

Safety and Efficacy of Biolimus-Eluting Stents: Real World Experience from Korea



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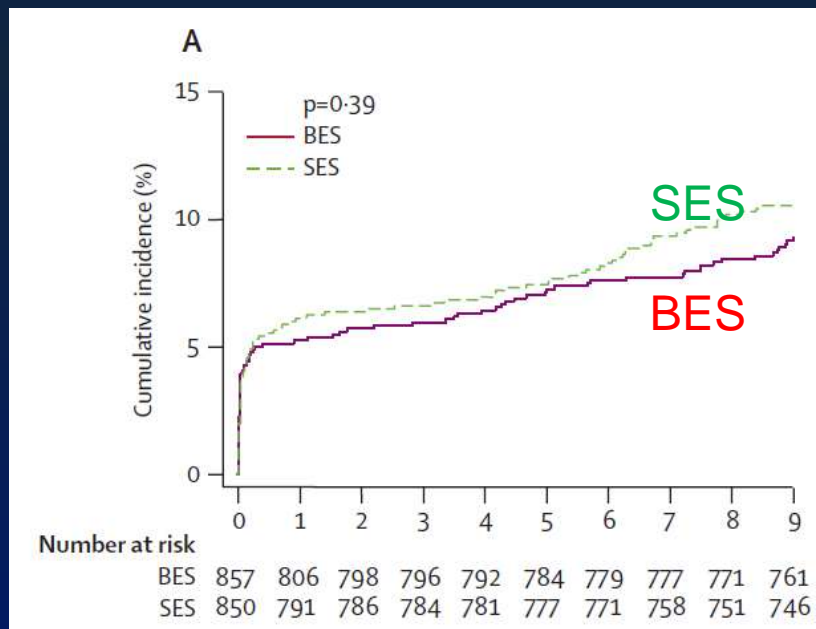
Part I.

Previous RCTs regarding Biolimus Eluting Stents

LEADERS trial in Europe

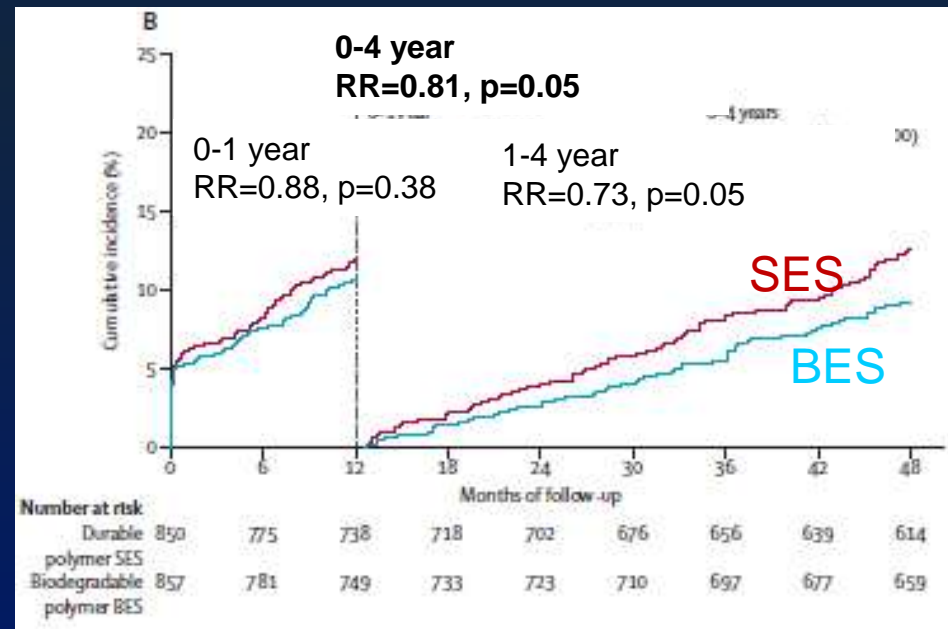
- Multicenter, assessor-blind, non-inferiority study
- Total N= 1,707 (2472 lesions)
- **BES (Biomatrix Flex) versus SES (Cypher)**
- Primary Efficacy end point: Cardiac death + MI + clinically-driven TVR at 9 months and at 4 years

At 9 months



BES (N=857) → 45 events (5.3%)
 SES (N=850) → 52 events (6.1%)

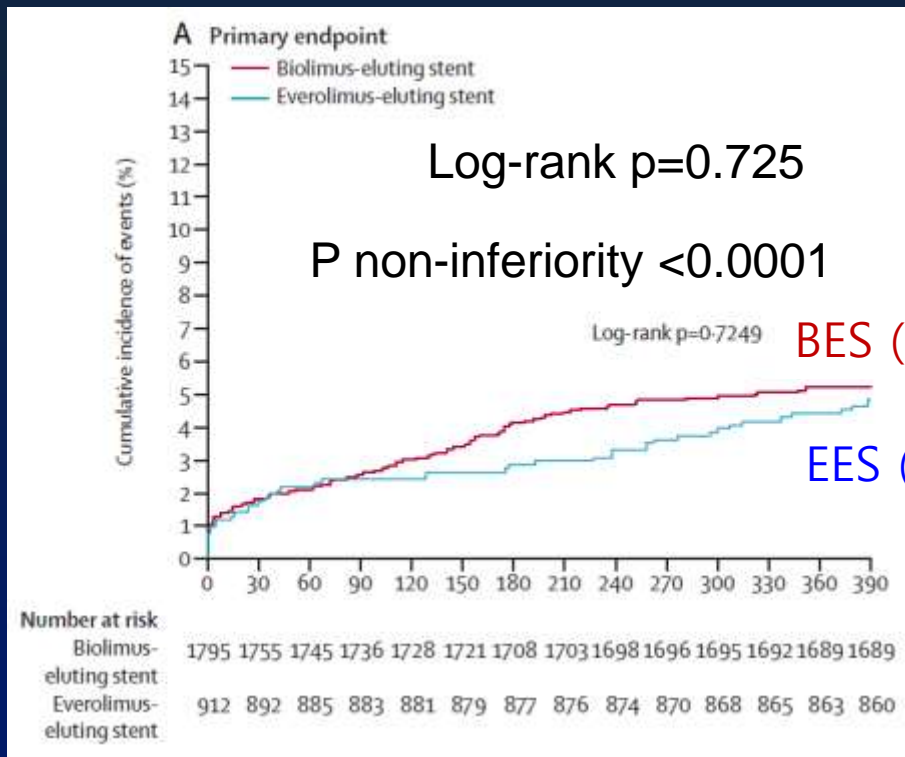
At 4 years



→ 160 events (19%)
 → 192 events (23%)

COMPARE II trial in Europe

- Open-label, prospective, randomized, controlled, non-inferiority trial
- Total N= 2,707 (4025 lesions)
(exclusion criteria :age >18YO, life expectancy > 5Y, ref.VD 2.0-4.0mm)
- **BES (Nobori) versus EES (Xience V or Promus)**
- **Primary end point:** composite of safety(cardiac death and non-fatal MI) and efficacy (clinically indicated TVR) at 12 months



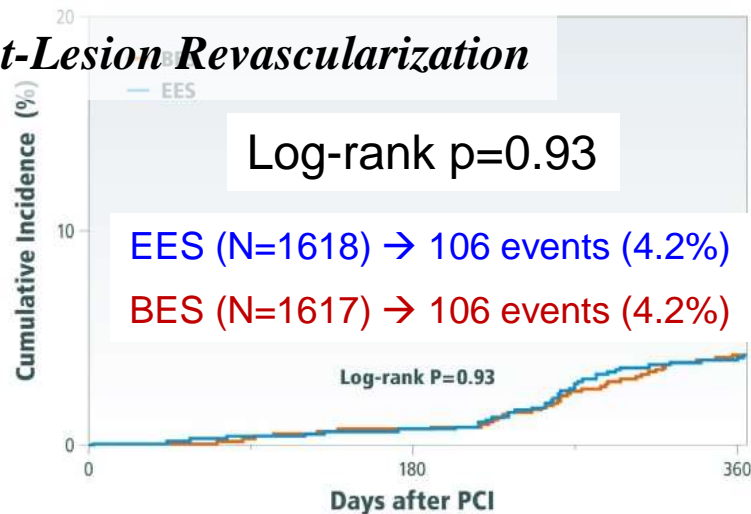
BES (N=1795) → 93 events (5.2%)

EES (N=912) → 44 events (4.8%)

NEXT trial in Japan

- Multicenter, randomized, non-inferiority trial
- Total N= 3,235 (4069 lesions) (mostly stable angina)
- **BES (Nobori) versus EES (Xience V or Promus)**
- Primary Efficacy end point: Any TLR at 1 year
Primary Safety end point: Death or Myocardial infarction at 3 years

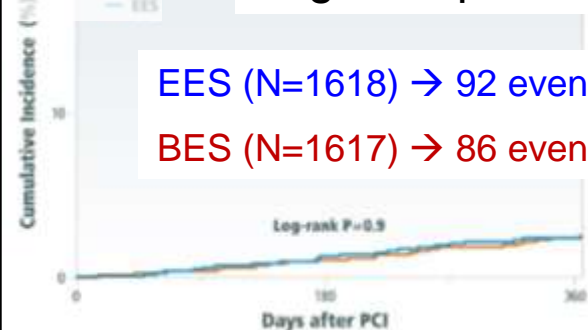
Target-Lesion Revascularization



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%

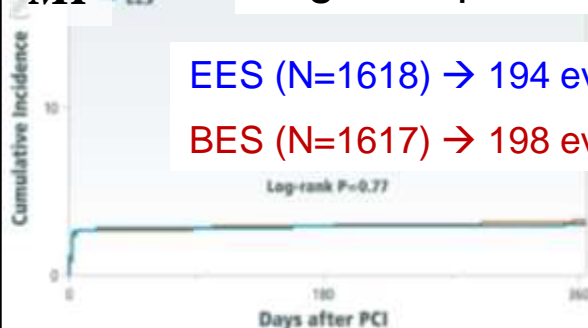
Death

Log-rank p=0.90



MI

Log-rank p=0.77



How is the BES in the real-world patients?

Part II.

