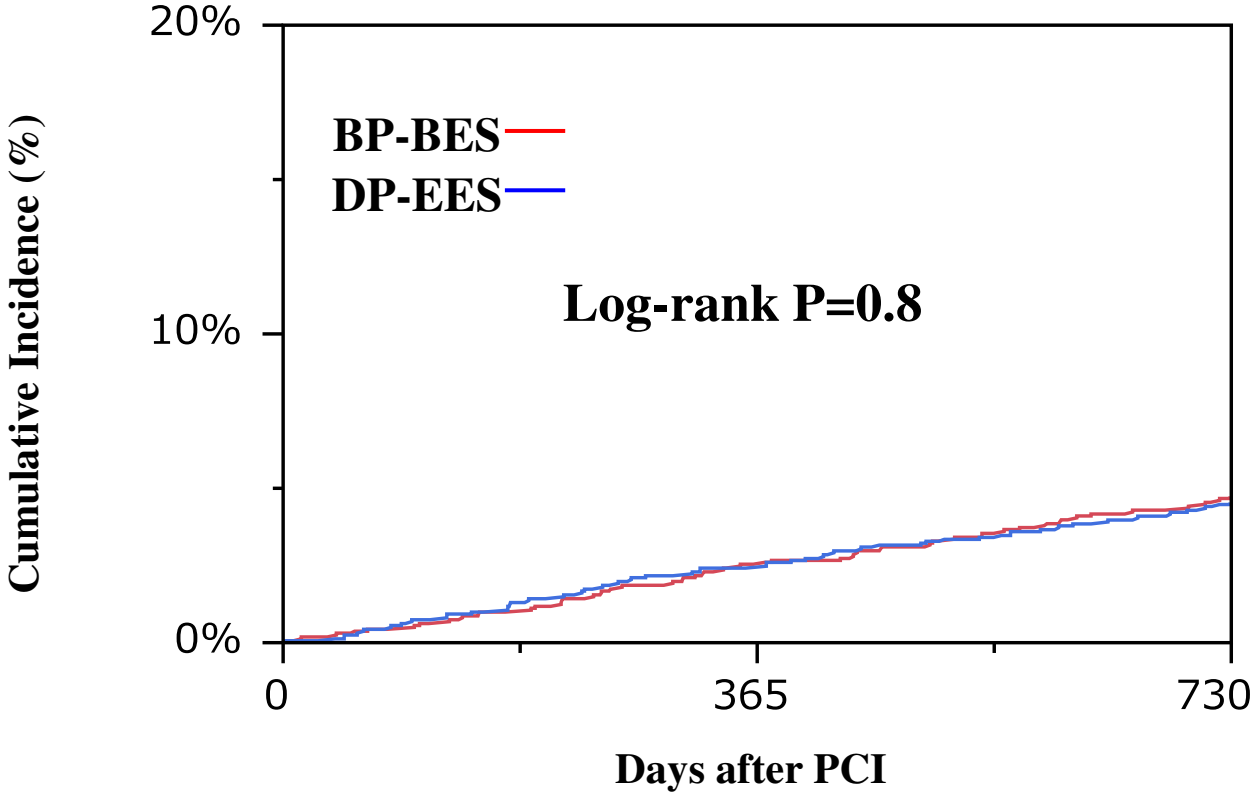


BP-BES:7.8%

DP-EES:7.7%

Interval	0 day	30 days	365 days	730 days
BP-BES group				
N of patients with at least 1 event		47	89	126
N of patients at risk	1617	1569	1524	1465
Cumulative Incidence		2.9%	5.5%	7.8%
DP-EES group				
N of patients with at least 1 event		47	87	124
N of patients at risk	1618	1571	1527	1466
Cumulative Incidence		2.9%	5.4%	7.7%

