

Percutaneous Treatment of LONG Native Coronary Lesions with Drug-Eluting Stent-V: Biolimus A9-Eluting (NOBORI) vs. Everolimus-eluting (PROMUS-ELEMENT) Stent

A Randomized LONG-DES V Trial Preliminary results

Seung-Whan Lee, MD, PhD

Heart Institute, University of Ulsan College of Medicine
Asan Medical Center, Seoul, Korea

Backgrounds

- Despite the strong antirestenotic efficacy of drug eluting stents (DES), the benefits of DES are often attenuated in patients with long coronary artery lesions.
- Furthermore, the first-generation DES were associated with delayed arterial healing and inflammatory reaction, which has potential property for late thrombosis especially in high-risk lesions such as long coronary segments.

Backgrounds

- Biolimus A9 has specifically been developed for local delivery to coronary arteries. The newly developed Nobori Biolimus A9 eluting stent (Terumo) has several unique features. The most important are biodegradable polymer carrier (polylactic acid), and coating only on the abluminal stent surface.
- To date, there have been limited data comparing Nobori with new version of everolimus-eluting stent (Promus Element).

Objective of LONG-DES IV Trial

- To compare long-term angiographic and clinical outcomes in patients with long coronary lesions treated with biolimus A9-eluting stent (NOBORI, Terumo) or new version of everolimus-eluting stent (PROMUS ELEMENT, Boston Scientific).

13 Participating Centers in Korea

- Asan Medical Center, Seoul, Korea
- Inje University Ilsan Paik Hospital, Goyang, Korea
- Kangwon National University Hospital, Chuncheon, Korea
- St. Carollo Hospital, Suncheon, Korea
- Inje University Pusan Paik Hospital, Pusan, Korea
- Soonchunhyang University Bucheon Hospital, Bucheon, Korea
- National Health Insurance Corporation Ilsan Hospital, Goyang, Korea
- Yeungnam University Medical Center, Daegu, Korea
- Soonchunhyang University Hospital Cheonan, Cheonan, Korea
- Dong-A Medical Center, Pusan, Korea
- Konyang University Hospital, Daejeon, Korea
- Kyunghee University Medical Center, Seoul, Korea
- Wonju Christian Hospital, Wonju, Korea

Design

Patients requiring PCI with DES for long coronary lesions:
Lesion length \geq 25mm (total stent length \geq 28mm)

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Biolimus A9-eluting stent:
Nobori
(n=250)

Everolimus-eluting stent:
Promus-Element
(n=250)

9 months Angiographic follow-up
12 months Clinical follow-up

Primary endpoint: **In-segment late loss** at 9 months angiographic follow-up

Inclusion Criteria

Clinical Criteria

- Patients with sAP, ACS or inducible ischemia
- At least 18 years old

Angiographic Criteria

- *De novo* long coronary lesion suitable for stenting
- Diameter stenosis $>50\%$ by visual estimation
- Reference vessel size ≥ 2.5 mm by visual estimation
- **Lesion length ≥ 25 mm by visual estimation
(planned total stent length ≥ 28 mm)**

Exclusion Criteria

- STEMI
- Severe LV dysfunction (EF<30%)
- Cardiogenic shock
- Drug allergy
- Left main coronary artery disease
- Renal dysfunction (creatinine >2.0mg/dL or dialysis)
- Terminal illness
- Elective surgery within 6 months after stent implantation
- Participation in another coronary-device study
- Inability to follow the protocol

Randomization

- Patients were randomly assigned to either Nobori or P-Element implantation on a 1:1 basis by means of an interactive web response system. The allocation sequence was computer-generated, stratified according to participating center and blocked with block sizes of 6 and 10 varying randomly.
- In patients with multiple lesions, the operator decided upon the hierarchy of lesions and declared the target lesion per a patient before the procedure.