**Current Status of
HOST-BIOLIMUS-3000 Korea registry**

HOST =Harmonized Optimal Strategy to Treat CAD

BES in real-world patients

Current Status of HOST-BIOLIMUS-3000 Korea registry

HOST = Harmonized Optimal Strategy to Treat CAD

Enrollment criteria for HOST-Biolimus registry

▪ Inclusion criteria

: All-comer registry of BIOLIMUS-eluting stents

(stable angina, acute coronary syndrome, silent MI)

→ Presence of more than 1 of the following

- Luminal stenosis > 50%

- No limitation for number of lesion/vessel, and vessel length

▪ Exclusion criteria

: Alleged drug allergy

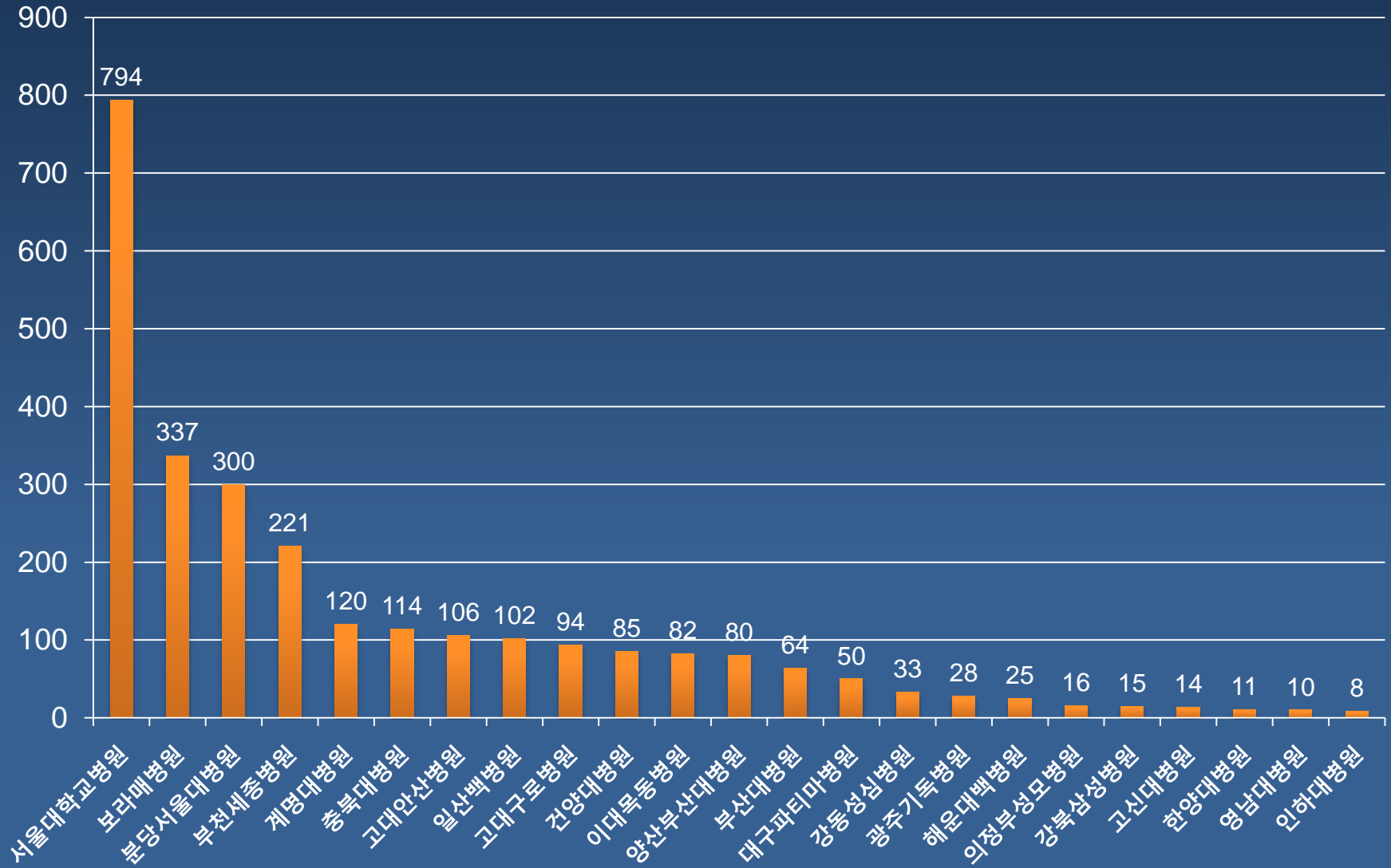
(aspirin, clopidogrel, heparin, stainless steel, sirolimus, biolimus, contrast material)

: Pregnancy

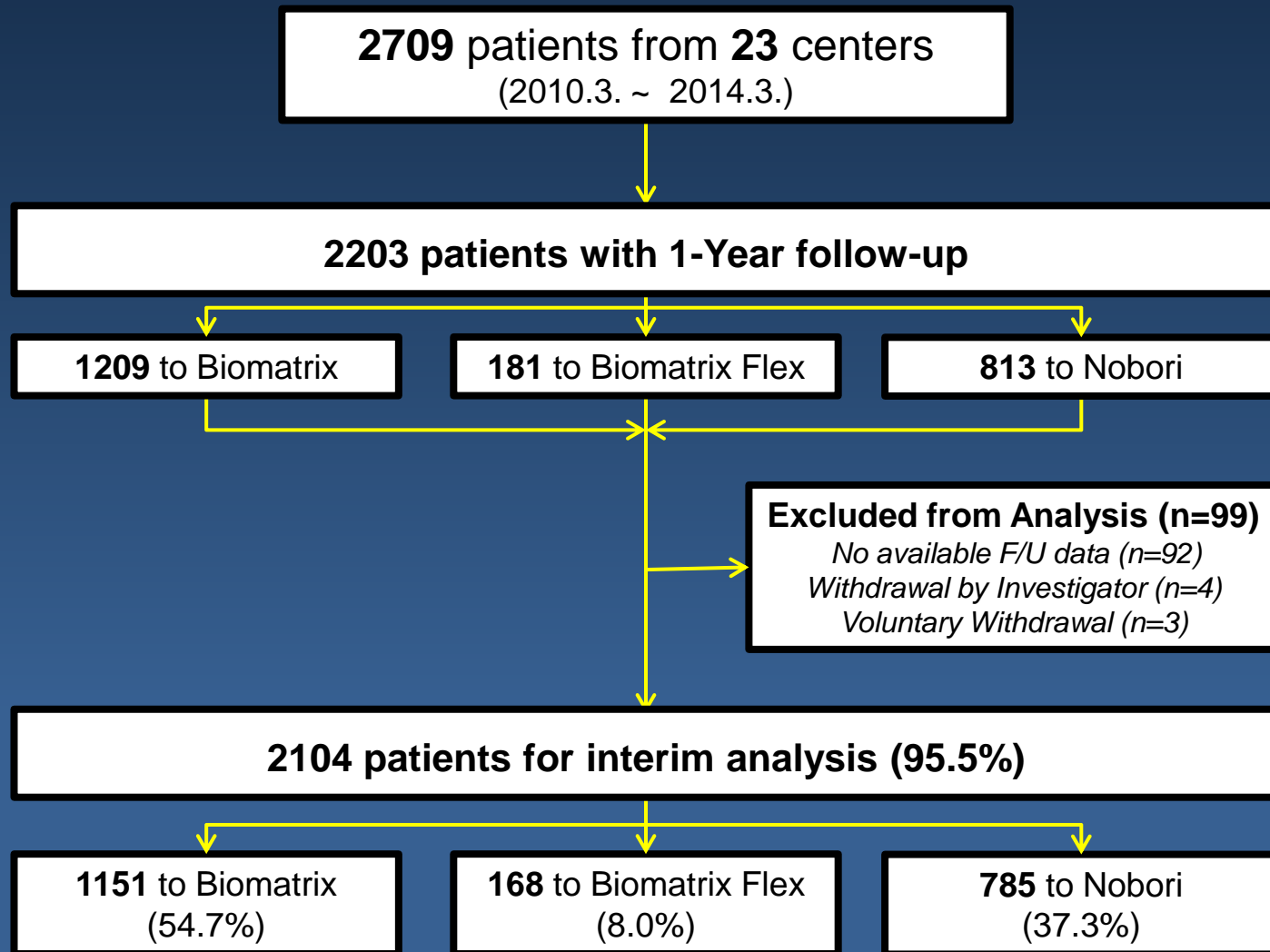
: Participants in other clinical trial

Active Participants of HOST-Biolimus registry

- Nation-wide registry, from 23 institutions of South Korea
- Number of patients = 2709 (upto 2014.3.31.)



Current status of HOST-Biolimus registry



Interim analysis

**To compare three 2nd-generation DES
with either Biodegradable or Durable Polymer**

- ▶ **BES from HOST-BIOLIMUS registry**
- ▶ **EES from EXCELLENT registry**
- ▶ **ZES-R from RESOLUTE-KOREA registry**

A. Clinical outcome in crude population

B. Clinical outcome in propensity score-matched population

C. 3 BESs in HOST-BIOLIMUS registry

D. Stent thrombosis

Study population and design to compare 3 HOST-DES cohorts

BES	EES	ZES-R
Biomatrix, Biomatrix Flex, Nobori (Biolimus-eluting stent)	Xience V/Promus (Everolimus-eluting stent)	Endeavor Resolute (Zotarolimus-eluting stent)
N=2,104	N=3,056	N=1,998

- **Follow-up** required at 1, 9, and 12 months
- ***Imaging Sub-studies at 8-12 months: Angiography ± IVUS***
(Scheduled follow-up angiography by local site protocol was allowed beyond 240 days.)
- **Primary outcome – TLF (target lesion failure)**
= cardiac death
 - + MI (not clearly attributed to a non-target vessel)
 - + clinically indicated TLR (target lesion revascularization)
- **Secondary outcome – POCO (patient-oriented composite outcome)**
= all-cause mortality
 - + any MI
 - + any revascularization

Clinical outcome in crude population in 3 second-generation DES cohorts

Baseline characteristics

	BES (N= 2,104)	EES (N= 3,056)	ZES-R (N= 1,998)
Demographics			
Age (years)	64.0 ± 11.0	63.9 ± 10.8	63.9 ± 10.9
Male gender	1487 (70.7%)	2053 (67.2%)	1366 (68.4%)
BMI (kg/m ²)	24.3 ± 10.6	25.0 ± 11.8	24.8 ± 3.1
Coexisting conditions			
Diabetes	718 (34.1%)	1149 (37.9%)	706 (35.3%)
Hypertension	1243 (59.1%)	1980 (65.4%)	1271 (63.6%)
Dyslipidemia	1342 (63.8%)	1850 (64.0%)	1418 (71.0%)
Peripheral artery disease	36 (1.7%)	47 (1.6%)	33 (1.7%)
Chronic kidney disease	78 (3.7%)	105 (3.5%)	81 (4.1%)
Risk factors			
Current smoker	619 (29.4%)	893 (29.8%)	613 (31.1%)
Prev. PCI	291 (13.8%)	440 (14.5%)	317 (15.9%)
Prev. CABG	34 (1.6%)	56 (1.8%)	31 (1.6%)
Prev. MI	104 (4.9%)	212 (7.0%)	114 (5.7%)
Prev. CHF	44 (2.1%)	62 (2.1%)	40 (2.0%)
Prev. CVA	169 (8.0%)	250 (8.3%)	145 (7.3%)
FHx. of coronary disease	120 (5.7%)	171 (5.9%)	92 (4.6%)
LV EF (%)	59.4 ± 11.0	59.3 ± 11.4	58.0 ± 11.4

Baseline characteristics

	BES (N= 2,104)	EES (N= 3,056)	ZES-R (N= 1,998)
Clinical indication of PCI			
Stable angina	746 (35.5%)	1113 (36.4%)	601 (30.1%)
Unstable angina	633 (30.1%)	1117 (36.6%)	739 (37.0%)
NSTEMI	318 (15.5%)	344 (11.3%)	280 (14.0%)
STEMI	326 (15.5%)	385 (12.6%)	321 (16.1%)
Silent ischemia	81 (3.8%)	97 (3.2%)	57 (2.9%)
Complexity of CAD			
Disease extent			
1VD	925 (44.0%)	1424 (46.7%)	783 (39.3%)
2VD	666 (31.7%)	923 (30.3%)	674 (33.9%)
3VD	513 (24.4%)	699 (22.9%)	534 (26.8%)
Number of treated lesion	1.4 ± 0.7	1.5 ± 0.7	1.5 ± 0.8
Lesion characteristics			
ISR as target lesion	96 (4.6%)	231 (7.6%)	142 (7.1%)
Bifurcation	703 (33.4%)	388 (12.7%)	444 (22.2%)
Thrombotic lesion	268 (12.7%)	293 (9.6%)	268 (13.4%)
Long lesion (≥28mm)	749 (35.6%)	1240 (40.6%)	975 (48.8%)
Small vessel (≤2.75mm)	455 (21.6%)	612 (20.0%)	421 (21.1%)
Lt. main disease	101 (4.8%)	172 (5.6%)	77 (3.9%)

Baseline characteristics

	BES (N= 2,104)	EES (N= 3,056)	ZES-R (N= 1,998)
Procedural characteristics			
Off-label* use	1876 (89.2%)	2217 (72.5%)	1613 (80.7%)
Multi-vessel PCI	379 (18.0%)	930 (30.4%)	639 (32.0%)
IVUS-guided procedure	747 (35.5%)	1134 (37.1%)	777 (38.9%)
Cardiogenic shock	1 (<0.1%)	16 (0.5%)	25 (1.3%)
Tamponade	1 (<0.1%)	3 (0.1%)	2 (0.1%)
Dissection	8 (0.4%)	5 (0.2%)	4 (0.2%)
Medication at discharge			
Aspirin	2075 (98.6%)	2969 (98.0%)	1960 (98.6%)
Clopidogrel	2076 (98.7%)	2974 (98.2%)	1963 (98.6%)
Beta-blockers	1417 (67.3%)	1853 (61.6%)	1306 (66.6%)
ACE inhibitors	750 (35.6%)	1113 (37.0%)	730 (37.3%)
ARBs	605 (28.8%)	939 (31.1%)	623 (32.4%)
Statins	1842 (87.5%)	2613 (86.4%)	1722 (87.2%)
Calcium antagonists	495 (23.5%)	830 (27.5%)	513 (26.8%)

* “Off-label” indication of BES ;

serum creatinine concentration ≥ 140 $\mu\text{mol/L}$ (1.6 mg/dL), left ventricular ejection fraction (LVEF) $< 30\%$, an acute MI within the previous 72 hours, more than one lesion per vessel, two or more vessels treated with a stent, a lesion length ≥ 28 mm, or a bifurcated lesion, bypass graft, in-stent restenosis, unprotected left main coronary artery, presence of thrombus, or total occlusion.