All-cause Death

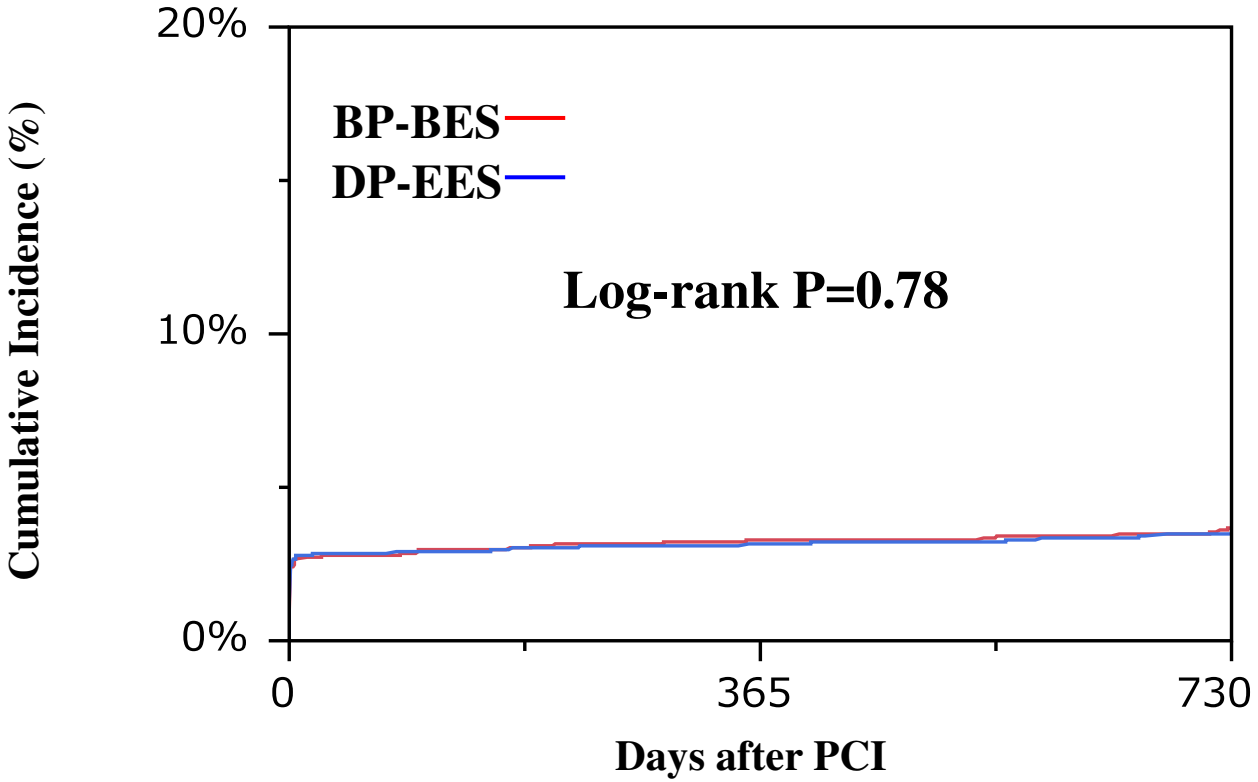


BP-BES:4.7%

DP-EES:4.5%

Interval	0 day	30 days	365 days	730 days
BP-BES group				
N of patients with at least 1 event		3	42	76
N of patients at risk	1617	1613	1570	1512
Cumulative Incidence		0.2%	2.6%	4.7%
DP-EES group				
N of patients with at least 1 event		2	40	73
N of patients at risk	1618	1616	1574	1517
Cumulative Incidence		0.1%	2.5%	4.5%

Myocardial Infarction

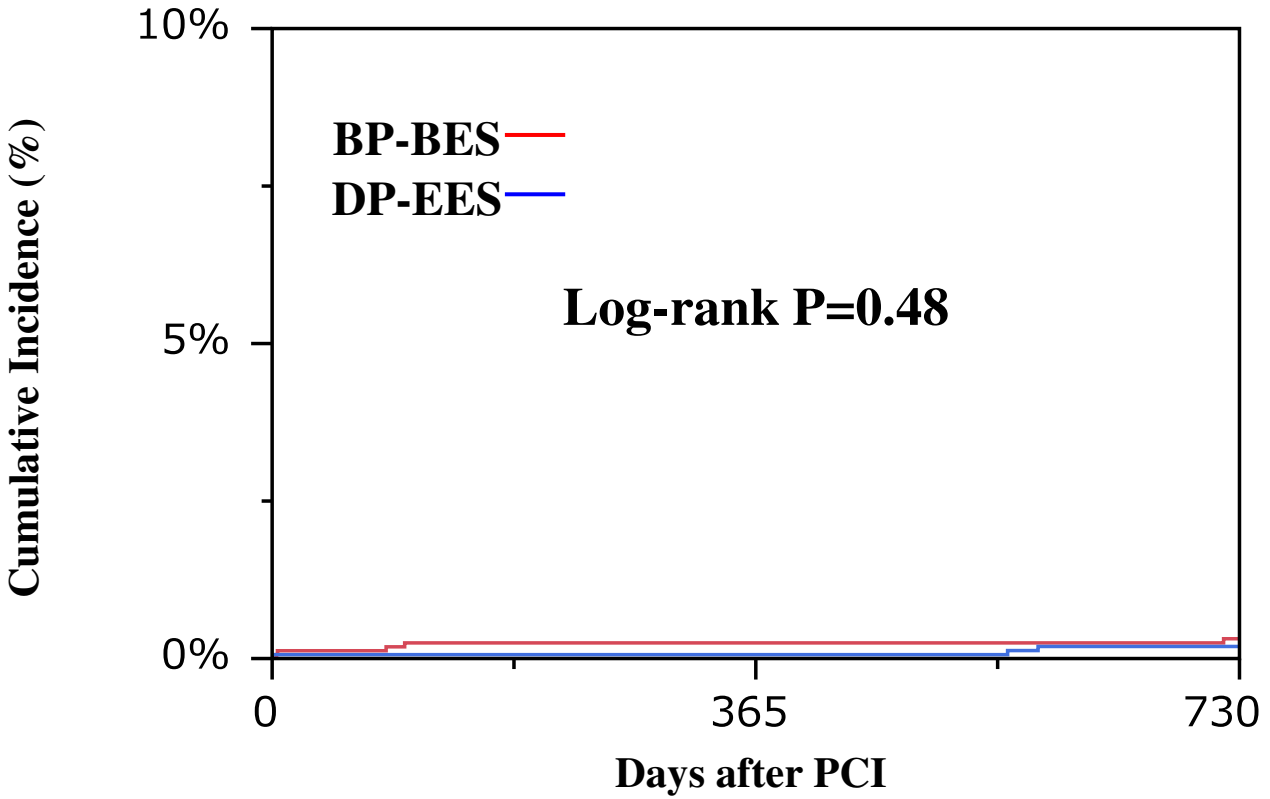


BP-BES:3.7%

DP-EES:3.5%

Interval	0 day	30 days	365 days	730 days
BP-BES group				
N of patients with at least 1 event		45	53	59
N of patients at risk	1617	1569	1524	1463
Cumulative Incidence		2.8%	3.3%	3.7%
DP-EES group				
N of patients with at least 1 event		46	51	56
N of patients at risk	1618	1571	1526	1463
Cumulative Incidence		2.8%	3.2%	3.5%

Definite Stent Thrombosis



BP-BES:0.31%

DP-EES:0.19%

Interval	0 day	30 days	365 days	730 days
BP-BES group				
N of patients with at least 1 event		2	4	5
N of patients at risk	1617	1612	1569	1508
Cumulative Incidence		0.12%	0.25%	0.31%
DP-EES group				
N of patients with at least 1 event		1	1	3
N of patients at risk	1618	1616	1573	1512
Cumulative Incidence		0.06%	0.06%	0.19%

