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Five-year outcome of a randomised 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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Introduction

In the meta-analysis of randomised clinical trials comparing the safety and efficacy of a biodegradable polymer drug-eluting stent (BP-DES) as compared with new-generation durable polymer drug-eluting stents (DP-DES), no significant differences were seen between BP-DES and DP-DES with a mean follow-up duration of 26 months[1]. However, longer-term follow-up would be required to evaluate the safety and efficacy profiles of BP-DES compared to DP-DES considering the occurrence of stent-related adverse events not attenuating over time. Therefore, we sought to evaluate the five-year clinical outcomes of a biodegradable polymer biolimus-eluting stent (BP-BES) as compared with new-generation durable polymer everolimus-eluting stents (DP-EES) in the extended follow-up study from NEXT (NOBORI Biolimus-Eluting versus XIENCE/PROMUS Everolimus-eluting Stent Trial)[2].

Methods

STUDY DESIGN, PATIENTS AND PROCEDURES

As previously described in detail, NEXT is a prospective, multicentre, randomised, non-inferiority trial comparing BP-BES with DP-EES in Japan[2]. Written informed consent was obtained from all the study patients. The study was registered at ClinicalTrials.gov (NCT01303640). The extended follow-up study of NEXT was designed with planned follow-up up to 10 years. All the centres were invited to participate in the extended study, but 20 centres refused to participate in the extended study **(Supplementary Appendix 1, Supplementary Appendix 2)**. Among a total of 3,241 patients for the entire NEXT study population from 98 centres, 2,568 patients (BP-BES 1,283 patients and DP-EES 1,285 patients) with 3,229 lesions were included in the extended follow-up study **(Supplementary Figure 1)**. These 2,568 patients represent 79.2% of the original patient population of the NEXT trial.

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Details of the study procedures have been described previously[2]. For the present analysis, the primary efficacy endpoint was any target lesion revascularisation (TLR), while the primary safety endpoint was a composite of death or myocardial infarction (MI).

STATISTICAL ANALYSIS

In the extended follow-up study, the non-inferiority margin for the primary safety and efficacy endpoints was set as a hazard ratio of 1.38 for the observed event rate in the DP-EES group[3]. The study protocol was updated in line with this amendment. The present analysis would yield 99% power to detect non-inferiority for the primary safety endpoint and 87% power to detect non-inferiority for the primary efficacy endpoint at a one-sided alpha level of 0.025.

Results

The two groups of patients were generally well balanced in terms of baseline clinical and lesion characteristics **(Supplementary Table 1)**.

Complete five-year follow-up was achieved in 2,408 patients (93.8%) **(Supplementary Figure 1)**. The cumulative incidence of persistent discontinuation of dual antiplatelet therapy (DAPT) was not significantly different between the BP-BES and DP-EES groups (15.3% versus 14.2% at one year, and 61.5% versus 62.8% at five years, p=0.74) **(Supplementary Figure 2)**. The primary safety endpoint of death/MI occurred in 190 patients (15.1%) in the BP-BES group, and in 208 patients (16.5%) in the DP-EES group up to five years, demonstrating non-inferiority of BP-BES to DP-EES (hazard ratio [HR] 0.91, 95% confidence interval [CI]: 0.75-1.11), demonstrating non-inferiority of BP-BES to DP-EES in terms of death/MI (p for non-inferiority <0.0001). Testing for superiority was not statistically significant (p for superiority=0.37) **(Table 1, Supplementary Table 2, Figure 1A)**. The primary efficacy endpoint of TLR occurred in 9.8% in the BP-BES group and in 9.3% in the DP-EES group, demonstrating non-inferiority of BP-BES to DP-EES (HR 1.04, 95% CI: 0.8-1.34), demonstrating non-inferiority of BP-BES to DP-EES in terms of TLR (p for non-inferiority=0.01). Testing for superiority was not statistically significant (p for superiority=0.79) **(Table 1, Supplementary Table 2, Figure 1B)**. A sensitivity analysis was conducted in 3,235 initially randomised subjects of this trial. The cumulative five-year incidences of death or MI and TLR were not significantly different between the two groups (14.8% versus 16.2%, p=0.36 and 9.6% versus 8.7%, p=0.5, respectively) **(Supplementary Figure 3)**.

Between one and five years, the cumulative incidences of death/MI and TLR were not different between the two groups **(Figure 2)**. The cumulative incidence of definite stent thrombosis (ST) was not different between the two groups **(Supplementary Table 3)**.

In the subgroup analysis, the risk for death/MI and TLR was not significantly different between the BP-BES and DP-EES groups in any pre-specified subgroup **(Supplementary Figure 4)**.

Discussion

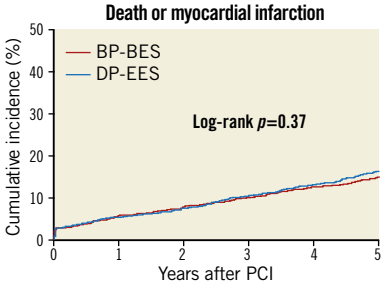
The present study is the third randomised trial reporting five-year clinical outcomes between BP-DES versus new-generation DP-DES following the ISAR-TEST 4 and COMPARE II trials[4,5]. The present five-year results from NEXT were fully consistent with those previous trials[4,5]. Taken together, new-generation DES using biodegradable polymer and durable polymer would

Table 1. Clinical outcomes at five years.

		No. of patients with at least one event (cumulative incidence)		Univariate HR (95% CI)	*p*-value
		Biolimus-eluting stent N=1,283	Everolimus-eluting stent N=1,285		
Death or myocardial infarction		190 (15.1%)	208 (16.5%)	0.91 (0.75-1.11)	0.37
Target lesion revascularisation		118 (9.8%)	114 (9.3%)	1.04 (0.8-1.34)	0.79
Target vessel revascularisation		173 (14.2%)	152 (12.4%)	1.15 (0.92-1.43)	0.22
Coronary revascularisation		323 (26.5%)	309 (25.3%)	1.05 (0.9-1.23)	0.53
Death	All-cause	146 (11.7%)	158 (12.6%)	0.93 (0.74-1.16)	0.51
	From cardiac causes	53 (4.4%)	47 (3.9%)	1.13 (0.76-1.68)	0.54
Myocardial infarction	Any	64 (5.2%)	60 (4.8%)	1.07 (0.75-1.52)	0.72
	Target vessel	45 (3.6%)	46 (3.7%)	0.98 (0.65-1.48)	0.91
	Stroke	58 (4.8%)	68 (5.7%)	0.86 (0.6-1.21)	0.38
Bleeding	TIMI major	56 (4.6%)	60 (5.0%)	0.94 (0.65-1.35)	0.73
	TIMI minor/major	79 (6.5%)	78 (6.4%)	1.02 (0.75-1.4)	0.90
Stent thrombosis	Definite	6 (0.49%)	4 (0.34%)	1.5 (0.43-5.88)	0.52
	Definite or probable	6 (0.49%)	4 (0.34%)	1.5 (0.43-5.88)	0.52
	Definite, probable or possible	34 (2.8%)	30 (2.5%)	1.14 (0.7-1.87)	0.60