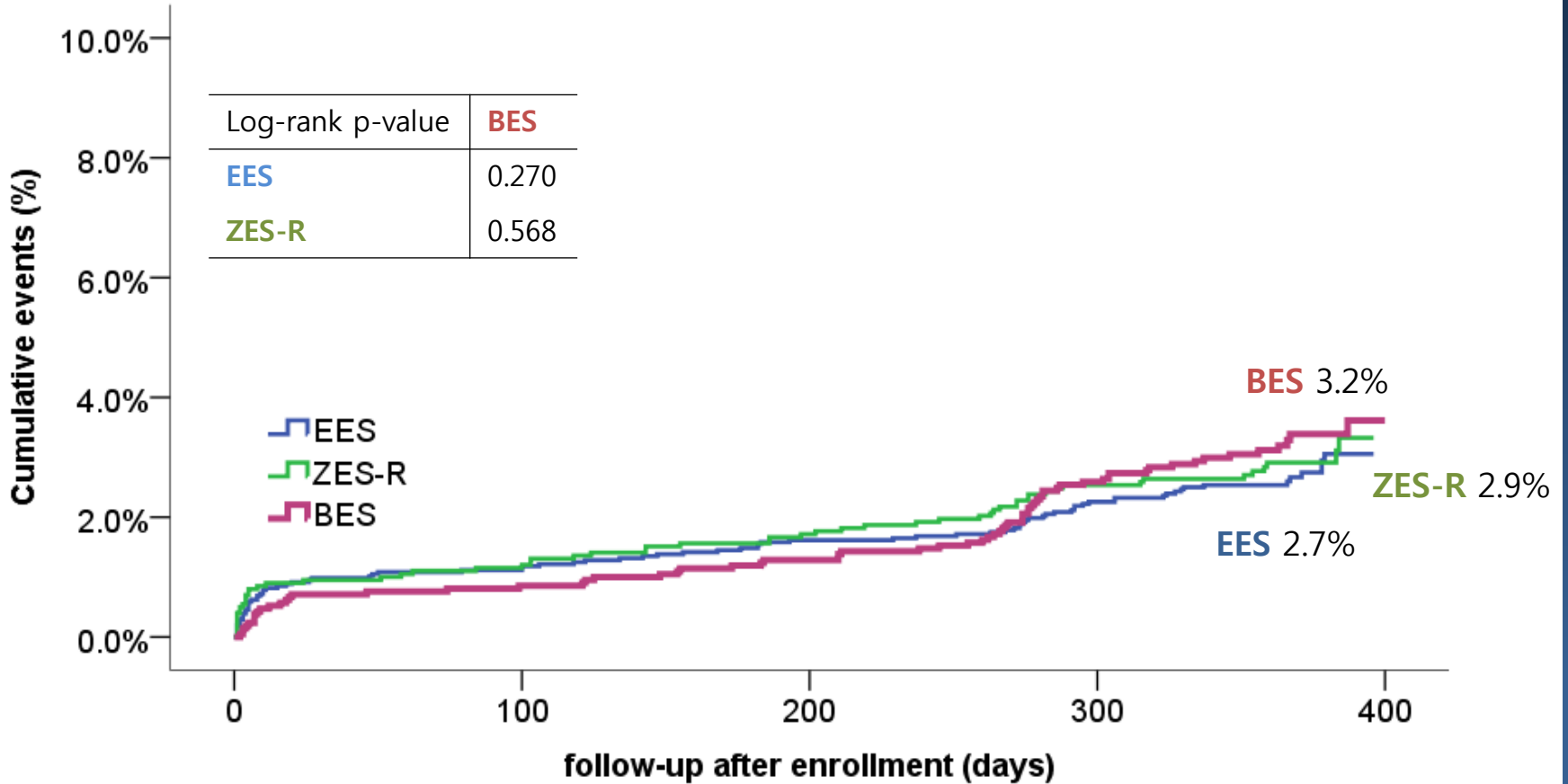
1 Year Clinical Outcomes

	BES	EES	ZES-R	BES vs. EES		BES vs. ZES-R	
	(N= 2,104)	(N= 3,056)	(N= 1,998)	RR	P-value	RR	P-value
Mortality							
All-cause death	43 (2.0%)	62 (2.0%)	46 (2.3%)	1.01 (0.68-1.49)	0.970	0.89 (0.58-1.35)	0.570
Cardiac death	20 (1.0%)	37 (1.2%)	28 (1.4%)	0.78 (0.45-1.35)	0.380	0.68 (0.38-1.20)	0.180
Myocardial infarction (MI)							
Any MI	15 (0.7%)	17 (0.6%)	8 (0.4%)	1.28 (0.64-2.58)	0.481	1.79 (0.76-4.22)	0.180
Target vessel MI	9 (0.4%)	14 (0.5%)	5 (0.3%)	0.93 (0.40-2.16)	0.872	1.71 (0.57-5.12)	0.330
MI due to stent thrombosis	3 (0.1%)	7 (0.2%)	3 (0.2%)	0.62 (0.16-2.41)	0.488	0.95 (0.19-4.71)	0.949
Repeated Revascularization (RR)							
Any RR	97 (4.6%)	161 (5.3%)	106 (5.3%)	0.87 (0.67-1.13)	0.286	0.86 (0.65-1.14)	0.305
Clinically driven RR	77 (3.7%)	120 (3.9%)	73 (3.7%)	0.93 (0.69-1.24)	0.623	1.00 (0.72-1.39)	0.992
Target vessel revascularization (TVR)	78 (3.7%)	102 (3.3%)	80 (4.0%)	1.12 (0.83-1.51)	0.477	0.92 (0.67-1.27)	0.622
Target lesion revascularization (TLR)	47 (2.2%)	40 (1.3%)	28 (1.4%)	1.72 (1.13-2.64)	0.011	1.61 (1.00-2.58)	0.047
Cerebrovascular accidents (CVA)	12 (0.6%)	18 (0.6%)	12 (0.6%)	0.97 (0.47-2.01)	0.931	0.95 (0.43-2.12)	0.899
TLF	68 (3.2%)	82 (2.7%)	58 (2.9%)	1.21 (0.87-1.68)	0.249	1.12 (0.78-1.60)	0.542
POCO	144 (6.8%)	225 (7.4%)	153 (7.7%)	0.92 (0.74-1.15)	0.478	0.89 (0.70-1.12)	0.315

TLF (target lesion failure); cardiac death + MI (not clearly attributed to a non-target vessel) + clinically driven TLR
 POCO (patient-oriented composite outcome); all-cause mortality + any MI + any RR

1 Year Clinical Outcomes

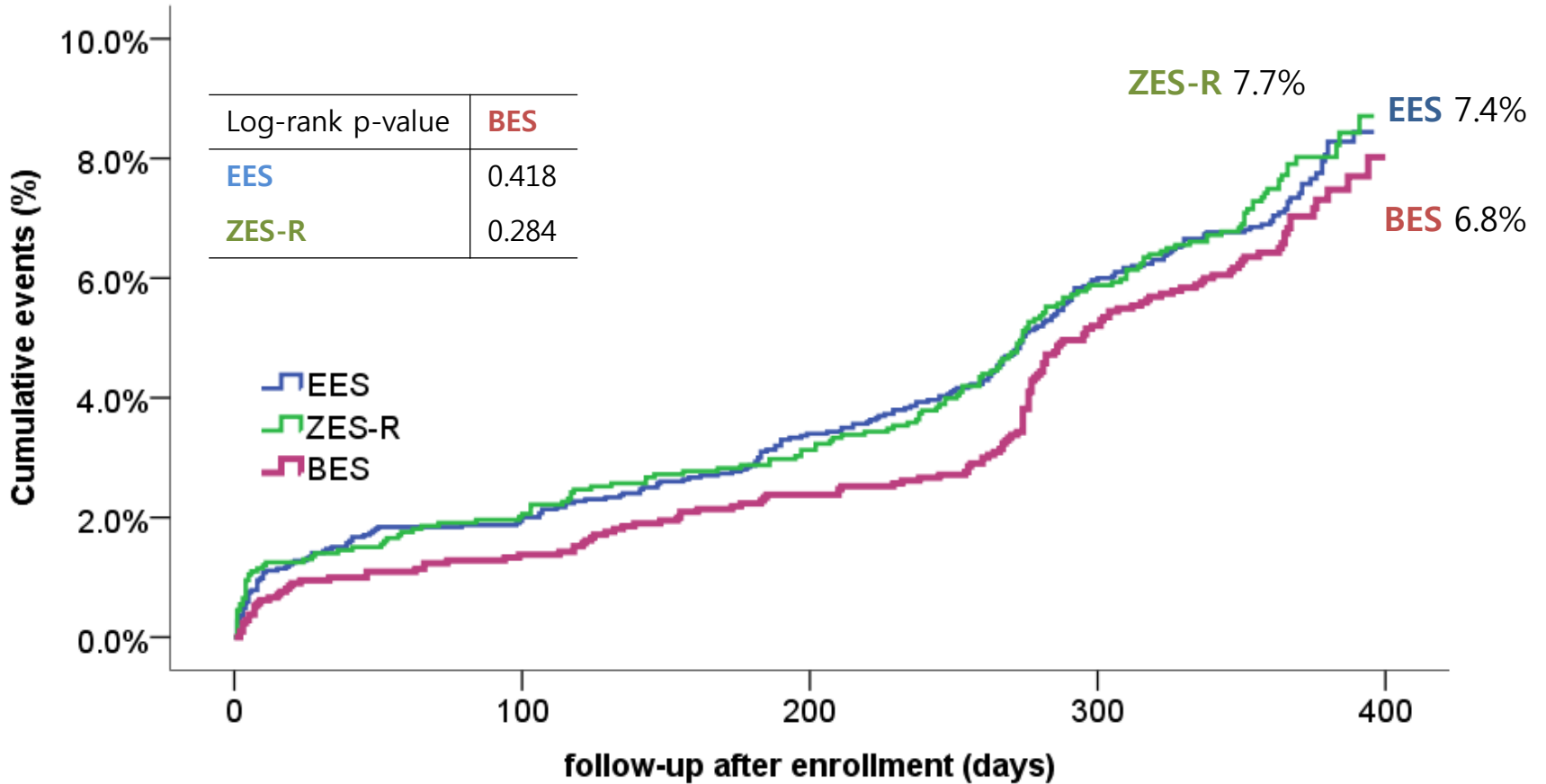
TLF (Target Lesion Failure) in 3 HOST-DES cohorts