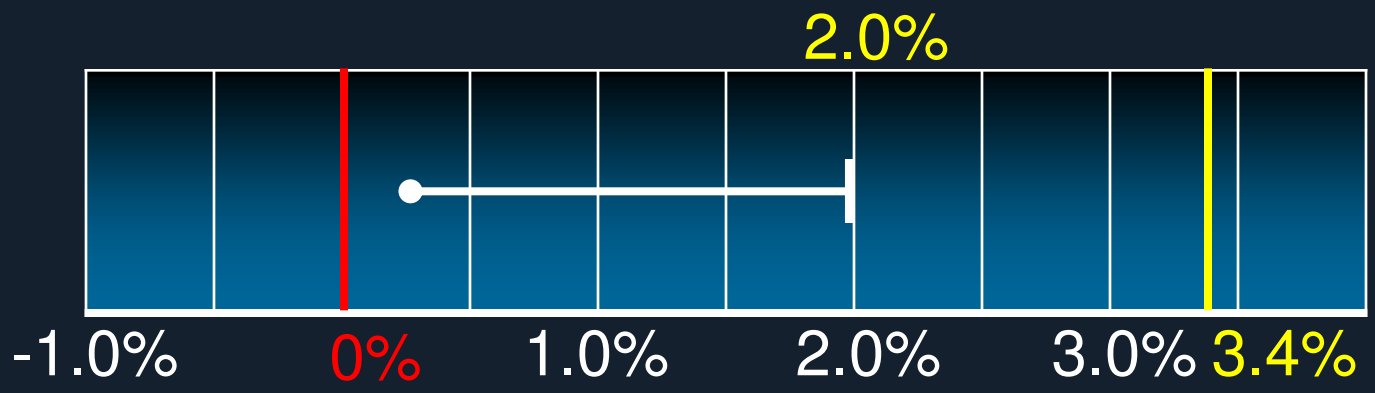
Non-inferiority Assessment for the Primary Efficacy Endpoint

Target-Lesion Revascularization (TLR)