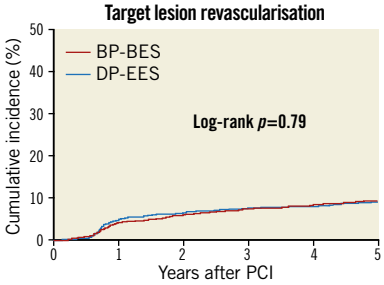
CI: confidence interval; HR: hazard ratio; TIMI: Thrombolysis In Myocardial Infarction

A



Interval	0 day	1 year	2 years	3 years	4 years	5 years
BP-BES group						
No. of patients with at least 1 event		77	104	131	161	190
No. of patients at risk	1,283	1,203	1,170	1,134	1,058	1,009
Cumulative incidence		6.0%	8.1%	10.0%	12.7%	15.1%
DP-EES group						
No. of patients with at least 1 event		71	100	137	171	208
No. of patients at risk	1,285	1,213	1,179	1,135	1,054	991
Cumulative incidence		5.5%	7.8%	10.7%	13.5%	16.5%

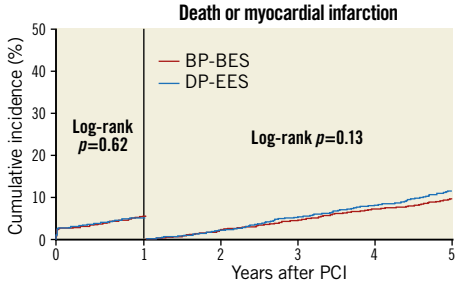
B



Interval	0 day	1 year	2 years	3 years	4 years	5 years
BP-BES group						
No. of patients with at least 1 event		55	78	95	106	118
No. of patients at risk	1,283	1,192	1,138	1,083	1,004	947
Cumulative incidence		4.4%	6.2%	7.7%	8.6%	9.8%
DP-EES group						
No. of patients with at least 1 event		63	84	97	102	114
No. of patients at risk	1,285	1,191	1,141	1,089	1,017	951
Cumulative incidence		5.0%	6.7%	7.8%	8.2%	9.3%

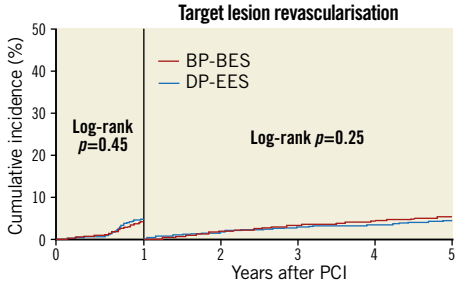
Figure 1. *Cumulative incidence of the primary endpoint events up to five-year follow-up. A) Death or myocardial infarction. B) Target lesion revascularisation. BP-BES: biodegradable polymer biolimus-eluting stent; DP-EES: durable polymer everolimus-eluting stent; PCI: percutaneous coronary intervention*

A



Interval	0 day	1 year	2 years	3 years	4 years	5 years
BP-BES group						
No. of patients with at least 1 event		77	27	54	84	113
No. of patients at risk	1,283	1,203	1,170	1,134	1,058	1,009
Cumulative incidence		6.0%	2.3%	4.5%	7.1%	9.7%
DP-EES group						
No. of patients with at least 1 event		71	29	66	100	137
No. of patients at risk	1,285	1,213	1,179	1,135	1,054	991
Cumulative incidence		5.5%	2.4%	5.5%	8.4%	11.6%

B



Interval	0 day	1 year	2 years	3 years	4 years	5 years
BP-BES group						
No. of patients with at least 1 event		55	23	40	51	63
No. of patients at risk	1,283	1,192	1,138	1,083	1,004	947
Cumulative incidence		4.4%	2.0%	3.5%	4.5%	5.6%
DP-EES group						
No. of patients with at least 1 event		63	31	34	39	51
No. of patients at risk	1,285	1,191	1,141	1,089	1,017	951
Cumulative incidence		5.0%	1.8%	2.9%	3.4%	4.5%

Figure 2. *Cumulative incidence of the primary endpoint events between one and five years by one-year landmark analysis. A) Death or myocardial infarction. B) Target lesion revascularisation. BP-BES: biodegradable polymer biolimus-eluting stent; DP-EES: durable polymer everolimus-eluting stent; PCI: percutaneous coronary intervention*

have similar safety and efficacy outcomes up to five years. Both biodegradable polymer and durable polymer might have achieved parallel improvements using more biocompatible polymer than used in first-generation DES. A very long-term follow-up study of BP-DES relative to DP-DES up to 10 years would also provide important information on the potential advantages of BP-DES over DP-DES.

Limitations

First, the number of study participants was reduced from 3,235 patients to 2,568 patients in the current extended follow-up study. However, the main reason for the reduced number of study patients was not incomplete follow-up, but the dropout of 20 centres. Centre was incorporated as one of the stratification factors for randomisation. Therefore, we believe that the reduction in the number of study participants did not have much influence on the study conclusion. Second, DAPT duration was longer than that reported outside Japan. Based on our findings, we cannot exclude that other BP-DES might show a better long-term outcome than DP-DES in the future.

Conclusion

Safety and efficacy outcomes of Nobori® BP-BES (Terumo Corp., Tokyo, Japan) were non-inferior to those of XIENCE/PROMUS DP-EES (Abbott Vascular, Santa Clara, CA, USA, and Boston Scientific, Marlborough, MA, USA, respectively) five years after stent implantation. Advantages of Nobori BP-BES over DP-EES were not apparent even at five-year follow-up after stent implantation.

Impact on daily practice

There is a scarcity of data on the clinical outcomes of BP-BES relative to DP-EES beyond three years after stent implantation. Advantages of BP-BES over current-generation DP-EES were not apparent up to five years and beyond one year after stent implantation.

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Conflict of interest statement

T. Kimura, Y. Morino, K. Tanabe, and K. Kozuma were advisory board members of Terumo Japan and Abbott Vascular Japan. K. Kozuma has received research grant and lecture fees from Abbott Vascular Japan. T. Akasaka has received laboratory funding, a grant, consulting fees and lecture fees from Abbott Vascular Japan. K. Tanabe, Y. Nakagawa and M. Natsuaki have received lecture fees from Abbott Vascular Japan and Terumo Japan. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Study organisation.

