Comparison of Everolimus- and Biolimus-Eluting Coronary Stents with Everolimus-Eluting Bioresorbable Scaffold – The Randomized Controlled EVERBIO II Trial (NCT01711931)

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In Partnership with the ACC
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Disclosure Statement of Financial Interest

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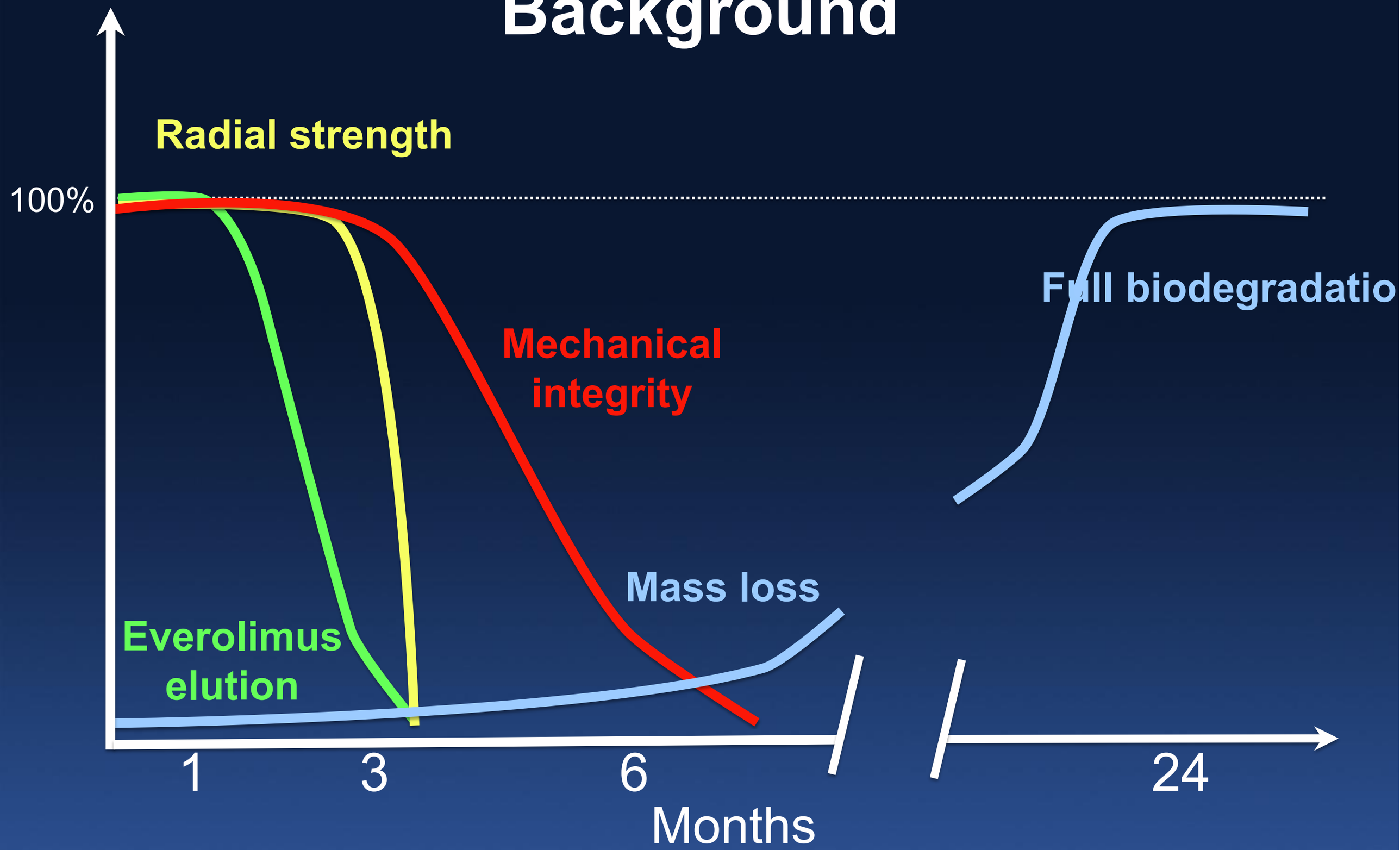
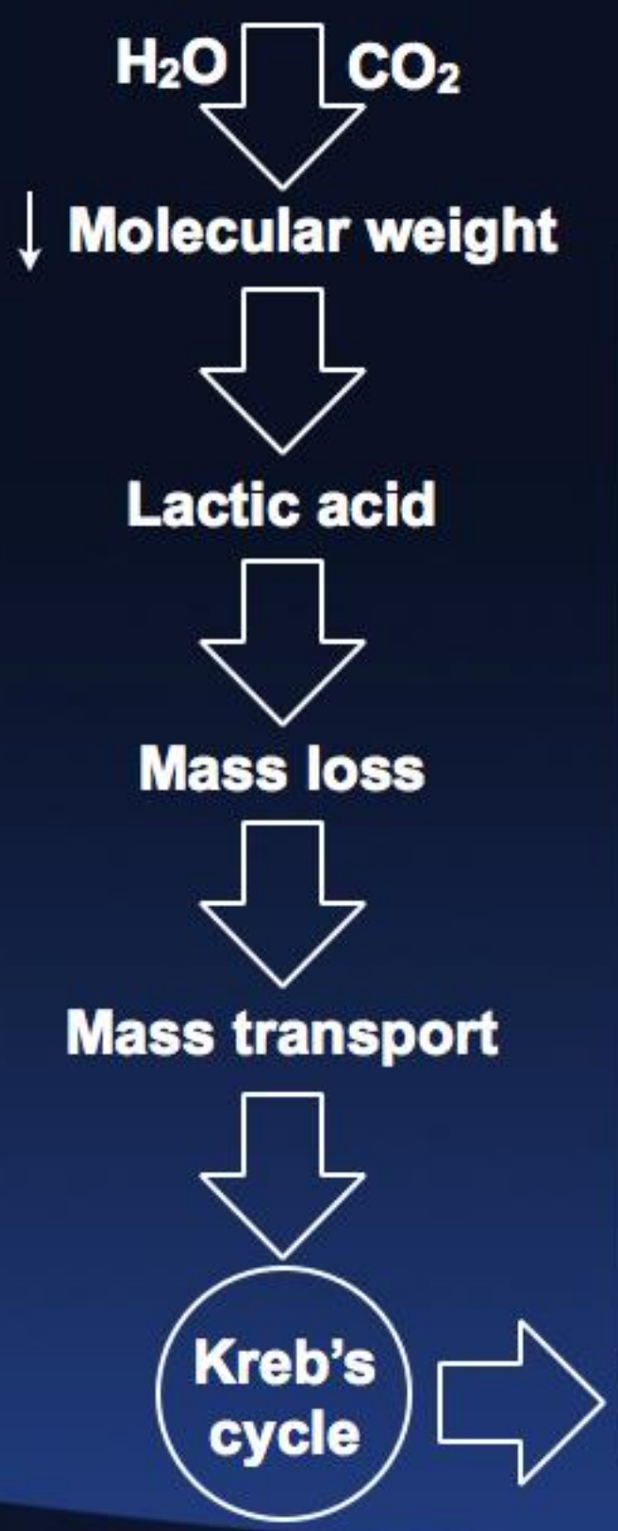
Background