BP-BES 6.23% vs. DP-EES 5.95%

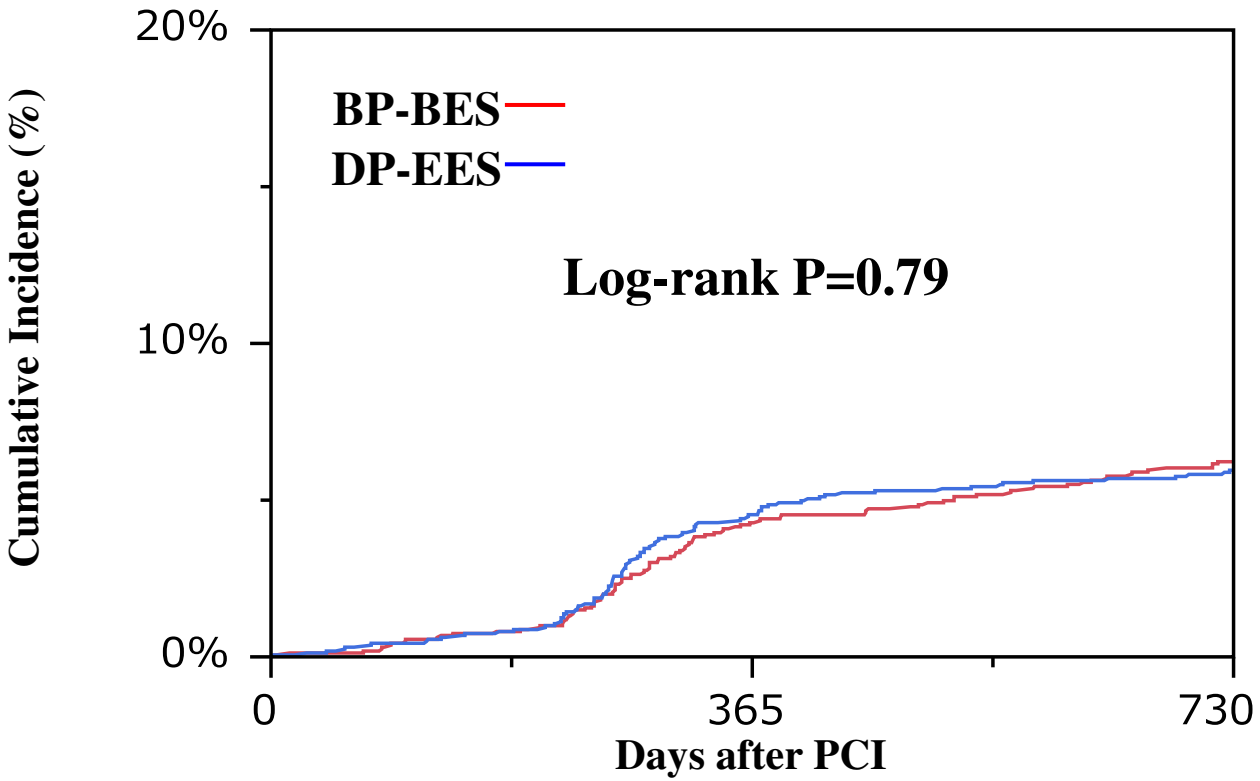
$P_{non\text{-}inferiority} = 0.0001$

Difference:	0.28%
Upper one-sided 97.5% CI:	2.0%



Efficacy Endpoint

Target-Lesion Revascularization

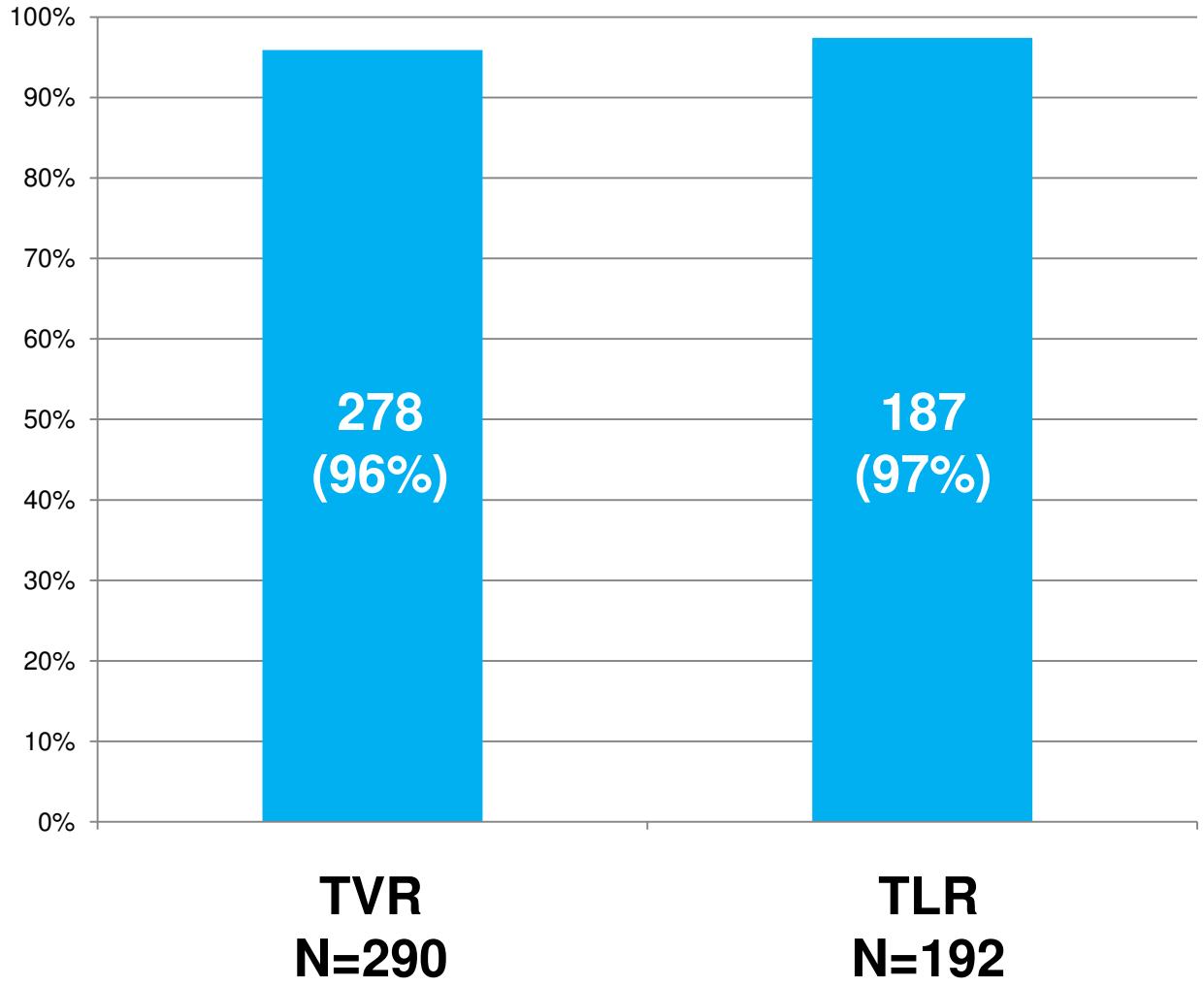


BP-BES:6.2%

DP-EES:6.0%

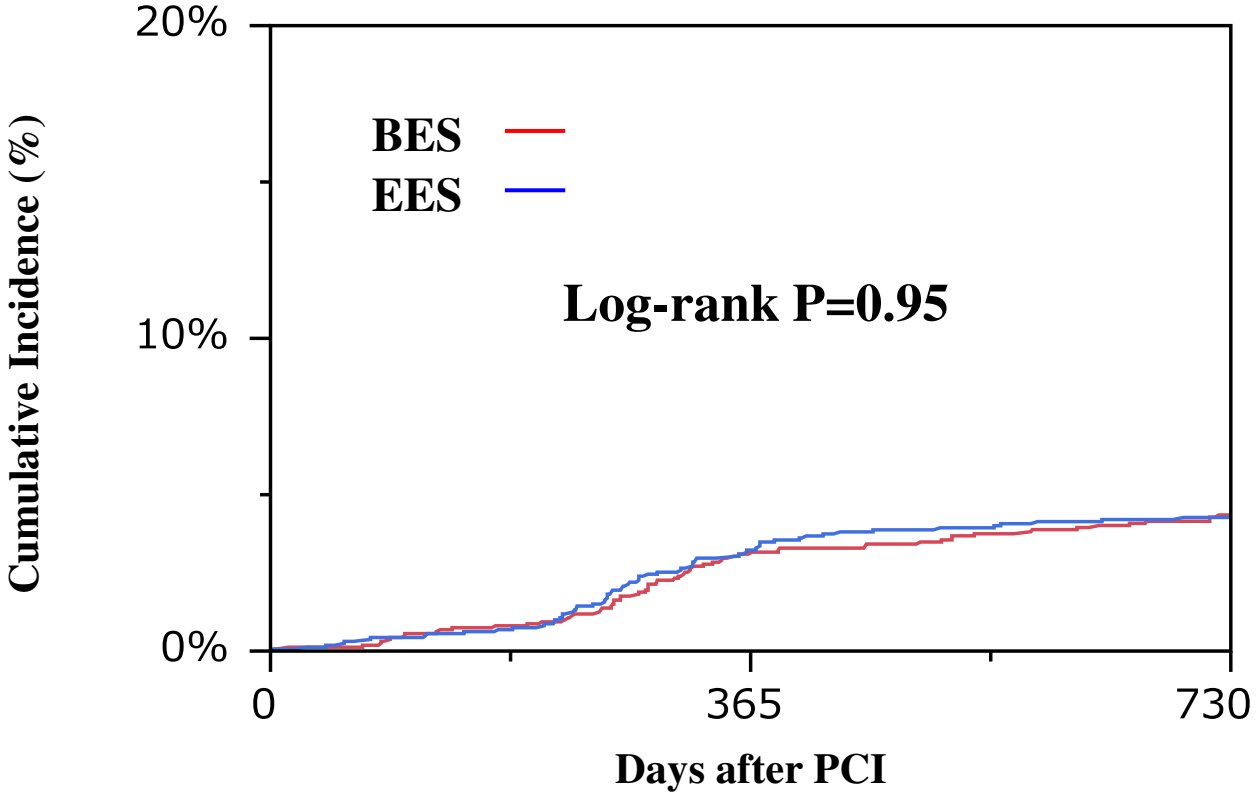
Interval	0 day	30 days	365 days	730 days
BP-BES group				
N of patients with at least 1 event		2	68	98
N of patients at risk	1617	1612	1506	1417
Cumulative Incidence		0.1%	4.3%	6.2%
DP-EES group				
N of patients with at least 1 event		2	72	94
N of patients at risk	1618	1614	1503	1424
Cumulative Incidence		0.1%	4.5%	6.0%