Patients at risk	0	30	180	270	365 (days)
EES	3056	3001	2952	2927	1588
ZES-R	1998	1956	1928	1905	1038
BES	2104	2083	2063	2038	1074

1 Year Clinical Outcomes

POCO (Patient-Oriented Composite Outcome) in 3 HOST-DES cohorts

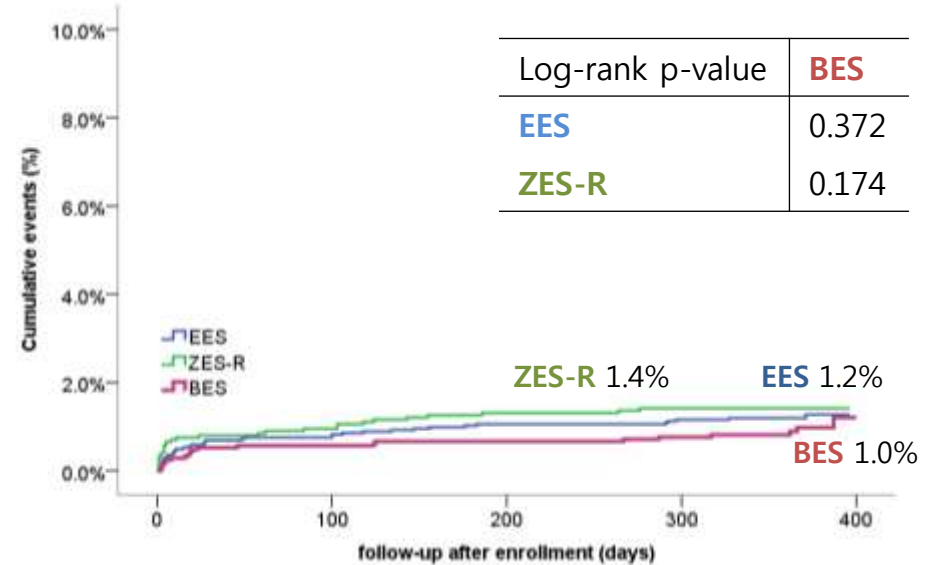
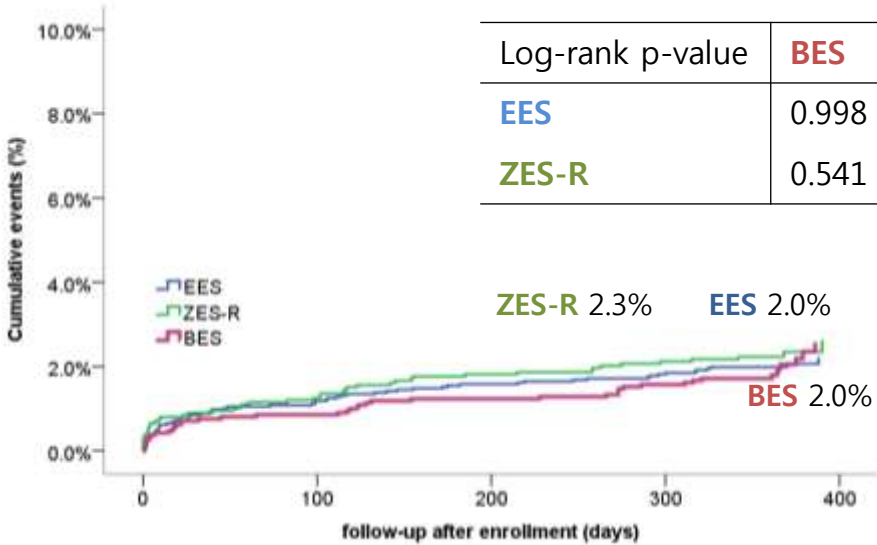


Patients at risk	0	30	180	270	365 (days)
EES	3056	2994	2927	2859	1527
ZES-R	1998	1949	1912	1866	998
BES	2104	2082	2053	2020	1050

Individual components of TLF and POCO

All-cause death

Cardiac death



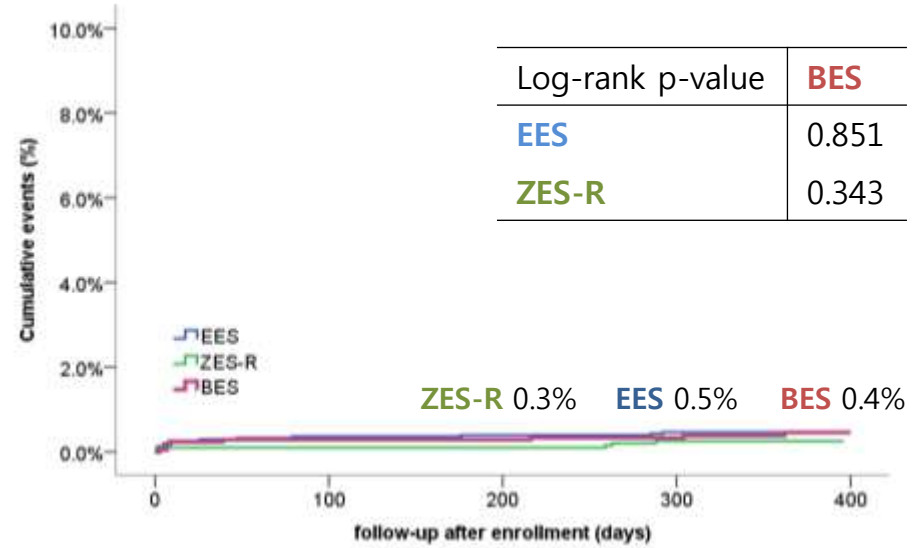
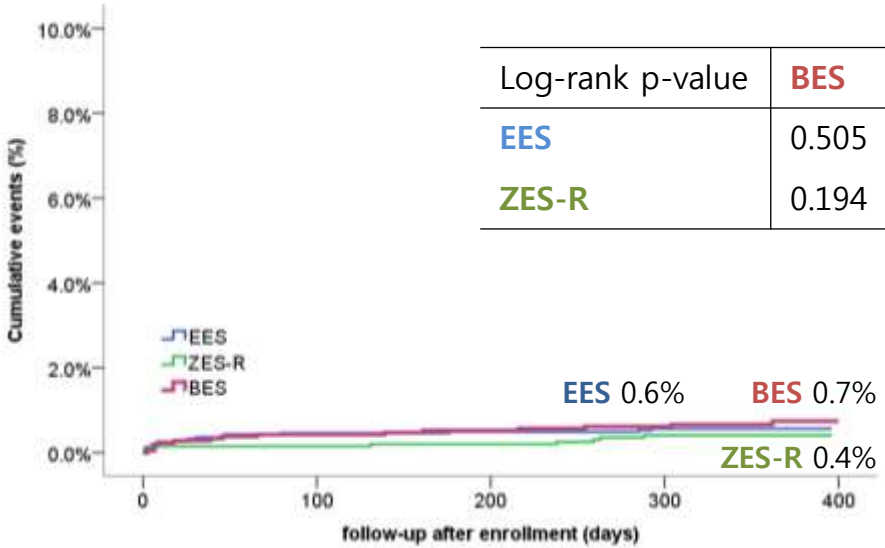
Patients at risk	0	30	180	270	365 (days)
EES	3056	3010	2966	2948	1611
ZES-R	1998	1959	1934	1920	1044
BES	2104	2088	2075	2065	1103

Patients at risk	0	30	180	270	365 (days)
EES	3056	3010	2966	2948	1611
ZES-R	1998	1959	1934	1920	1044
BES	2104	2088	2075	2065	1103

Individual components of TLF and POCO

All events of MI

Target vessel MI



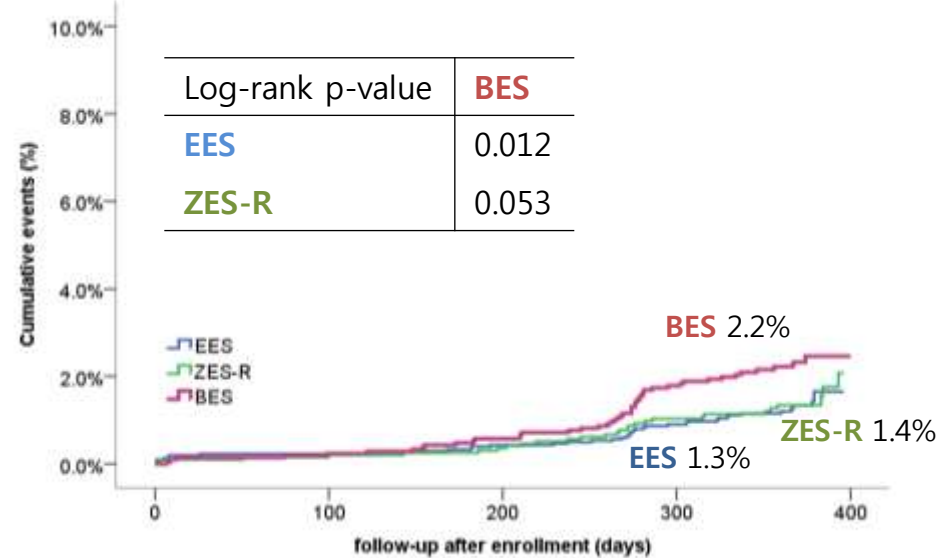
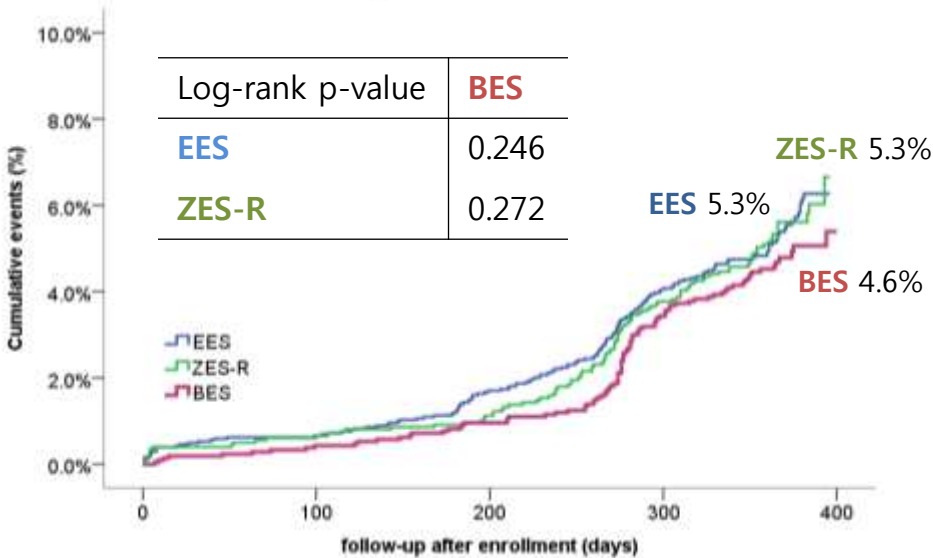
Patients at risk	0	30	180	270	365 (days)
EES	3056	3007	2968	2952	1609
ZES-R	1998	1956	1933	1917	1041
BES	2104	2096	2089	2079	1113

Patients at risk	0	30	180	270	365 (days)
EES	3056	3003	2957	2940	1605
ZES-R	1998	1957	1931	1915	1041
BES	2104	2096	2092	2083	1114

Individual components of TLF and POCO

Any revascularization

TLR (Target Lesion Revascularization)