Supplementary Appendix 2. List of the participating centres and investigators.

Supplementary Table 1. Patient, lesion and procedural characteristics.

Supplementary Table 2. Clinical outcomes at 5 years.

Supplementary Table 3. Clinical outcomes between 1 year and 5 years.

Supplementary Figure 1. Study patient flow.

Supplementary Figure 2. Cumulative incidence of persistent discontinuation of dual antiplatelet therapy.

Supplementary Figure 3. Cumulative incidences of the primary safety and efficacy endpoint events up to 5-year follow-up in the original entire study population of 3,235 patients.

Supplementary Figure 4. Hazard ratio plot for the primary safety and efficacy endpoints in the pre-specified subgroups.

The supplementary data are published online at: http://www.pcronline.com/eurointervention/140th_issue/141

Supplementary data

Supplementary Appendix 1. Study organisation.

Steering committee:
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Caress Sappro Hokko Memorial Hospital: Yoichi Nozaki
Aomori Prefectural Central Hospital: Atsushi Konta, Takashi Yokota
Iwate Prefectural Central Hospital: Akihiro Nakamura, Sohta Nakajima, Masanori Kanazawa
Iwate Medical University Hospital: Tetsuya Fusazaki
Tohoku Medical and Pharmaceutical University Hospital: Yoshiaki Katahira, Takao Nakano
Sendai Open Hospital: Atsushi Kato, Toru Takii
Fukushima Medical University Hospital: Yasuchika Takeishi, Kazuhiko Nakazato
Dokkyo Medical University Koshigaya Hospital: Takaaki Komatsu
New Tokyo Hospital: Sunao Nakamura, Naoyuki Kurita
Juntendo University Hospital: Hiroyuki Daida, Katsumi Miyauchi
Sakakibara Heart Institute: Itaru Takamisawa
NTT Medical Center Tokyo: Masao Yamasaki
The Cardiovascular Institute Hospital: Junji Yajima, Yoshiyuki Hatakeyama
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Teikyo University Hospital: Ken Kozuma, Nobuaki Suzuki
Tokyo Women's Medical University Hospital: Nobuhisa Hagiwara, Junichi Yamaguchi
Itabashi Chuo Medical Center: Hiroshi Ohta
Yokohama Rosai Hospital: Kazuhiko Yumoto
Tokai University Hospital: Yuji Ikari, Toshiharu Fujii
Yokohama City University Medical Center: Kazuo Kimura, Kiyoshi Hibi
Kitasato University Hospital: Taiki Tojo, Takao Shimohama
Kanazawa Cardiovascular Hospital: Masanobu Namura, Yuki Horita
University of Fukui Hospital: Hiroyasu Uzui
Fukui Cardiovascular Center: Sumio Mizuno, Katsushi Misawa

Ogaki Municipal Hospital: Hideyuki Tsuboi, Yasuhiro Morita, Kensuke Takagi
Juntendo University Shizuoka Hospital: Satoru Suwa
Shizuoka General Hospital: Hiroki Sakamoto, Hideaki Moriwaki
Okamura Memorial Hospital: Yasuhiro Tarutani
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Mie University Hospital: Tairo Kurita
Mie Heart Center: Hideo Nishikawa, Hiroyuki Suzuki
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Shiga University of Medical Science Hospital: Takashi Yamamoto
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National Hospital Organization Kyoto Medical Center: Masaharu Akao, Mitsuru Abe
Osaka Saiseikai Noe Hospital: Yoshihiro Kato
Osaka Red Cross Hospital: Tsukasa Inada, Fujio Hayashi
National Cerebral and Cardiovascular Center Hospital: Satoshi Yasuda, Yasuhide Asaumi
Sumitomo Hospital: Yuji Yasuga, Nobuhiro Mitsusada
Bell Land General Hospital: Toru Kataoka
Kobe City Medical Center General Hospital: Natsuhiko Ehara
Kobe University Hospital: Toshihiro Shinke, Yuichiro Nagano
Kansai Rosai Hospital: Takayuki Ishihara
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Tenri Hospital: Yoshihisa Nakagawa, Toshihiro Tamura

Japanese Red Cross Society Wakayama Medical Center: Takashi Tamura, Mamoru Toyofuku
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Kurume University Hospital: Takafumi Ueno, Hidetoshi Chibana
Kokura Memorial Hospital: Shinichi Shirai, Yuhei Yamaji
Kouseikai Hospital: Masahiko Ishizaki
Saiseikai Kumamoto Hospital: Koichi Nakao, Shinzo Miyamoto
National Hospital Organization Kumamoto Medical Center: Kazuteru Fujimoto
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Tenyoukai Central Hospital: Junichiro Takaoka, Nobuhiko Atsuchi
National Hospital Organization Kagoshima Medical Center: Hitoshi Nakashima, Tetsuro Kataoka, Keisuke Kusumoto

Supplementary Table 1. Patient, lesion and procedural characteristics.

	Biolimus-eluting stent N=1,283	Everolimus-eluting stent N=1,285	*p*-value
Patient characteristics			
Age, years	69.2±9.8	69.5±9.7	0.36
Age >=75 years	392 (31%)	449 (35%)	0.02
Male gender	982 (77%)	979 (76%)	0.83
Body mass index	24.1±3.5 (1,278)	24.1±3.4 (1,277)	0.90
Coexisting condition			
Hypertension	1,035 (81%)	1,039 (81%)	0.91
Diabetes mellitus	619 (48%)	589 (46%)	0.22
Insulin-treated diabetes	143 (11%)	140 (11%)	0.84
Treated with oral medication only	336 (26%)	341 (27%)	0.84
Treated with diet therapy only	140 (11%)	108 (8.4%)	0.03
Dyslipidaemia	1,033 (81%)	1,024 (80%)	0.60
ESRD (eGFR <30 mL/min/1.73 m^2) not on haemodialysis	32/1,279 (2.5%)	33/1,281 (2.6%)	0.91
Haemodialysis	92 (7.2%)	67 (5.2%)	0.04
Atrial fibrillation	73 (5.7%)	93 (7.2%)	0.11
Anaemia (haemoglobin <11.0 g/dL)	170/1,282 (13%)	154/1,285 (12%)	0.33
Chronic obstructive pulmonary disease	22 (1.7%)	32 (2.5%)	0.17
Malignancy	87 (6.8%)	102 (7.9%)	0.26
Cardiac risk factor			
Current smoker	236 (18%)	231 (18%)	0.78
Family history of coronary artery disease	230/1,258 (18%)	218/1,253 (17%)	0.56
Prior myocardial infarction	372 (29%)	376 (29%)	0.88
Prior stroke	126 (9.8%)	149 (11%)	0.16
Heart failure	160 (12%)	147 (11%)	0.42
Peripheral vascular disease	127 (9.9%)	147 (11%)	0.21