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

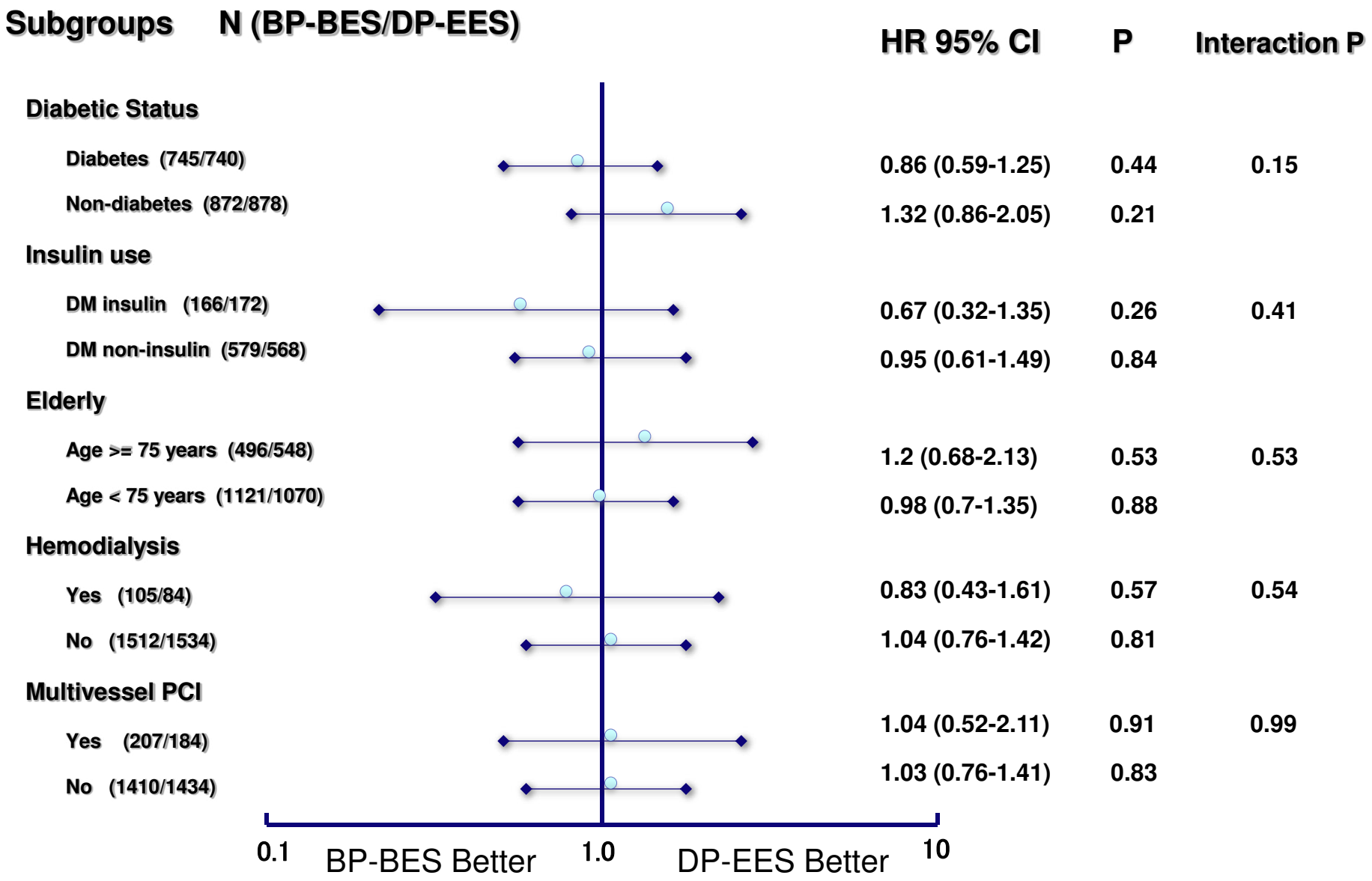


BP-BES:4.4%

DP-EES:4.3%

Interval	0 day	30 days	365 days	730 days
BES group				
N of patients with at least 1 event		2	50	68
N of patients at risk	1617	1612	1506	1417
Cumulative Incidence		0.1%	3.2%	4.4%
EES group				
N of patients with at least 1 event		2	51	67
N of patients at risk	1618	1614	1503	1424
Cumulative Incidence		0.1%	3.2%	4.3%