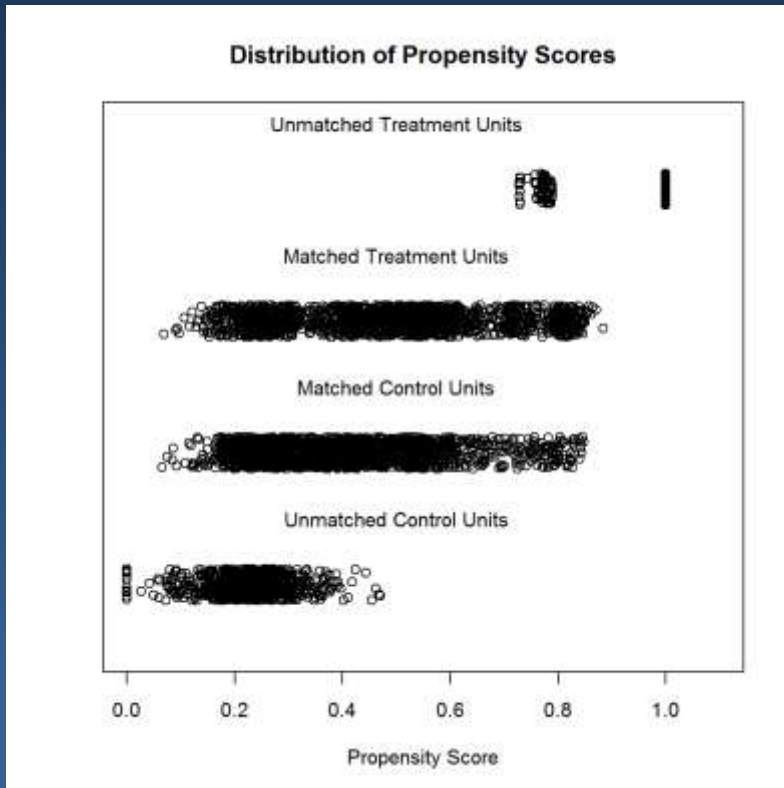
Patients at risk	Any revascularization					TLR (Target Lesion Revascularization)				
	0	30	180	270	365 (days)	0	30	180	270	365 (days)
EES	3056	2997	2933	2865	1531	3056	3009	2971	2946	1598
ZES-R	1998	1951	1916	1869	1002	1998	1957	1929	1906	1039
BES	2104	2085	2060	2028	1053	2104	2086	2067	2042	1075

* Rate of f/u angiography in HOST-BIOLIMUS registry ; 41.5% (873/2104)
 (cf. mandatory 9 mo. f/u angiography ; 22.8% (479/2104))

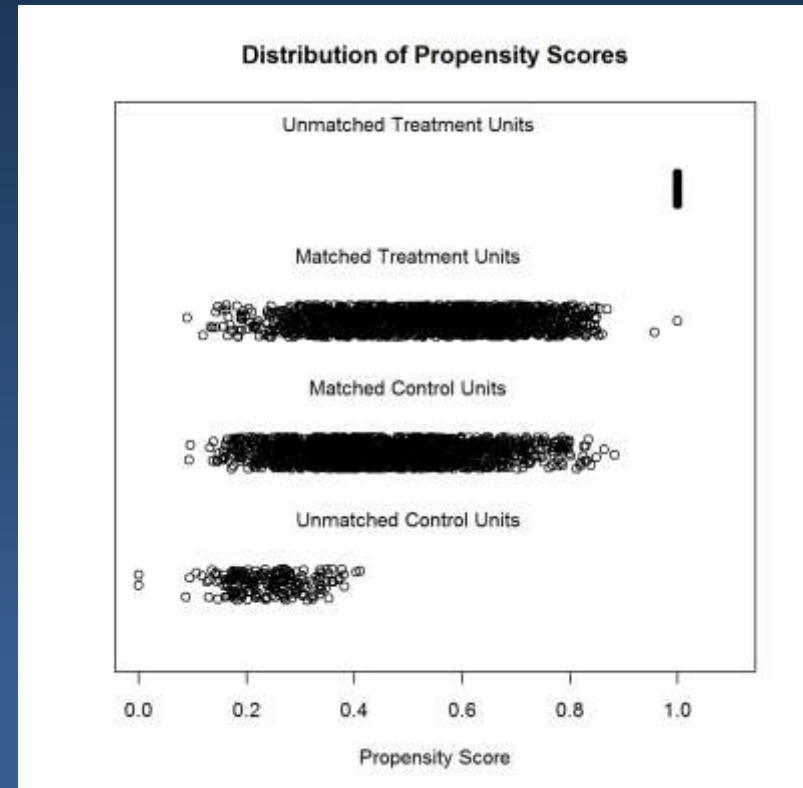
Clinical outcome
in propensity score-matched population
BES vs. EES
BES vs. ZES-R

Propensity score matching

BES vs. EES
1:1 matching (N=1,676)



BES vs. ZES-R
1:1 matching (N=1,755)



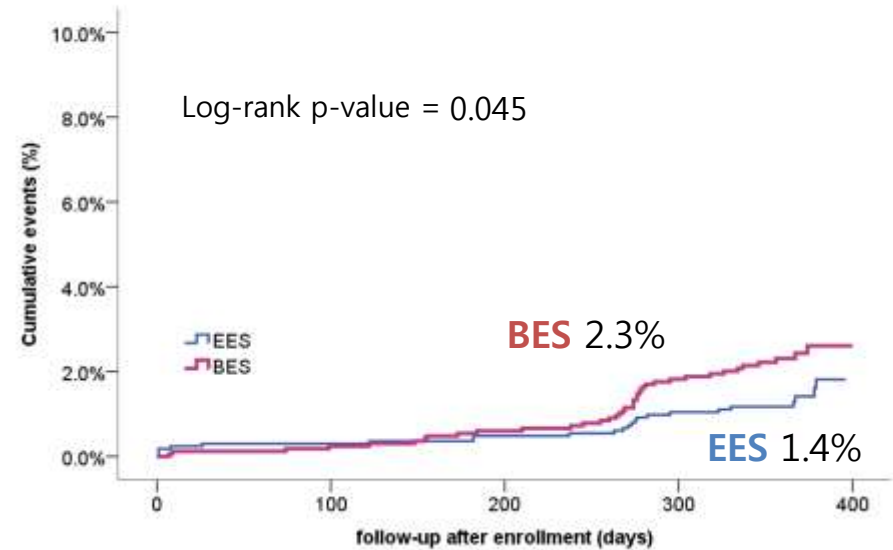
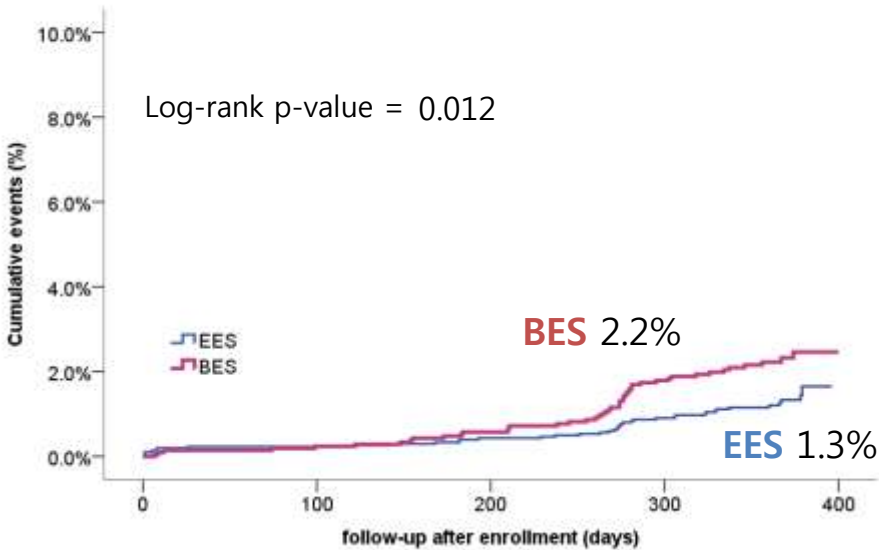
* Variables for logistic regression to calculate propensity score;
gender, age, hypertension, diabetes mellitus, current smoker, dyslipidemia(\pm statin), chronic renal failure, peripheral vascular disease, family history of coronary disease, severe left ventricular dysfunction (LVEF<30%), value of serum creatinine, history of previous coronary intervention or bypass surgery / MI / CHF / CVA, burden of coronary disease (number of involved vessels, Lt. main disease, in-stent restenosis as target lesion, bifurcation lesion, long lesion (\geq 28mm), small vessel (diameter <2.75mm), presence of thrombus), use of GP IIb/IIIa inhibitor, off-label usage of BES, multi-lesion PCI, clinical indication for PCI

Clinically-driven TLR after propensity score matching, BES vs. EES

* 1,676 patients from each cohort after matching

TLR in crude population

TLR in matched patients



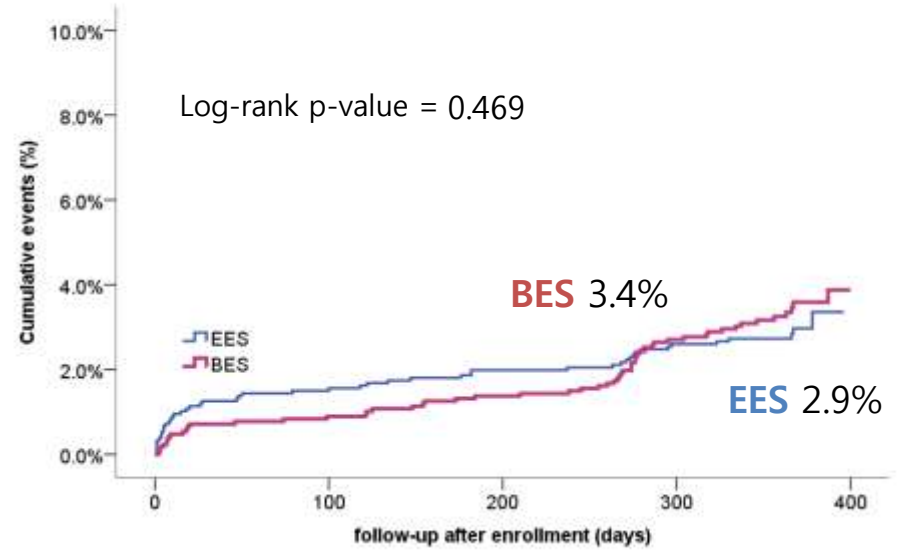
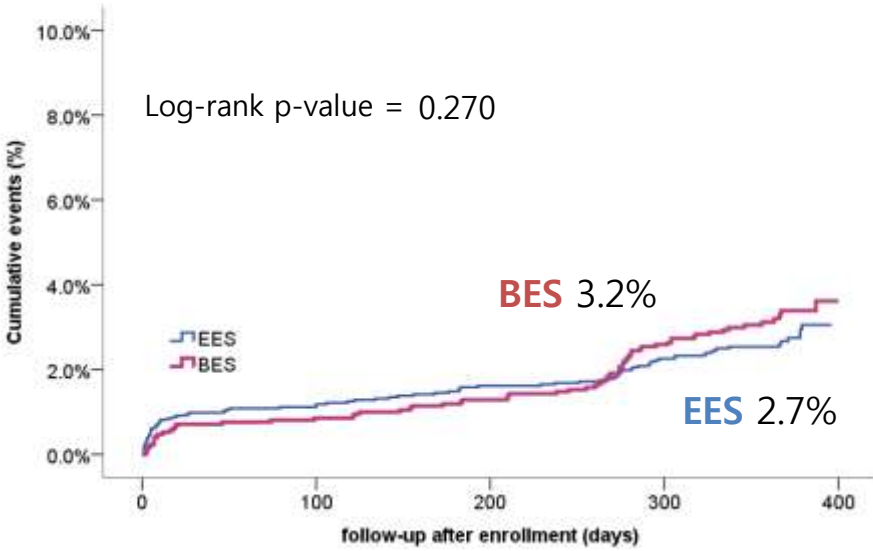
Patients at risk	Crude Population					Matched Patients				
	0	30	180	270	365 (days)	0	30	180	270	365 (days)
EES	3056	3009	2971	2946	1598	1676	1645	1622	1604	863
BES	2104	2086	2067	2042	1075	1676	1663	1646	1625	857