Prior percutaneous coronary intervention	638 (50%)	638 (50%)	0.97
Prior coronary artery bypass grafting	64 (5.0%)	65 (5.1%)	0.94
Clinical characteristics			
Clinical presentation			0.57
Stable coronary artery disease	1,067 (83%)	1,088 (85%)	
Unstable angina	154 (12%)	142 (11%)	
Acute myocardial infarction	62 (4.8%)	55 (4.3%)	
Left ventricular ejection fraction <30%	28/1,114 (2.1%)	19/1,110 (1.7%)	0.19
Multivessel disease	673 (52%)	692 (54%)	0.48
Target vessel location			
Left main coronary artery	41 (3.2%)	41 (3.2%)	0.99
Left anterior descending coronary artery	630 (49%)	605 (47%)	0.31
Left circumflex coronary artery	305 (24%)	347 (27%)	0.06
Right coronary artery	443 (35%)	413 (32%)	0.20
Bypass graft	9 (0.7%)	13 (1.0%)	0.39
Complexity of coronary artery disease			
No. of treated lesions per patient	1.27±0.57	1.25±0.51	0.25
SYNTAX score			
Number of patients analysed	1,188	1,193	
Median (interquartile range)	10 (6-17)	10 (6-16)	0.22
Tertiles			0.83
Low (<23)	1,053 (89%)	1,059 (89%)	
Intermediate (>=23 - <33)	105 (8.8%)	100 (8.4%)	
High (>=33)	30 (2.5%)	34 (2.9%)	
Medications			
Aspirin	1,282 (99.9%)	1,280 (99.6%)	0.09
Thienopyridines	1,278 (99.6%)	1,273 (99.1%)	0.08
Clopidogrel	1,127 (88%)	1,156 (90%)	0.18
Ticlopidine	134 (10%)	102 (8.0%)	
Statins	1,001 (78%)	990 (77%)	0.55

Beta-blockers	472 (87%)	468 (36%)	0.85
ACE-I/ARB	783 (61%)	802 (62%)	0.47
Calcium channel blockers	606 (47%)	578 (45%)	0.25
Nitrates	360 (28%)	316 (25%)	0.046
Coumadin	87 (6.8%)	102 (7.9%)	0.26
Lesion and procedural characteristics			
Number of lesions treated	1,629	1,600	
Before index procedure			
Lesion length, mm	19.6±13.2 (1,475)	19.0±12.8 (1,470)	0.21
Reference vessel diameter, mm	2.62±0.59 (1,551)	2.62±0.56 (1,542)	0.97
Minimum lumen diameter, mm	0.77±0.43 (1,555)	0.76±0.42 (1,545)	0.35
Percent diameter stenosis, %	71.0±14.6 (1,555)	71.3±14.6 (1,545)	0.61
Thrombus	28/1,555 (1.8%)	32/1,545 (2.1%)	0.58
Chronic total occlusion	134 (8.2%)	123 (7.7%)	0.57
In-stent restenosis	184 (11%)	170 (11%)	0.54
Culprit for STEMI	44 (2.7%)	40 (2.5%)	0.72
Bifurcation	689/1,556 (44%)	698/1,542 (45%)	0.58
Moderate or heavy calcification	334/1,556 (21%)	307/1,545 (20%)	0.27
Small vessel (reference vessel diameter, <=2.75 mm)	945/1,551 (61%)	951/1,542 (62%)	0.67
Long lesion (lesion length >18 mm)	632/1,475 (43%)	597/1,470 (41%)	0.22
After index procedure			
No. of stents used			
Per patient	1.59±0.86	1.58±0.84	0.76
Per lesion	1.25±0.61	1.27±0.64	0.46
Total stent length, mm			
Per patient	33.0±20.8	32.4±20.9	0.52
Per lesion	26.0±16.0	26.1±17.0	0.88

Stent diameter, mm	2.87±0.68	2.86±0.65	0.64
Multivessel treatment	159/1,283 (12%)	150/1,285 (12%)	0.58
Direct stenting	325/1,568 (21%)	309/1,548 (20%)	0.60
Maximum stent inflation pressure, atm	17.3±4.6 (1,568)	17.0±4.5 (1,548)	0.06
Post-dilatation	1,201 (74%)	1,165 (73%)	0.56
Bifurcation 2-stent approach	22 (1.4%)	17 (1.1%)	0.45
Intravascular ultrasound use	1,438 (88%)	1,395 (87%)	0.35
Received study stent only	1,547/1,557 (99.4%)	1,536/1,541 (99.7%)	0.20
Minimum lumen diameter, mm			
In-stent	2.51±0.47 (1,550)	2.47±0.45 (1,535)	0.04
In-segment	2.09±0.56 (1,556)	2.07±0.52 (1,540)	0.45
Percent diameter stenosis, %			
In-stent	9.7±7.7 (1,550)	10.0±7.8 (1,535)	0.64
In-segment	21.9±12.1 (1,556)	21.2±11.3 (1,540)	0.08
Acute gain, mm			
In-stent	1.73±0.5 (1,549)	1.71±0.5 (1,535)	0.24
In-segment	1.32±0.54 (1,555)	1.31±0.53 (1,540)	0.92
Duration of procedure, minutes	72.3±44.5 (1,283)	71.1±44.4 (1,285)	0.48
Successful outcome			
Lesion success by any treatment modality	1,621 (99.5%)	1,587 (99.2%)	0.25
Lesion success by study stents (acute device success)	1,551/1,557 (99.6%)	1,537/1,541 (99.7%)	0.54
Procedural success (patient level)	1,242/1,283 (96.8%)	1,242/1,285 (96.7%)	0.83
Staged PCI procedures	340/1,283 (27%)	339/1,285 (26%)	0.95

ACE-I: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blockers; eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; SYNTAX: Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery

Supplementary Table 2. Clinical outcomes at 5 years.