Pre-specified Subgroup Analysis for TLR
BP-BES versus DP-EES

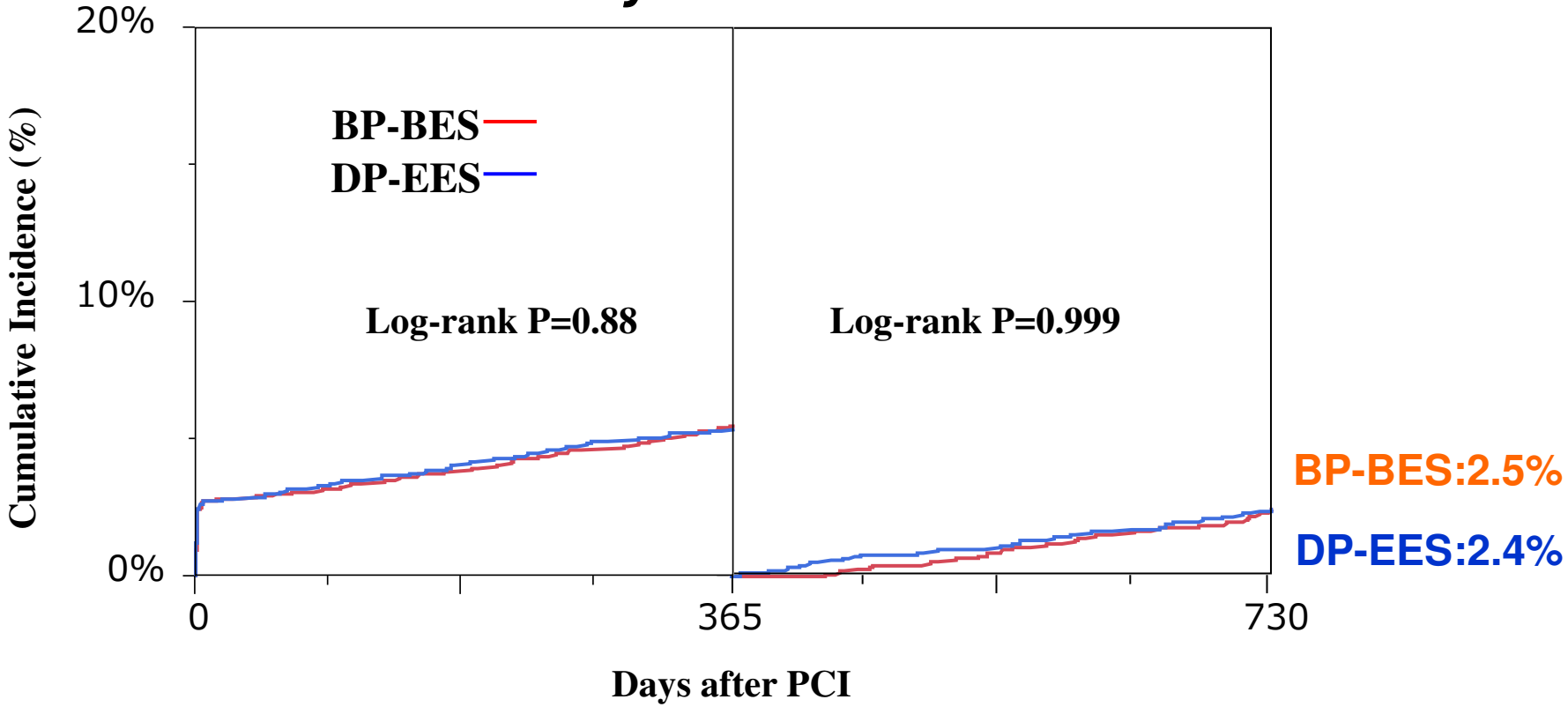


Clinical Outcomes Between 1-year and 2-year

-Landmark Analysis-

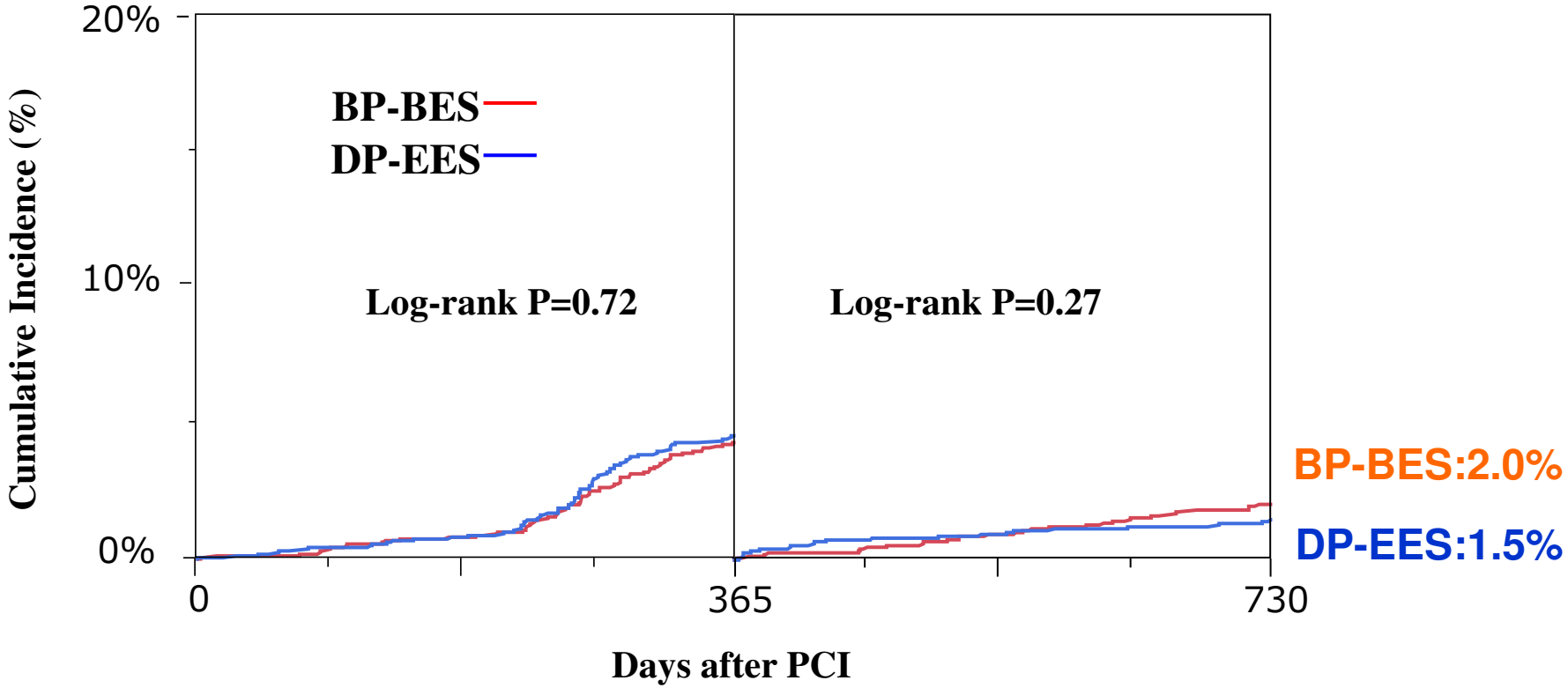
Landmark Analysis at 1-year

Death or Myocardial Infarction



Interval	0 day	30 days	365 days	730 days
BP-BES group				
N of patients with at least 1 event		47	89	37
N of patients at risk	1617	1569	1524	1465
Cumulative Incidence		2.9%	5.5%	2.5%
DP-EES group				
N of patients with at least 1 event		47	87	37
N of patients at risk	1618	1571	1527	1466
Cumulative Incidence		2.9%	5.4%	2.4%

Landmark Analysis at 1-year
Target-Lesion Revascularization



Interval	0 day	30 days	365 days	730 days
BP-BES group				
N of patients with at least 1 event		2	68	30
N of patients at risk	1617	1612	1506	1417
Cumulative Incidence		0.1%	4.3%	2.0%
DP-EES group				
N of patients with at least 1 event		2	72	22
N of patients at risk	1618	1614	1503	1424
Cumulative Incidence		0.1%	4.5%	1.5%

Limitations

- *Two-year follow-up is not sufficient to compare the long-term outcome between BP-BES and DP-EES.*