TLF after matching, BES vs. EES

* 1,676 patients from each cohort after matching

TLF in crude population

TLF in matched patients



Patients at risk	0	30	180	270	365 (days)
EES	3056	3001	2952	2927	1588
BES	2104	2083	2063	2038	1074

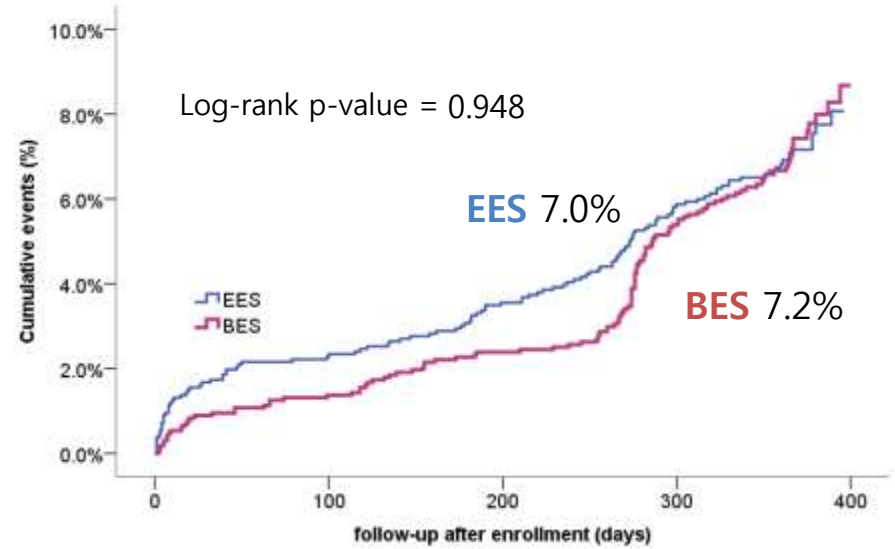
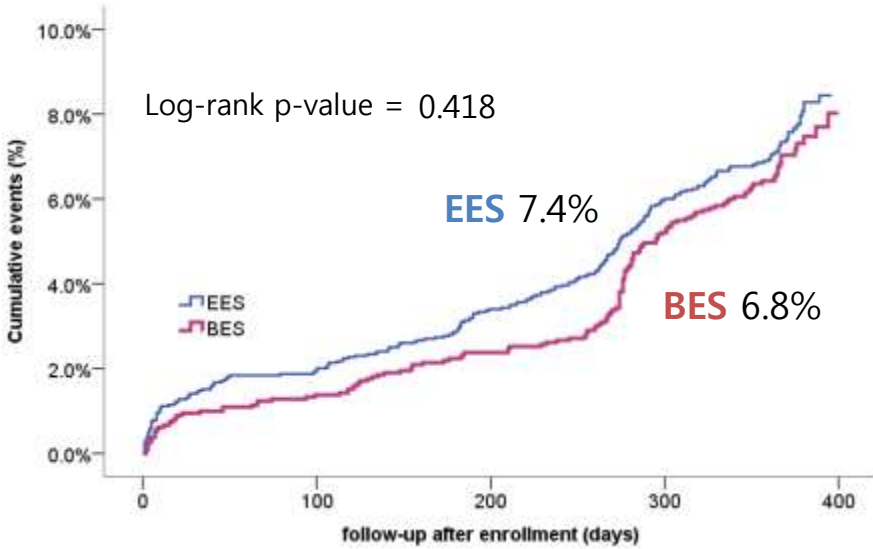
Patients at risk	0	30	180	270	365 (days)
EES	1676	1640	1610	1593	858
BES	1676	1661	1643	1622	856

POCO after matching, BES vs. EES

* 1,676 patients from each cohort after matching

POCO in crude population

POCO in matched patients



Patients at risk	0	30	180	270	365 (days)
EES	3056	2994	2927	2859	1527
BES	2104	2082	2053	2020	1050

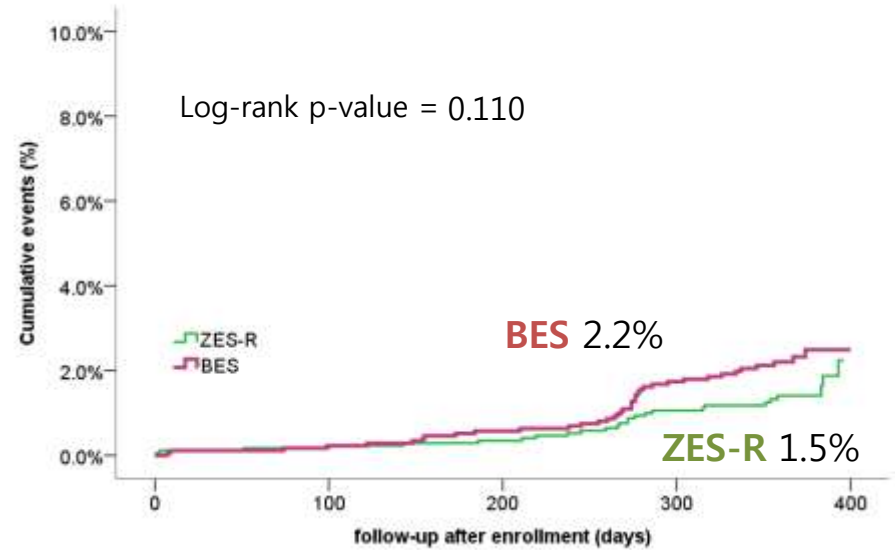
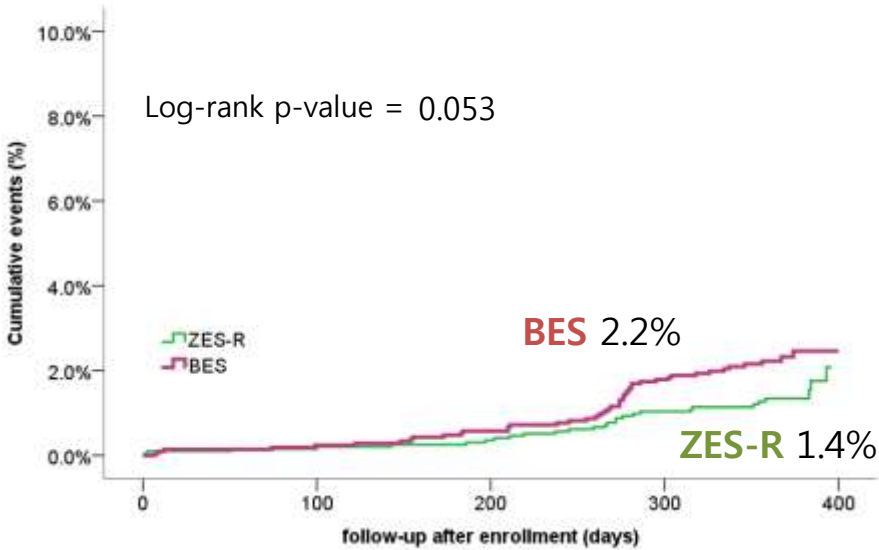
Patients at risk	0	30	180	270	365 (days)
EES	1676	1635	1597	1560	831
BES	1676	1660	1636	1608	834

Clinically-driven TLR after propensity score matching, BES vs. ZES-R

* 1,755 patients from each cohort after matching

TLR in crude population

TLR in matched patients



Patients at risk	0	30	180	270	365 (days)
ZES-R	1998	1957	1929	1906	1039
BES	2104	2086	2067	2042	1075

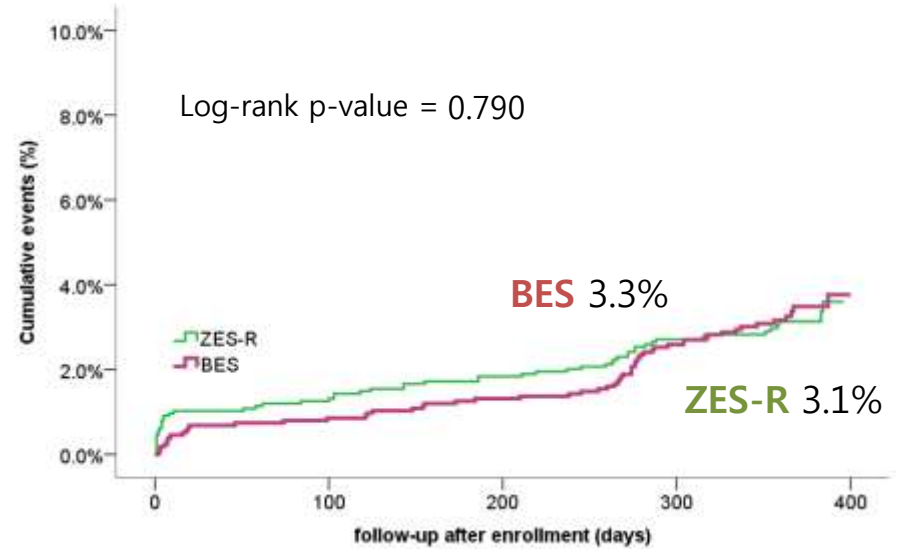
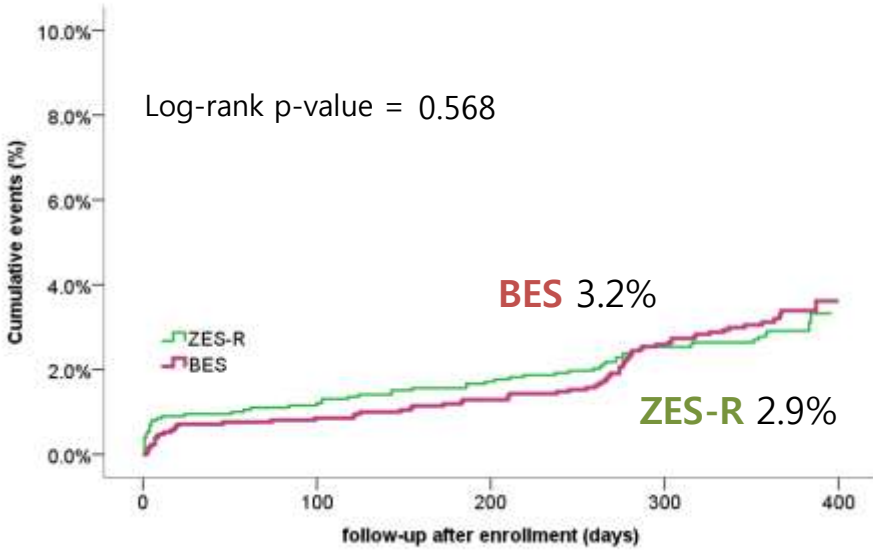
Patients at risk	0	30	180	270	365 (days)
ZES-R	1755	1721	1696	1678	922
BES	1755	1742	1724	1703	898

TLF after matching, BES vs. ZES-R

* 1,755 patients from each cohort after matching

TLF in crude population

TLF in matched patients



Patients at risk	0	30	180	270	365 (days)
ZES-R	1998	1956	1928	1905	1038
BES	2104	2083	2063	2038	1074