Procedures and Pharmacology

- Predilation or direct stenting were allowed.
- All patients received aspirin (100 mg daily) and clopidogrel (a loading dose of 300 or 600 mg and then 75 mg daily for at least 12 months).
- The use of glycoprotein IIb/IIIa inhibitors was at the operators' discretion.
- Serum levels of creatine kinase, its MB isoenzyme, and troponin I were assessed 8, 12 and 24 hours after the procedure, and thereafter if considered necessary.

Follow-Up

- Clinical follow-up visits were scheduled at 30 days, 9 months, 12 month.
- All eligible patients were asked to return for an angiographic follow-up at 9 months after the procedure, or earlier if anginal symptoms occurred.
- All adverse clinical events were adjudicated by an independent Events Committee blinded to the treatment groups.

Sample Size Estimation

- Assumed primary end point of in-segment late loss : 0.24 ± 0.38 mm
- A margin of non-inferiority : 0.11 mm
- A one-sided type I error rate : 0.05
- Power : 80%
- Assumption : a total of 456 patients (228 per group)
- A final sample size : 500 patients (250 per group) assuming 10% of loss

Statistical Analysis

- Analyses were performed according to the intention-to-treat principle.
- Student's unpaired t or Mann-Whitney U tests for continuous variables.
- χ^2 or Fisher's exact tests for categorical variables.
- Kaplan-Meier method to estimate survivals with comparison using log-rank test.

Baseline Characteristics

	NOBORI (N=245)	P-Element (N=255)	P Value
Age	63.06±10.46	63.49±10.63	0.65
Male sex	167 (68.2)	184 (72.2)	0.38
Diabetes mellitus	79 (32.2)	89 (34.9)	0.33
Hypertension	161 (65.7)	154 (60.4)	0.23
Hyperlipidemia	131 (53.5)	145 (56.9)	0.36
Current smoker	63 (25.7)	74 (29.0)	0.42
Previous coronary angioplasty	16 (6.5)	26 (10.2)	0.15
Previous myocardial infarction	6 (2.4)	11 (4.3)	0.32
Left ventricular ejection fraction, %	60.29±7.56	60.23±7.48	0.93

Baseline Characteristics

	NOBORI (N=245)	P-Element (N=255)	P Value
Clinical indication			0.80
Silent ischemia	22 (9.0)	17 (6.7)	
Stable angina	120 (49.0)	128 (50.2)	
Unstable angina	68 (27.8)	74 (29.0)	
Myocardial infarction	35 (14.3)	36 (14.1)	
Number of Diseased Vessel			0.34
1-vessel	121 (49.4)	115 (45.1)	
2-vessel	76 (31.0)	95 (37.3)	
3-vessel	48 (19.6)	45 (17.6)	
multi-vessel disease	124 (50.6)	140 (54.9)	0.37

Lesion Characteristics

	NOBORI (N=245)	P-Element (N=255)	P Value
Target vessel			0.72
Left anterior descending	159 (64.9)	171 (67.1)	
Left circumflex	33 (13.5)	32 (12.5)	
Right coronary	53 (21.6)	52 (20.4)	
TIMI flow grade=0 or 1	25 (10.2)	21 (8.2)	0.46
Bifurcation lesions	79 (32.2)	63 (24.7)	0.04
Thrombus	11 (4.5)	8 (3.1)	0.48
Severe tortuosity	3 (1.2)	4 (1.6)	0.93
Severe Calcification	26 (10.6)	32 (12.5)	0.10
Ulceration	16 (6.5)	16 (6.2)	0.95

Procedural Characteristics

	NOBORI (N=245)	P-Element (N=255)	P Value
No. of stents used at the target lesion			0.20
1 stent	115 (46.9)	117 (45.9)	
2 stents	116 (47.3)	110 (43.1)	
3 stents	13 (5.3)	26 (10.2)	
4 stents	1 (0.4)	2 (0.8)	
mean	1.59±0.61	1.65±0.69	0.25