	No. of patients with at least one event (cumulative incidence)		Univariate HR (95% CI)	*p*-value
	Biolimus-eluting stent N=1,283	Everolimus-eluting stent N=1,285		
Death or myocardial infarction	190 (15.1%)	208 (16.5%)	0.91 (0.75-1.11)	0.37
Target lesion revascularisation				
Any	118 (9.8%)	114 (9.3%)	1.04 (0.8-1.34)	0.79
Clinically driven	93 (7.3%)	89 (7.3%)	1.05 (0.78-1.4)	0.76
Target vessel revascularisation	173 (14.2%)	152 (12.4%)	1.15 (0.92-1.43)	0.22
Coronary revascularisation				
Any	323 (26.5%)	309 (25.3%)	1.05 (0.9-1.23)	0.53
Coronary artery bypass grafting	19 (1.6%)	24 (2.0%)	0.79 (0.43-1.44)	0.45
Death				
All-cause	146 (11.7%)	158 (12.6%)	0.93 (0.74-1.16)	0.51
From cardiac causes	53 (4.4%)	47 (3.9%)	1.13 (0.76-1.68)	0.54
Myocardial infarction				
Any	64 (5.2%)	60 (4.8%)	1.07 (0.75-1.52)	0.72
Q-wave	13 (1.1%)	14 (1.2%)	0.93 (0.43-1.99)	0.85

Target vessel	45 (3.6%)	46 (3.7%)	0.98 (0.65-1.48)	0.91
Hospitalisation for heart failure	67 (5.6%)	83 (6.9%)	0.81 (0.58-1.11)	0.19
Stroke				
Any	58 (4.8%)	68 (5.7%)	0.86 (0.6-1.21)	0.38
Ischaemic	37 (3.1%)	45 (3.8%)	0.82 (0.53-1.27)	0.38
Haemorrhagic	21 (1.7%)	25 (2.1%)	0.84 (0.47-1.51)	0.57
Bleeding				
TIMI major	56 (4.6%)	60 (5.0%)	0.94 (0.65-1.35)	0.73
TIMI minor/major	79 (6.5%)	78 (6.4%)	1.02 (0.75-1.4)	0.90
TIMI minimal/minor/major	131 (10.7%)	143 (11.7%)	0.92 (0.72-1.16)	0.48
GUSTO severe	52 (4.3%)	55 (4.5%)	0.95 (0.65-1.39)	0.79
GUSTO moderate/severe	77 (6.3%)	83 (6.8%)	0.93 (0.68-1.27)	0.65
Device-oriented composite endpoint	195 (15.7%)	192 (15.5%)	1.01 (0.83-1.24)	0.90
Patient-oriented composite endpoint	456 (36.1%)	463 (36.6%)	0.99 (0.87-1.12)	0.83
TLF	172 (13.9%)	168 (13.6%)	1.02 (0.83-1.27)	0.84
TVF	221 (17.8%)	206 (16.7%)	1.08 (0.89-1.3)	0.44
MACE	184 (14.9%)	178 (14.4%)	1.03 (0.84-1.27)	0.75

Definite stent thrombosis				
All patients	6 (0.49%)	4 (0.34%)	1.5 (0.43-5.88)	0.52
Acute (0-1 day)	0 (0%)	1 (0.08%)		
Subacute (2-30 days)	2 (0.16%)	0 (0%)		
Late (31-365 days)	2 (0.16%)	0 (0%)		
Very late (beyond 365 days)	2 (0.17%)	3 (0.26%)		0.66
Stent thrombosis				
Possible	28 (2.3%)	26 (2.1%)	1.08 (0.63-1.85)	0.77
Definite or probable	6 (0.49%)	4 (0.34%)	1.5 (0.43-5.88)	0.52
Definite, probable or possible	34 (2.8%)	30 (2.5%)	1.14 (0.7-1.87)	0.60

CI: confidence interval; GUSTO: Global Utilisation of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries; HR: hazard ratio; MACE: major adverse cardiovascular events; TIMI: Thrombolysis In Myocardial Infarction; TLF: target lesion failure; TVF: target vessel failure

Supplementary Table 3. Clinical outcomes between 1 year and 5 years.

	No. of patients with at least one event (cumulative incidence)		Univariate HR (95% CI)	*p*-value
	Biolimus-eluting stent N=1,283	Everolimus-eluting stent N=1,285		
Death or myocardial infarction	113 (9.7%)	137 (11.6%)	0.82 (0.64-1.06)	0.13
Target lesion revascularisation				
Any	63 (5.6%)	51 (4.5%)	1.24 (0.86-1.8)	0.25
Clinically driven	50 (4.5%)	44 (3.9%)	1.14 (0.76-1.72)	0.52
Target vessel revascularisation	89 (8.1%)	65 (5.9%)	1.39 (1.01-1.92)	0.04
Coronary revascularisation				
Any	162 (15.6%)	136 (13.4%)	1.21 (0.96-1.52)	0.10
Coronary artery bypass grafting	9 (0.8%)	15 (1.3%)	0.6 (0.25-1.35)	0.22
Death				
All-cause	109 (9.1%)	126 (10.4%)	0.87 (0.67-1.12)	0.28
From cardiac causes	31 (2.7%)	32 (2.8%)	0.97 (0.59-1.6)	0.91
Myocardial infarction				
Any	18 (1.6%)	18 (1.6%)	0.99 (0.52-1.93)	0.99
Q-wave	5 (0.4%)	6 (0.5%)	0.84 (0.24-2.78)	0.77