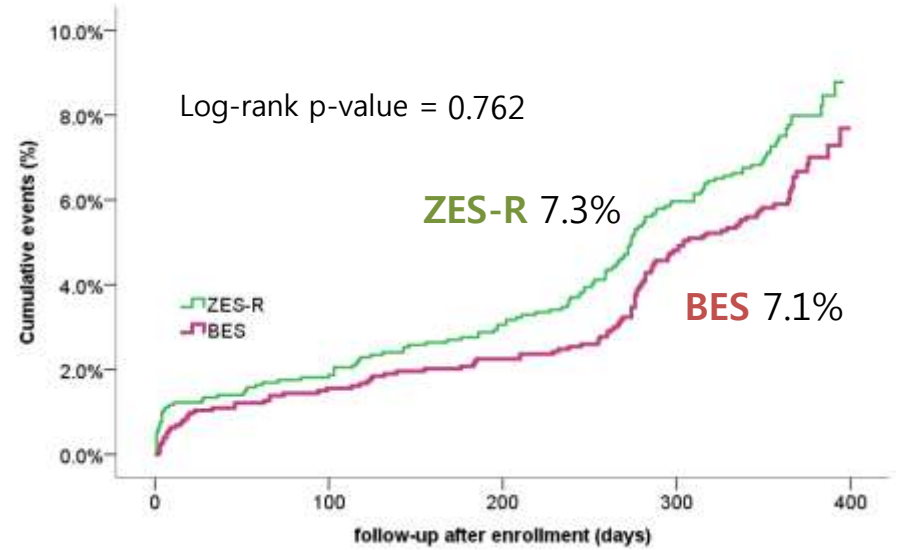
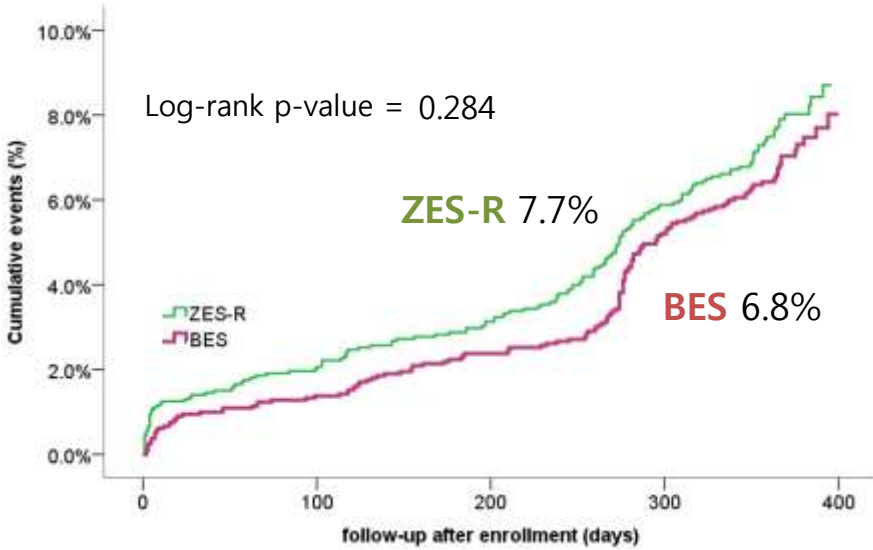
Patients at risk	0	30	180	270	365 (days)
ZES-R	1755	1720	1695	1677	920
BES	1755	1740	1721	1700	897

POCO after matching, BES vs. ZES-R

* 1,755 patients from each cohort after matching

POCO in crude population

POCO in matched patients

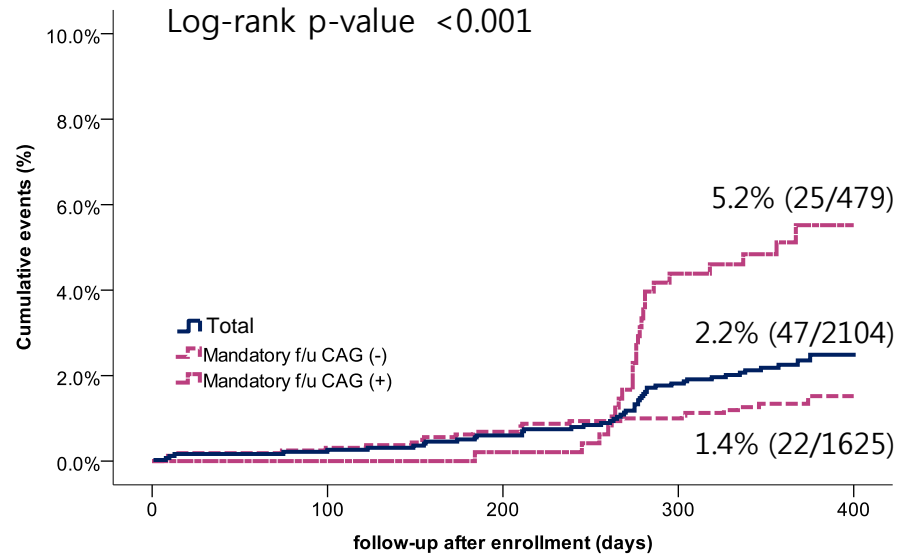
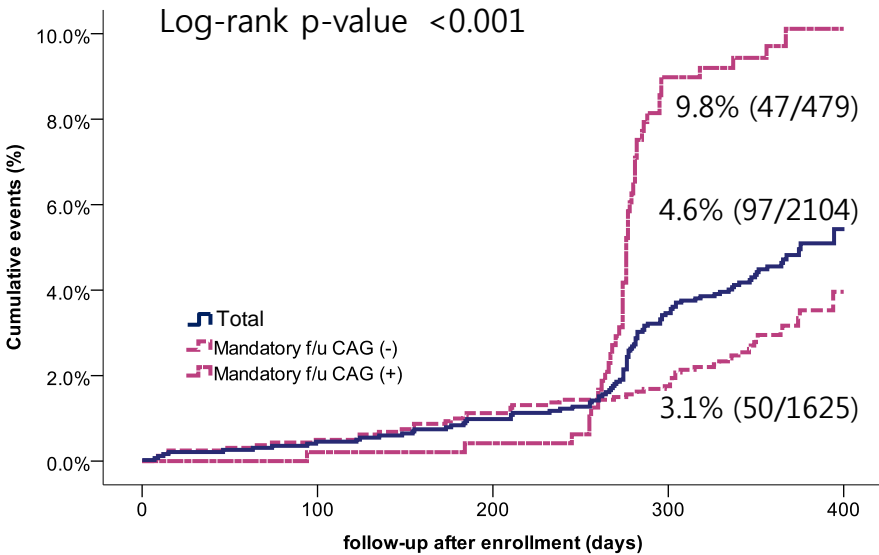


Patients at risk	Crude Population					Matched Patients				
	0	30	180	270	365 (days)	0	30	180	270	365 (days)
ZES-R	1998	1949	1912	1866	998	1755	1714	1681	1646	892
BES	2104	2082	2053	2020	1050	1755	1739	1714	1686	875

Impact on TLR of mandatory f/u angiography at 9 mo.

Any revascularization

TLR



Patients at risk	0	30	180	270	365 (days)
f/u CAG (+)	479	479	478	465	247
f/u CAG (-)	1625	1606	1582	1563	805
Total	2104	2085	2060	2028	1053

Patients at risk	0	30	180	270	365 (days)
f/u CAG (+)	479	479	479	471	261
f/u CAG (-)	1625	1607	1588	1571	814
Total	2104	2086	2067	2042	1075

* Rate of f/u angiography in HOST-BIOLIMUS registry ; 41.5% (873/2104) (cf. mandatory 9 mo. f/u angiography ; 22.8% (479/2104))

Stent thrombosis

in 3 DES cohorts within 1 year f/u

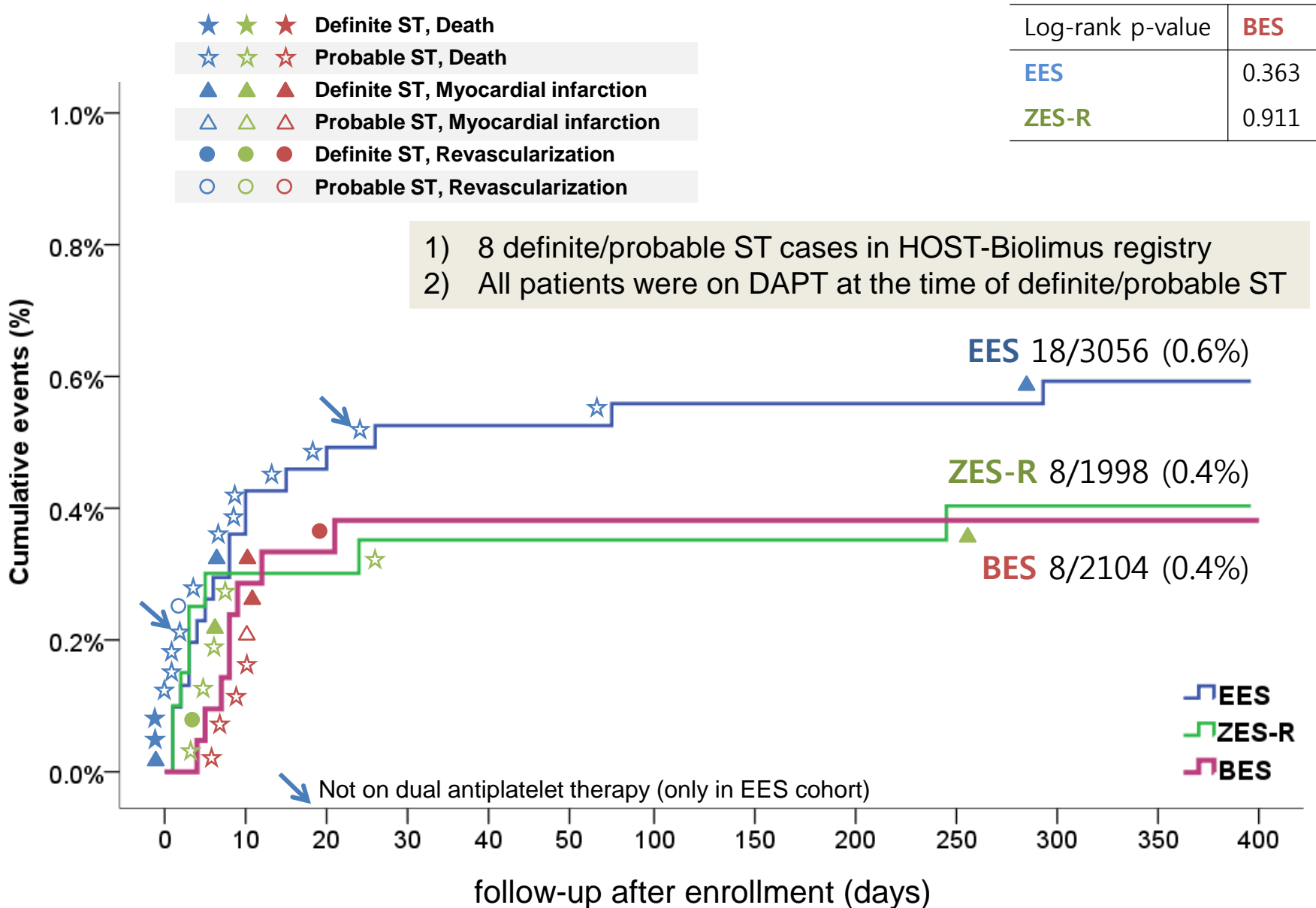
Stent thrombosis (ST)