Procedural Characteristics

	Nobori (N=245)	P-Element (N=255)	P Value
Stented Length at target, mm	38.06±11.48	39.32±13.82	0.10
Average stent diameter, mm	3.16±0.29	3.18±0.37	0.41
Maximal pressure, atm	12.05±4.01	13.51±3.51	<0.001
Direct stenting	16 (6.5)	12 (4.7)	0.44
Post-additional balloon inflation	190 (77.6)	178 (69.8)	0.06
Intravascular ultrasound guidance	189 (77.1)	188 (73.7)	0.41
Glycoprotein IIb/IIIa antagonists	5 (2.0)	6 (2.4)	0.99

QCA Before Procedure

	NOBORI (N=245)	P-Element (N=255)	P Value
Lesion length, mm	31.24±12.17	32.27±13.84	0.16
Reference vessel diameter, mm	3.02±0.46	3.03±0.45	0.80
Minimal luminal diameter, mm	0.85±0.42	0.83±0.42	0.41
Diameter stenosis, %	71.71±13.38	72.61±13.95	0.48

QCA After Procedure

	NOBORI (N=245)	P-Element (N=255)	P Value
Minimal luminal diameter, mm			
In segment	2.23±0.43	2.21±0.40	0.52
In stent	2.52±0.40	2.52±0.36	0.49
Proximal margin	3.01±0.56	3.07±0.52	0.33
Distal margin	2.26±0.45	2.24±0.43	0.48
Diameter stenosis, %			
In segment	17.80±9.97	17.12±10.0	0.46
In stent	10.62±8.77	9.99±8.27	0.36
Proximal margin	12.28±9.18	11.15±9.14	0.20
Distal margin	15.18±9.73	14.90±10.20	0.76
Acute gain, mm			
In segment	1.36±0.53	1.38±0.61	0.88
In stent	1.67±0.51	1.68±0.57	0.86

Study Endpoint

Primary Endpoint

- **In-segment late luminal loss**

At 9 months after the index procedure

Follow-up Analysis

Nobori
N=245

95 pts refused follow-up
2 pts died

**9-month angiographic
follow-up**
N=148 (60%)

12-month clinical follow-up
N=245 (100%)