  The advantage of polymer degradation and no permanent polymer in the vessel wall might emerge with longer-term follow-up.

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

- *The current study was underpowered for the interim analysis of the safety endpoint, even if this is the largest trial comparing BP-BES with DP-EES.*

Conclusions

- *The safety and efficacy outcomes of BP-BES remained comparable to those of DP-EES through 2-year and beyond 1-year after stent implantation.*

- *There was no apparent signal suggesting long-term safety concerns on BP-BES compared with DP-EES.*

- *Network meta-analyses may be hypothesis generating but require confirmation in appropriately designed head-to-head randomized controlled trials.*

- *Longer-term follow-up is mandatory to fully understand whether BP-BES could provide any long-term benefit over DP-EES.*

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

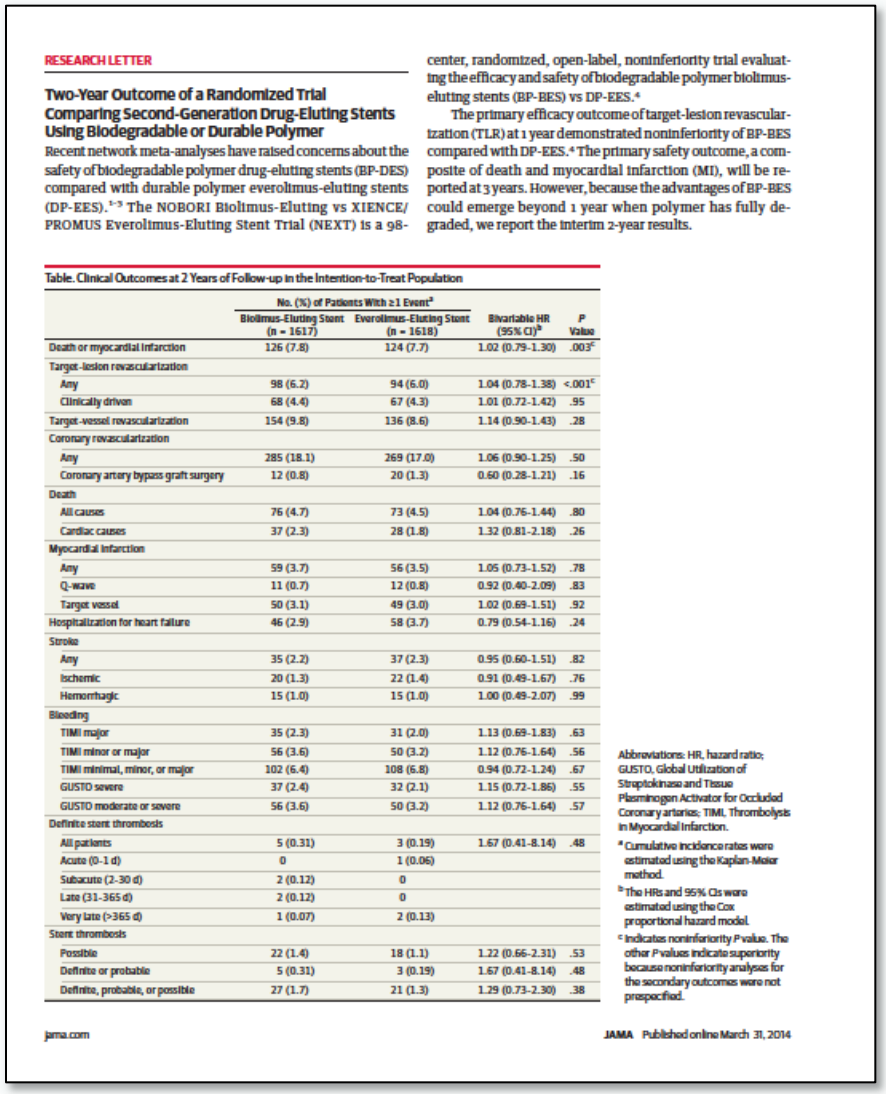
National Hospital Organization Kumamoto Medical Center