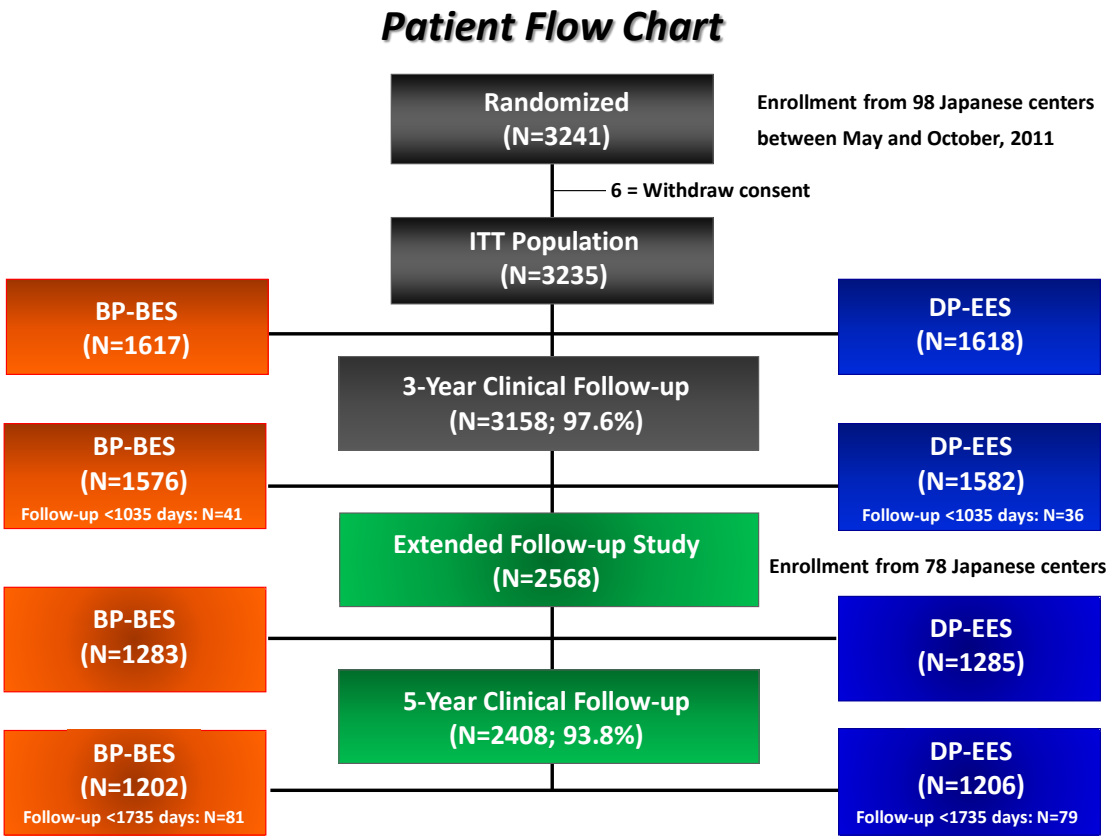
Target vessel	5 (0.4%)	8 (0.7%)	0.62 (0.19-1.87)	0.40
Hospitalisation for heart failure	42 (3.7%)	49 (4.3%)	0.85 (0.56-1.29)	0.45
Stroke				
Any	41 (3.6%)	45 (3.9%)	0.91 (0.6-1.4)	0.68
Ischaemic	29 (2.5%)	30 (2.6%)	0.97 (0.58-1.62)	0.91
Haemorrhagic	12 (1.0%)	17 (1.4%)	0.71 (0.33-1.47)	0.36
Bleeding				
TIMI major	35 (3.0%)	44 (3.8%)	0.8 (0.51-1.25)	0.32
TIMI minor/major	41 (3.6%)	52 (4.4%)	0.8 (0.53-1.2)	0.27
TIMI minimal/minor/major	73 (6.5%)	84 (7.4%)	0.87 (0.64-1.19)	0.39
GUSTO severe	27 (2.4%)	35 (3.0%)	0.78 (0.47-1.28)	0.32
GUSTO moderate/severe	40 (3.5%)	50 (4.3%)	0.8 (0.53-1.22)	0.30
Device-oriented composite endpoint	87 (8.0%)	79 (7.3%)	1.1 (0.81-1.49)	0.55
Patient-oriented composite endpoint	242 (23.3%)	236 (23.0%)	1.03 (0.86-1.24)	0.73
TLF	75 (6.8%)	73 (6.7%)	1.03 (0.74-1.42)	0.87
TVF	103 (9.5%)	92 (8.5%)	1.13 (0.85-1.5)	0.40
MACE	82 (7.5%)	81 (7.4%)	1.01 (0.75-1.38)	0.93

Stent thrombosis				
Definite	2 (0.17%)	3 (0.26%)	0.67 (0.09-4.04)	0.66
Definite or probable	2 (0.17%)	3 (0.26%)	0.67 (0.09-4.04)	0.66
Definite, probable or possible	17 (1.5%)	21 (1.8%)	0.81 (0.42-1.54)	0.53

Patients who had the endpoint event within one year were excluded from the landmark analysis for the endpoint of interest.

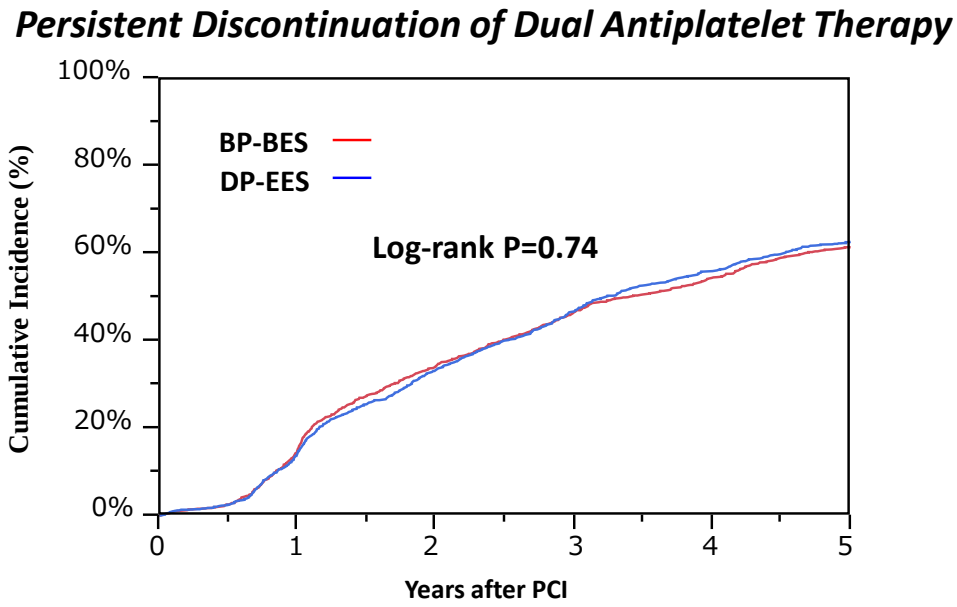
CI: confidence interval; GUSTO: Global Utilisation of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries; HR: hazard ratio; MACE: major adverse cardiovascular events; TIMI: Thrombolysis In Myocardial Infarction; TLF: target lesion failure; TVF: target vessel failure

Supplementary Figure 1. Study patient flow.



BP-BES: biodegradable polymer biolimus-eluting stent; DP-EES: durable polymer everolimus-eluting stent

Supplementary Figure 2. Cumulative incidence of persistent discontinuation of dual antiplatelet therapy.