Promus Element
N=255

107 pts refused follow-up
1 pts died

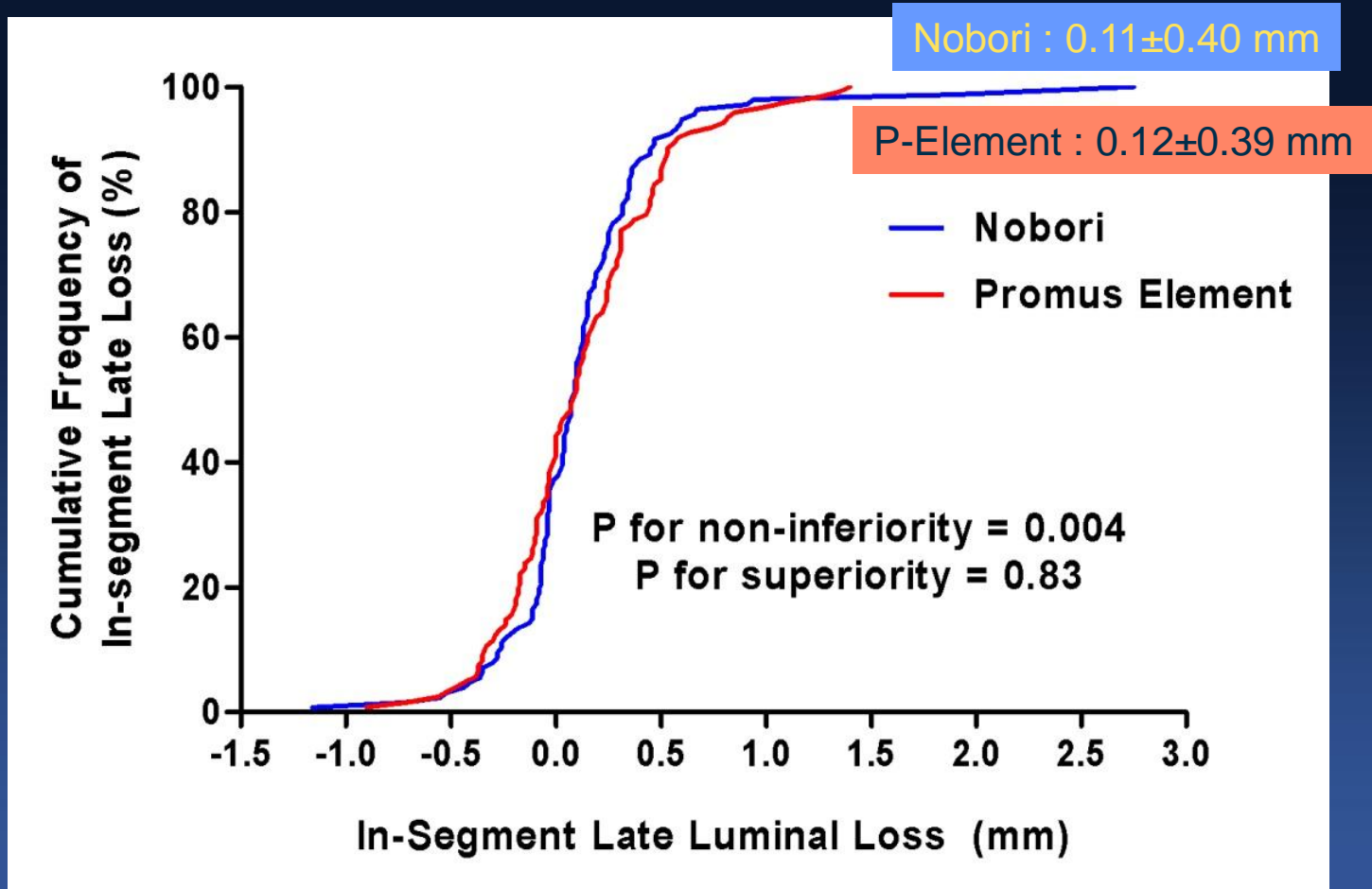
**9-month angiographic
follow-up**
N=147 (58%)

12-month clinical follow-up
N=250 (100%)