Kumamoto Rousai Hospital

Miyazaki Medical Association Hospital

Tenyokai Central Hospital

National Hospital Organization Kagoshima Medical Center



RESEARCH LETTER

Two-Year Outcome of a Randomized Trial Comparing Second-Generation Drug-Eluting Stents Using Biodegradable or Durable Polymer

Recent network meta-analyses have raised concerns about the safety of biodegradable polymer drug-eluting stents (BP-DES) compared with durable polymer everolimus-eluting stents (DP-EES).[1-3] The NOBORI Biolimus-Eluting vs XIENCE/PROMUS Everolimus-Eluting Stent Trial (NEXT) is a 98-center, randomized, open-label, noninferiority trial evaluating the efficacy and safety of biodegradable polymer biolimus-eluting stents (BP-BES) vs DP-EES.[4]

The primary efficacy outcome of target-lesion revascularization (TLR) at 1 year demonstrated noninferiority of BP-BES compared with DP-EES.[4] The primary safety outcome, a composite of death and myocardial infarction (MI), will be reported at 3 years. However, because the advantages of BP-BES could emerge beyond 1 year when polymer has fully degraded, we report the interim 2-year results.

Table. Clinical Outcomes at 2 Years of Follow-up in the Intention-to-Treat Population

	No. (%) of Patients With ≥1 Event[a]			
	Biolimus-Eluting Stent (n = 1617)	Everolimus-Eluting Stent (n = 1618)	Bivariable HR (95% CI)[b]	P Value
Death or myocardial infarction	126 (7.8)	124 (7.7)	1.02 (0.79-1.30)	.003[c]
Target-lesion revascularization				
Any	98 (6.2)	94 (6.0)	1.04 (0.78-1.38)	<.001[c]
Clinically driven	68 (4.4)	67 (4.3)	1.01 (0.72-1.42)	.95
Target-vessel revascularization	154 (9.8)	136 (8.6)	1.14 (0.90-1.43)	.28
Coronary revascularization				
Any	285 (18.1)	269 (17.0)	1.06 (0.90-1.25)	.50
Coronary artery bypass graft surgery	12 (0.8)	20 (1.3)	0.60 (0.28-1.21)	.16
Death				
All causes	76 (4.7)	73 (4.5)	1.04 (0.76-1.44)	.80
Cardiac causes	37 (2.3)	28 (1.8)	1.32 (0.81-2.18)	.26
Myocardial infarction				
Any	59 (3.7)	56 (3.5)	1.05 (0.73-1.52)	.78
Q-wave	11 (0.7)	12 (0.8)	0.92 (0.40-2.09)	.83
Target vessel	50 (3.1)	49 (3.0)	1.02 (0.69-1.51)	.92
Hospitalization for heart failure	46 (2.9)	58 (3.7)	0.79 (0.54-1.16)	.24
Stroke				
Any	35 (2.2)	37 (2.3)	0.95 (0.60-1.51)	.82
Ischemic	20 (1.3)	22 (1.4)	0.91 (0.49-1.67)	.76
Hemorrhagic	15 (1.0)	15 (1.0)	1.00 (0.49-2.07)	.99
Bleeding				
TIMI major	35 (2.3)	31 (2.0)	1.13 (0.69-1.83)	.63
TIMI minor or major	56 (3.6)	50 (3.2)	1.12 (0.76-1.64)	.56
TIMI minimal, minor, or major	102 (6.4)	108 (6.8)	0.94 (0.72-1.24)	.67
GUSTO severe	37 (2.4)	32 (2.1)	1.15 (0.72-1.86)	.55
GUSTO moderate or severe	56 (3.6)	50 (3.2)	1.12 (0.76-1.64)	.57
Definite stent thrombosis				
All patients	5 (0.31)	3 (0.19)	1.67 (0.41-8.14)	.48
Acute (0-1 d)	0	1 (0.06)		
Subacute (2-30 d)	2 (0.12)	0		
Late (31-365 d)	2 (0.12)	0		
Very late (>365 d)	1 (0.07)	2 (0.13)		
Stent thrombosis				
Possible	22 (1.4)	18 (1.1)	1.22 (0.66-2.31)	.53
Definite or probable	5 (0.31)	3 (0.19)	1.67 (0.41-8.14)	.48
Definite, probable, or possible	27 (1.7)	21 (1.3)	1.29 (0.73-2.30)	.38

Abbreviations: HR, hazard ratio; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary arteries; TIMI, Thrombolysis in Myocardial Infarction.

[a] Cumulative incidence rates were estimated using the Kaplan-Meier method.

[b] The HRs and 95% CIs were estimated using the Cox proportional hazard model.

[c] Indicates noninferiority P value. The other P values indicate superiority because noninferiority analyses for the secondary outcomes were not prespecified.

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