	BES	EES	ZES-R	P-values for BES vs.	
	(N= 2,104)	(N= 3,056)	(N= 1,998)	EES	ZES-R
Definite ST	3 (0.1%)	6 (0.2%)	3 (0.2%)	0.746	1.000
Acute (0-1 day)	0 (0%)	3 (0.1%)	1 (0.1%)	0.275	0.487
Subacute (2-30 days)	3 (0.1%)	2 (0.1%)	1 (0.1%)	0.404	0.625
Late (31-365 days)	0 (0%)	1 (<0.1%)	1 (0.1%)	1.000	0.487
Probable ST	5 (0.2%)	12 (0.4%)	5 (0.3%)	0.340	1.000
Acute	0 (0%)	1 (<0.1%)	3 (0.2%)	1.000	0.115
Subacute	5 (0.2%)	10 (0.3%)	2 (0.1%)	0.557	0.454
Late	0 (0%)	1 (<0.1%)	0 (0%)	1.000	-
ST, definite or probable	8 (0.3%)	18 (0.6%)	8 (0.4%)	0.298	0.874
Possible ST	3 (0.1%)	0 (0%)	0 (0%)	0.068	0.250

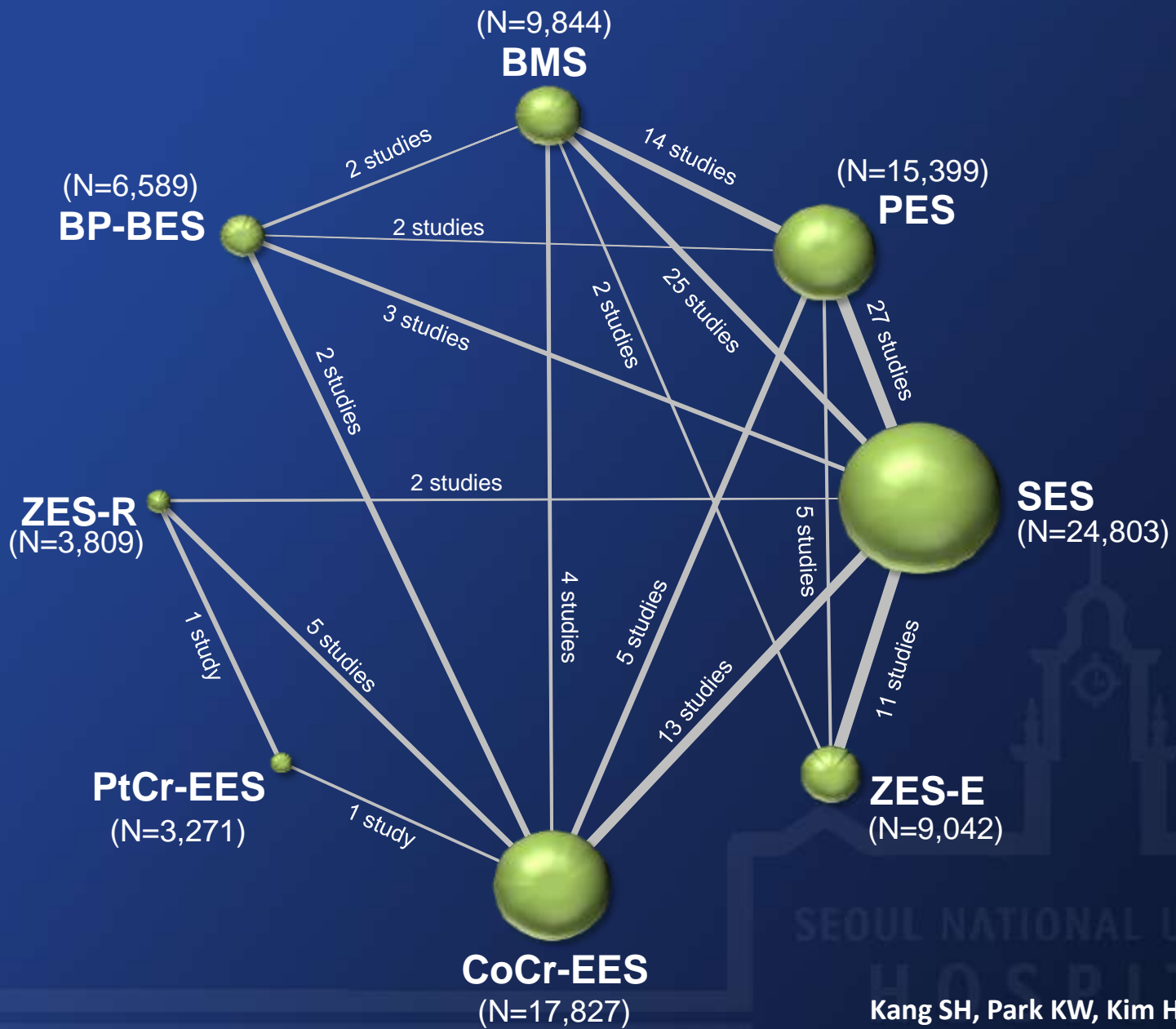
Duration of dual antiplatelet therapy (DAPT %, among the reported patients)

DAPT at discharge	2085 (99.1%)	2935 (97.0%)	1953 (98.2%)	<0.001	0.016
Upto 9 months	1963 (93.3%)	2638 (93.2%)	1702 (93.2%)	0.954	0.911
Upto 1 year	1878 (89.3%)	2264 (81.5%)	1436 (80.0%)	<0.001	<0.001

Definite/probable ST according to the ARC definition



Network Plot of Included Trials: 113 trials 90584 patients

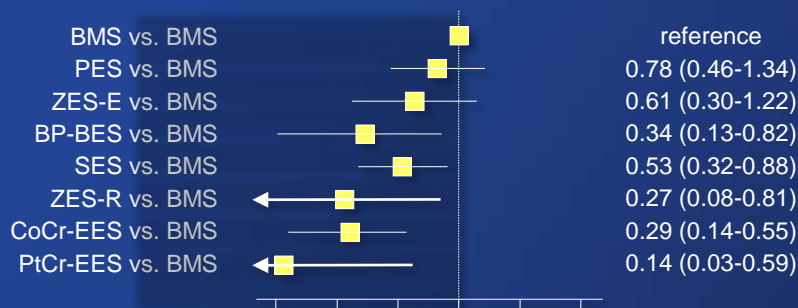


- Polygonal network configuration with mixed connections
- Almost fully closed loops with limited comparisons of PtCr-EES and ZES-R

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Definite or Probable ST with Reference to BMS

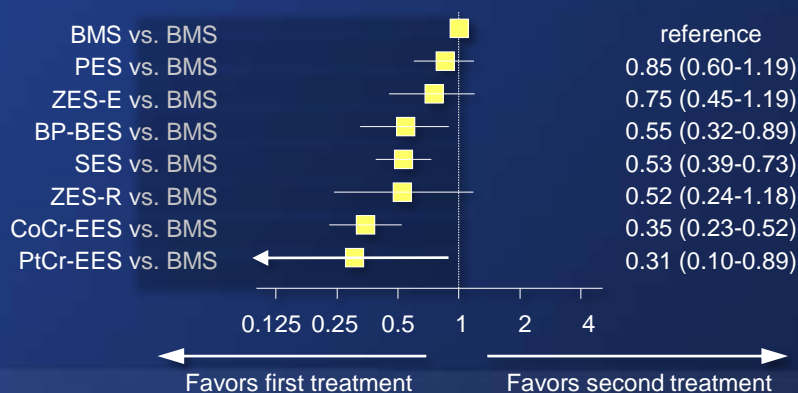
(A) Early ST (≤ 30 days)



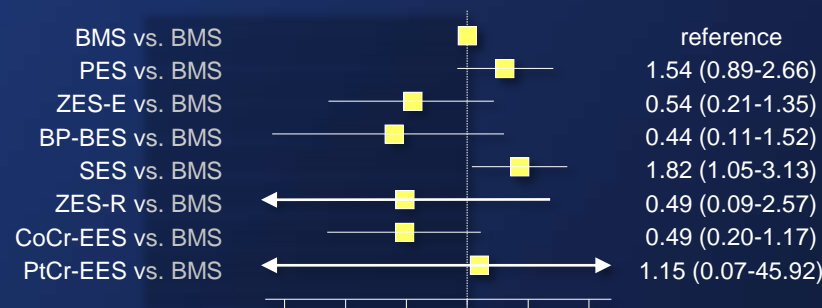
(B) Late ST (31-365 days)



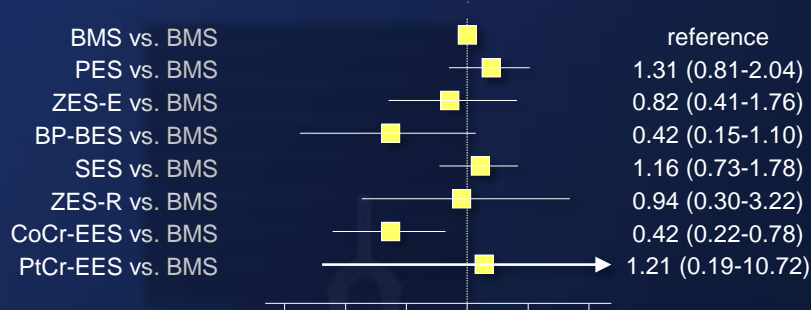
(C) ST within 1 Year (< 365 days)



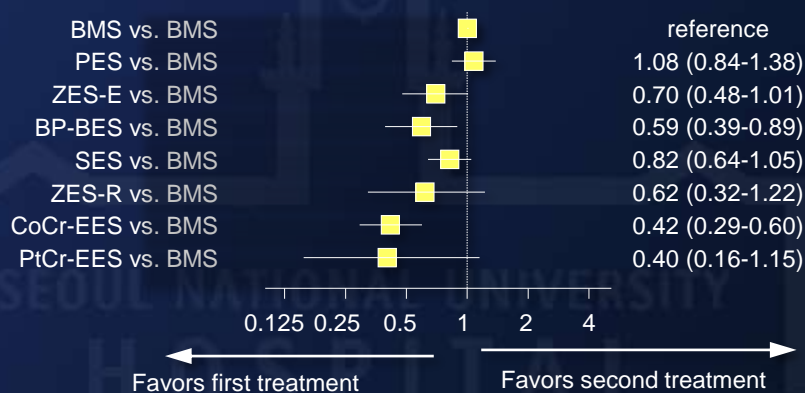
(D) Very Late ST (> 365 days)



(E) Late and Very Late ST (> 30 days)



(F) ST at the Longest Follow-Up



Summary

1. BES showed good efficacy and safety up to 1 year in an all comer PCI population with low TLF rates.
2. When compared with data from an all comer registry of EES and ZES, BES showed similar outcomes regarding cardiac death and myocardial infarction.
3. TLR rates seem to be slightly higher in BES, but this was probably driven by a higher rates of TLR in those receiving routine f/u angiograms.
4. In a network meta-analysis, BES showed significant benefits compared with BMS both up to 1 year and after 1yr regarding ST

HOST-Biolimus-3000-Korea

Participating Centers

Seoul National University Hospital

Pusan National University Hospital

Seoul National University Bundang Hospital

Daegu Fatima Hospital

Seoul National University Boramae Hospital

Gangdong Sungshim Hospital

Sejong Heart Institute, Sejong General Hospital

Kwangju Christian hospital

Korea University Ansan Hospital

Catholic University Uijeongbu St. Mary's

Keimyung University Hospital

Hospital

Chungbuk National University Hospital

Kosin University Hospital

Konyang University Hospital

Hanyang University Hospital

Ilsan Baek Hospital

YOUNG NAM University Hospital

Korea University Guro-Hospital

Inha University Hospital

Yangsan Pusan National University Hospital

Soon-chun-hyang University Hoapital, Gumi

Ewha Womans University Mokdong Hospital

Jeju University Hospital