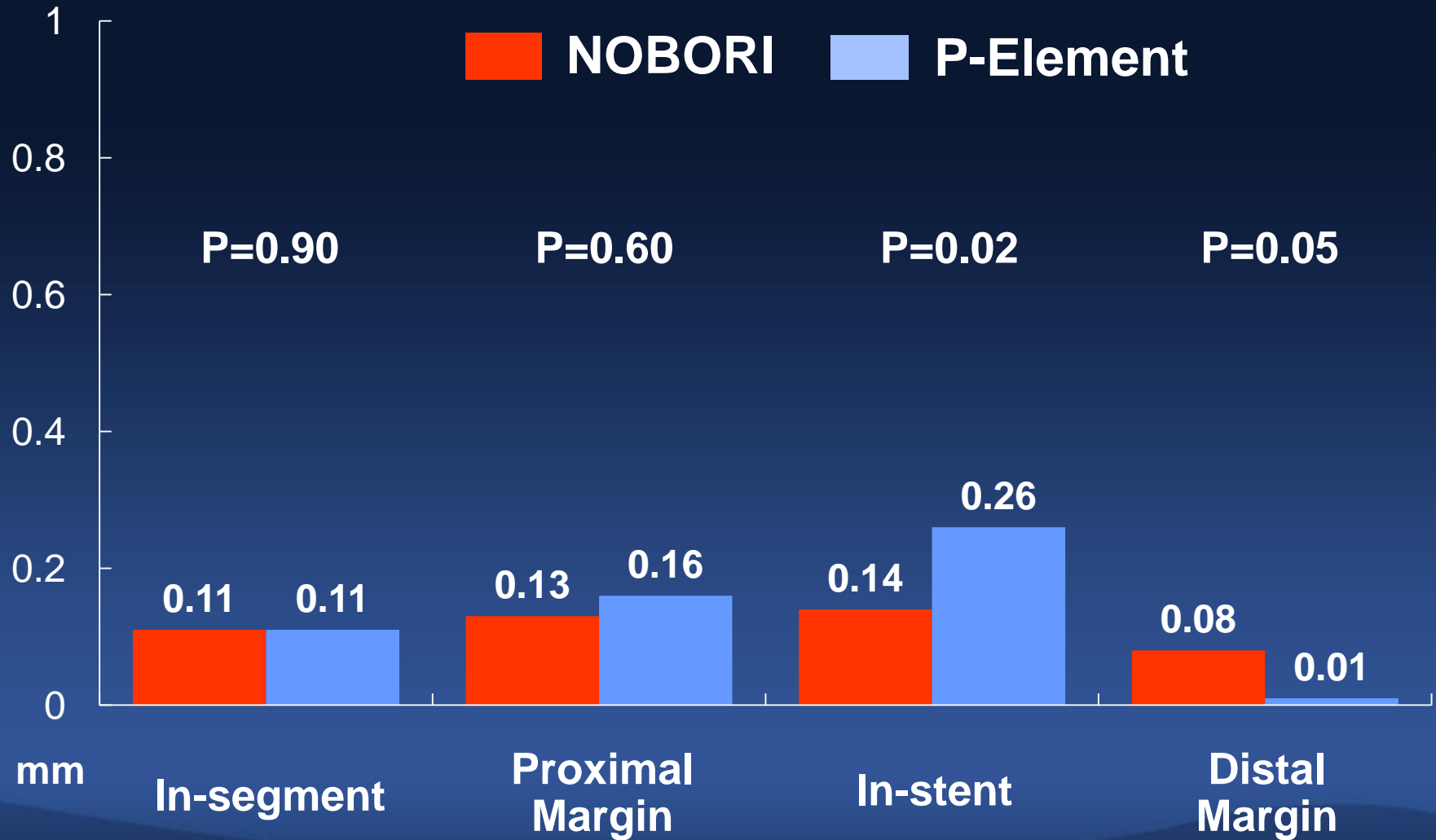
QCA at Follow-up

	NOBORI (N=148)	P-Element (N=147)	P Value
Minimal luminal diameter, mm			
In segment	2.09±0.47	2.08±0.49	0.86
In stent	2.39±0.48	2.22±0.45	0.009
Proximal margin	2.89±0.60	2.82±0.60	0.33
Distal margin	2.15±0.44	2.22±0.45	0.27
Diameter stenosis , %			
In segment	20.95±15.43	24.11±14.24	0.10
In stent	14.92±14.14	21.63±15.50	<0.001
Proximal margin	15.48±12.03	16.55±12.42	0.50
Distal margin	17.17±12.77	14.59±9.70	0.07