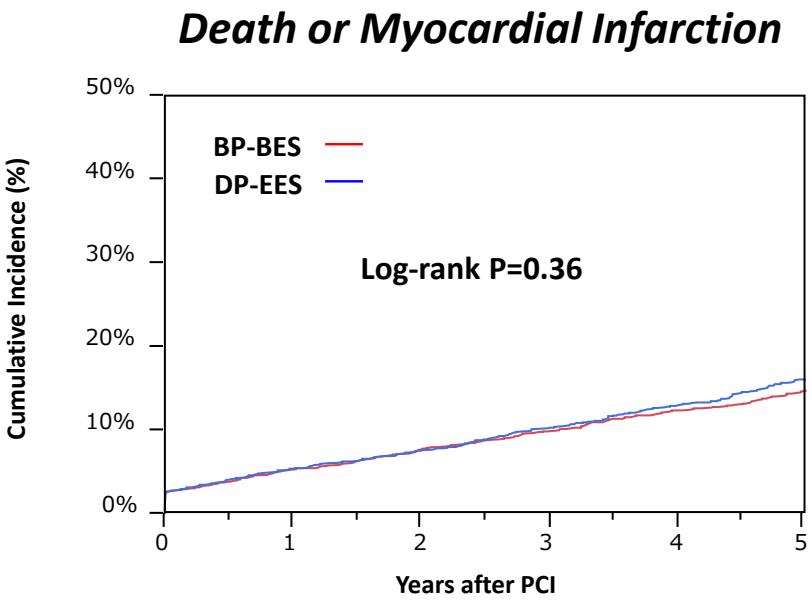


Interval	0 day	1 year	2 years	3 years	4 years	5 years
BP-BES group						
N of patients with discontinuation		192	425	572	659	734
N of patients at risk	1283	1051	794	622	492	396
Cumulative Incidence		15.3%	34.3%	46.7%	54.5%	61.5%
DP-EES group						
N of patients with discontinuation		179	417	578	685	758
N of patients at risk	1285	1073	813	630	490	398
Cumulative Incidence		14.2%	33.5%	46.8%	56.1%	62.8%

BP-BES: biodegradable polymer biolimus-eluting stent; DP-EES: durable polymer everolimus-eluting stent; PCI: percutaneous coronary intervention

Supplementary Figure 3. Cumulative incidences of the primary safety and efficacy endpoint events up to 5-year follow-up in the original entire study population of 3,235 patients. A) Death or myocardial infarction; B) target lesion revascularisation.

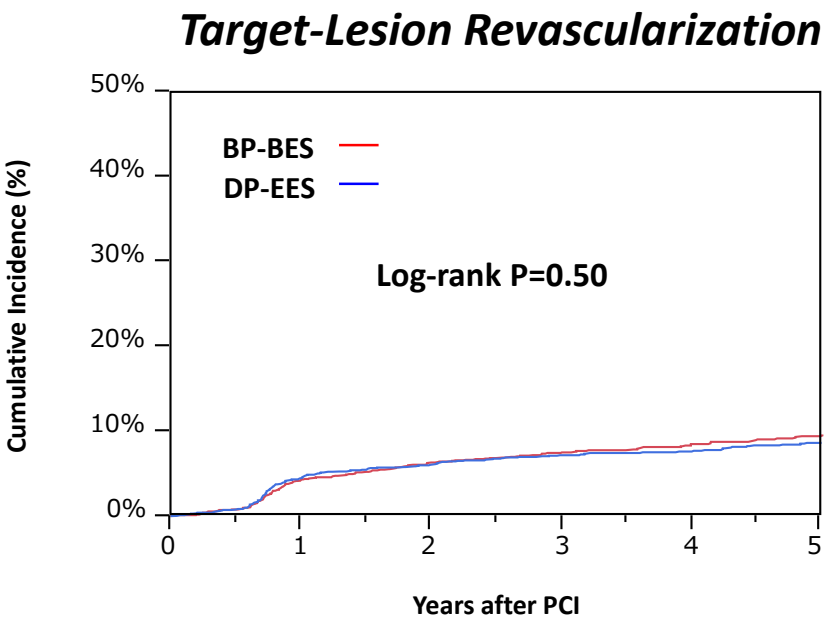
(A)



Interval	0 day	30 days	1 year	2 years	3 years	4 years	5 years
BP-BES group							
N of patients with at least 1 event		47	89	126	160	190	219
N of patients at risk	1617	1569	1524	1478	1429	1058	1009
Cumulative Incidence		2.9%	5.5%	7.8%	10.0%	12.4%	14.8%
DP-EES group							
N of patients with at least 1 event		47	87	124	167	201	238
N of patients at risk	1618	1571	1529	1484	1428	1054	991
Cumulative Incidence		2.9%	5.4%	7.7%	10.4%	13.1%	16.2%

BP-BES: biodegradable polymer biolimus-eluting stent; DP-EES: durable polymer everolimus-eluting stent; PCI: percutaneous coronary intervention

(B)