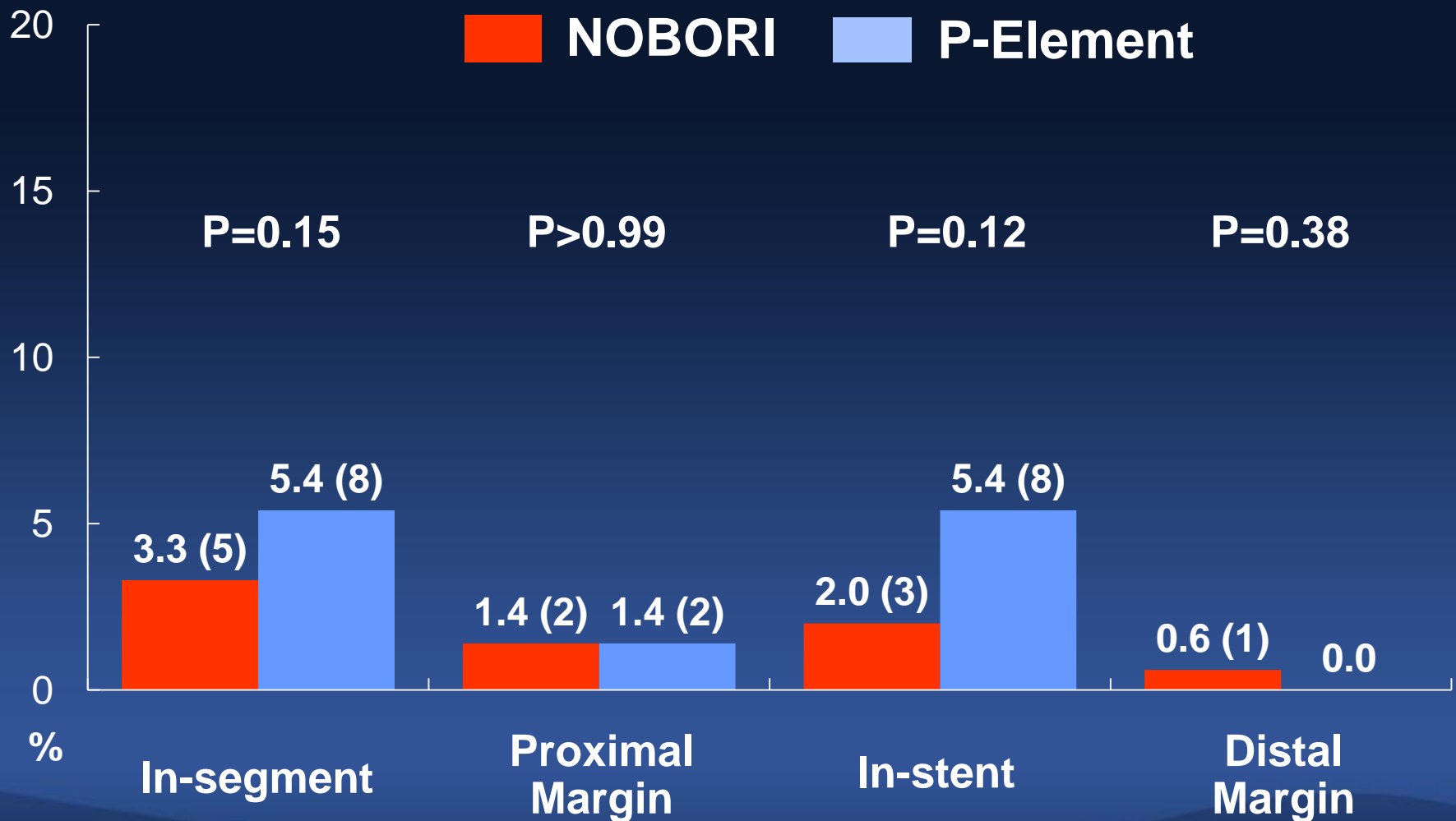
Primary Endpoint: In-Segment Late Loss at 9 months