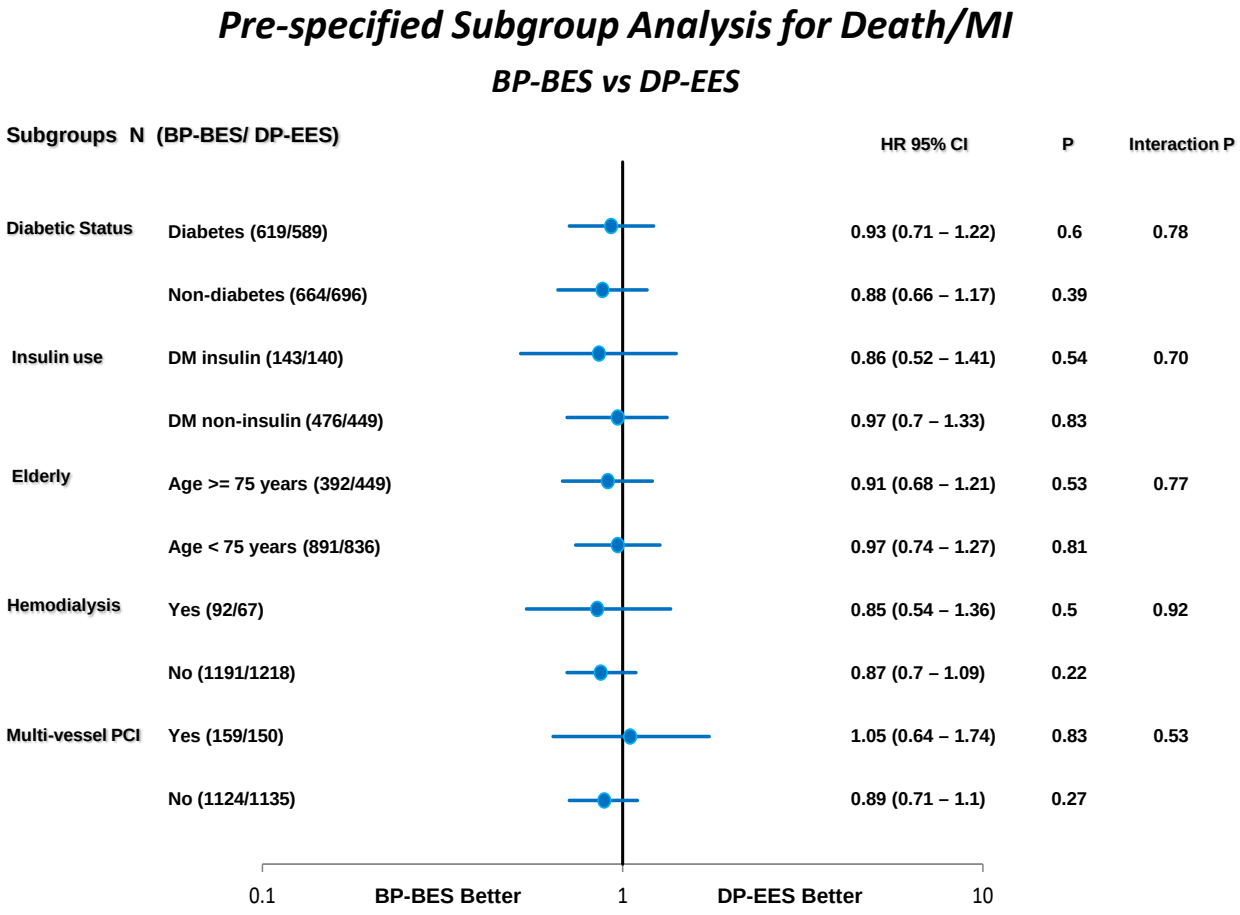


Interval	0 day	30 days	1 year	2 years	3 years	4 years	5 years
BP-BES group							
N of patients with at least 1 event		2	68	100	118	129	141
N of patients at risk	1617	1612	1506	1431	1364	1004	947
Cumulative Incidence		0.1%	4.3%	6.3%	7.5%	8.5%	9.6%
DP-EES group							
N of patients with at least 1 event		2	72	97	113	118	130
N of patients at risk	1618	1614	1506	1442	1373	1017	951
Cumulative Incidence		0.1%	4.5%	6.1%	7.2%	7.6%	8.7%

BP-BES: biodegradable polymer biolimus-eluting stent; DP-EES: durable polymer everolimus-eluting stent; PCI: percutaneous coronary intervention

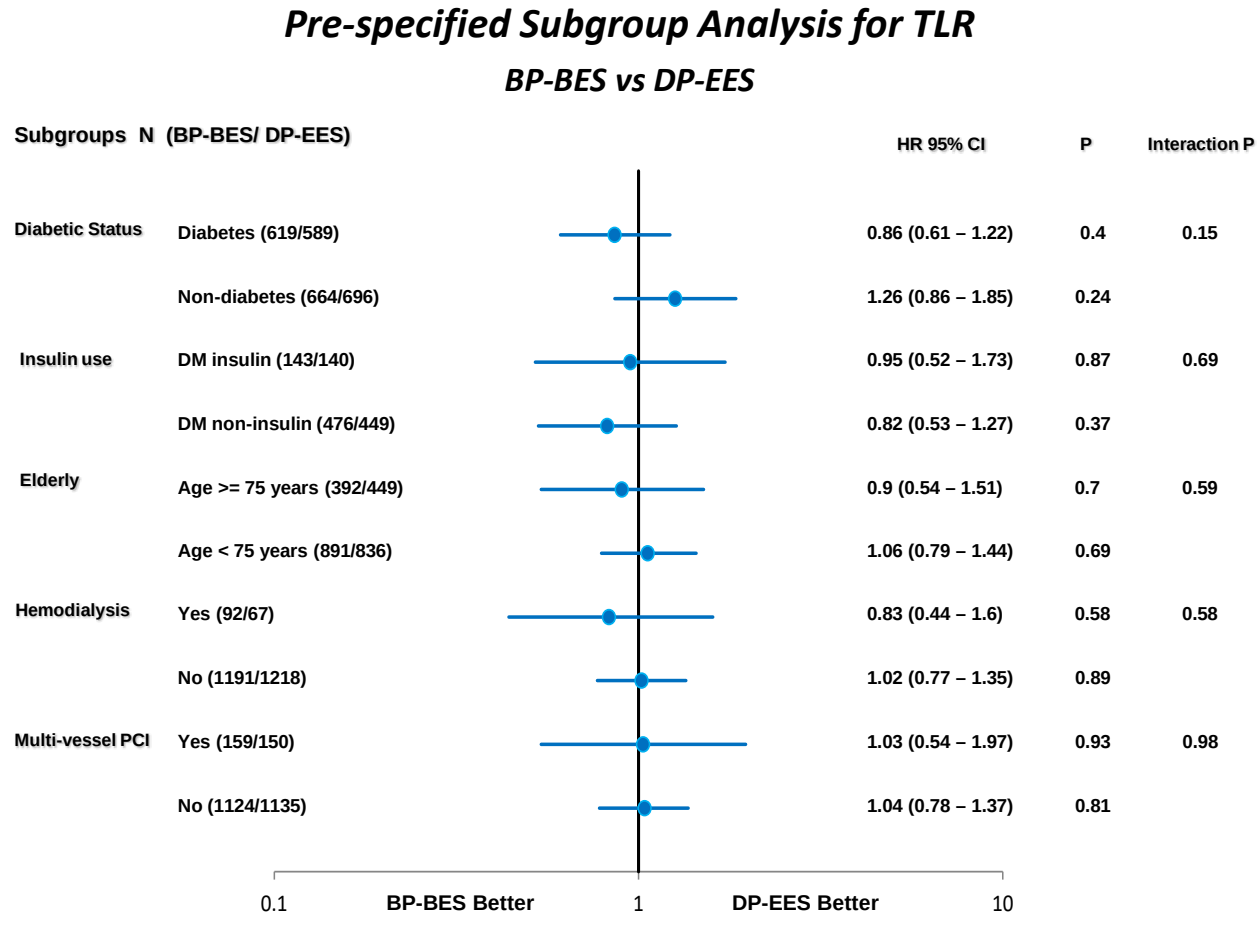
Supplementary Figure 4. Hazard ratio plot for the primary safety and efficacy endpoints in the pre-specified subgroups. A) Death or myocardial infarction; B) target lesion revascularisation.

(A)



BP-BES: biodegradable polymer biolimus-eluting stent; CI: confidence interval; DM: diabetes mellitus; DP-EES: durable polymer everolimus-eluting stent; HR: hazard ratio; MI: myocardial infarction; PCI: percutaneous coronary intervention; TLR: target lesion revascularisation

(B)



BP-BES: biodegradable polymer biolimus-eluting stent; CI: confidence interval; DM: diabetes mellitus; DP-EES: durable polymer everolimus-eluting stent; HR: hazard ratio; MI: myocardial infarction; PCI: percutaneous coronary intervention; TLR: target lesion revascularisation