Late Luminal Loss



Binary Restenosis Rate



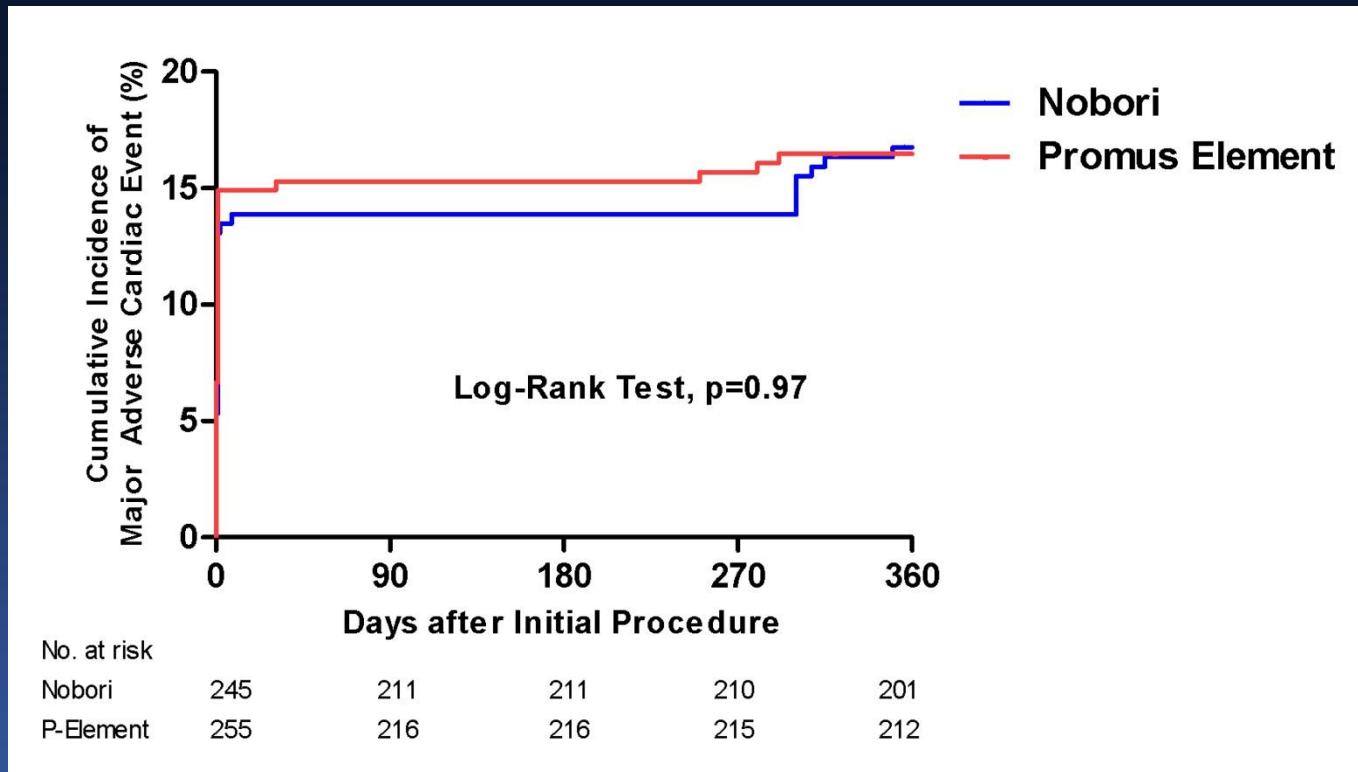
Pattern of Restenosis

	NOBORI	P-Element	P Value
Overall number of ISR	5	8	0.15
Focal, %			
IA (gap)		1	
IB (margin)	1	1	
IC (focal body)	2	4	
ID (multifocal)			
Diffuse, %			
II (intrastent)	1	1	
III (proliferative)			
IV (total occlusion)	1	0	

Clinical Outcomes at 12 months

	NOBORI (N=245)	P-Element (N=255)	P Value
Death	2 (0.8)	1 (0.4)	0.62
Cardiac	2 (0.8)	1 (0.4)	
Non-cardiac	0	0	
Myocardial infarction	33 (13.5)	40 (15.7)	0.53
Q-wave	1 (0.4)	0	
Non-Q-wave	32 (12.9)	40 (15.7)	
Stent thrombosis, definite or probable	3 (1.2)	0	0.12
Acute, definite	2		
Subacute, probable	1		
Target-lesion revascularization	8 (3.3)	5 (2.0)	0.44
Target-vessel revascularization	9 (3.7)	5 (2.0)	0.28

MACE (death/MI/TVR) at 12 months



Conclusions

- In this prospective, randomized trial involving patients with long coronary artery lesions, Biolimus A9 eluting, Nobori implantation was noninferior to Everolimus-eluting, Promus-Element implantation as assessed by 9-month angiographic in-segment late luminal loss.
- Furthermore, both stent platforms were associated with comparable low rates of clinical end points for 12 months, suggesting that both stents are equally effective in the treatment of long coronary artery lesions.