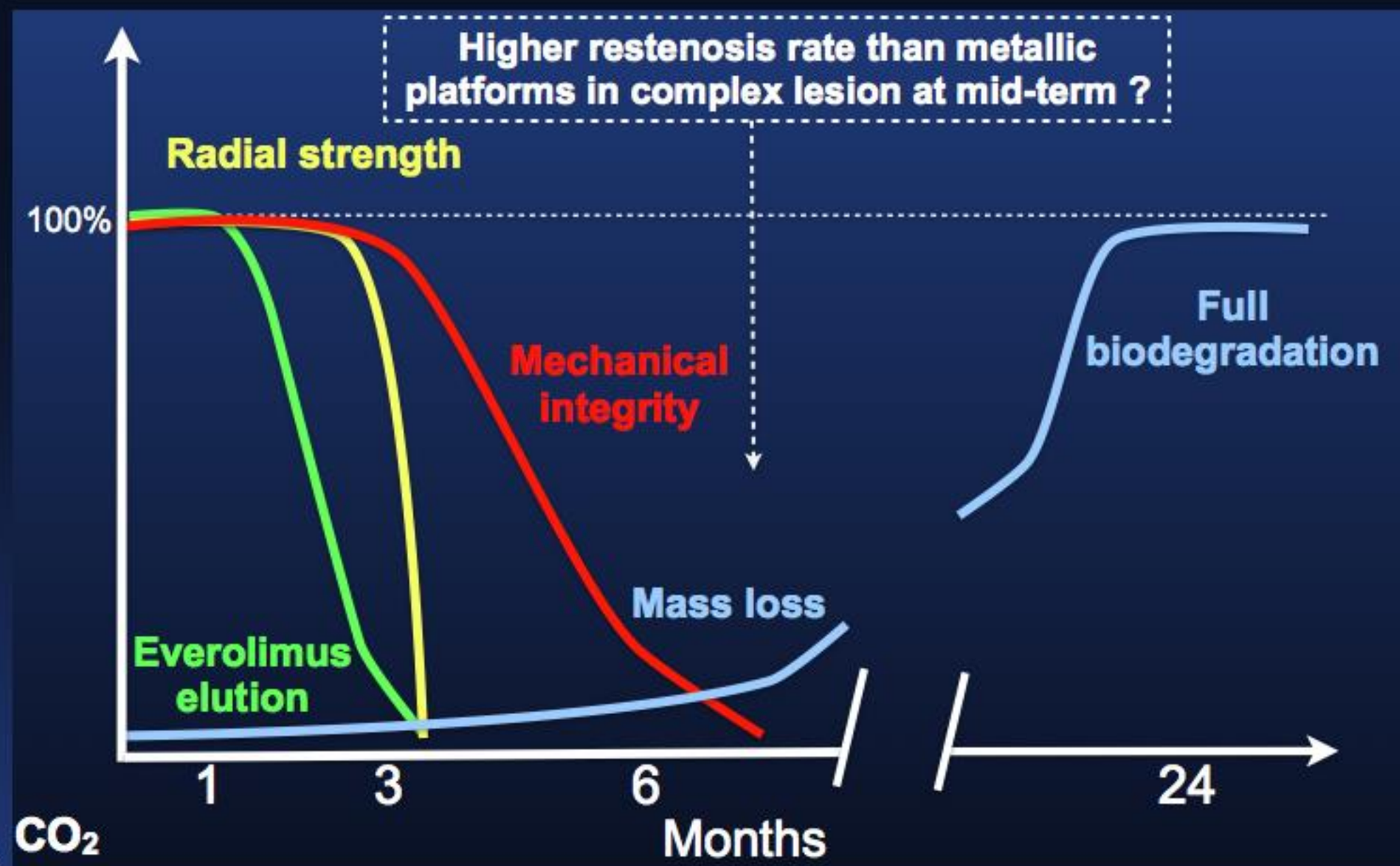

Radial strength
100%
Full biodegradatio
Mechanical
integrity
Mass loss
Everolimus
elution
1
3
6
24
Months

BACKGROUND

- New generation drug-eluting stents (DES) are increasingly efficient and safe.
- The Absorb™ bioresorbable vascular scaffold (BVS) thought to reduce long-term complications, such as neoatherosclerosis and very late stent thrombosis.
- There is evidence on BVS implantation in simple patients and non-complex lesions.
- BVS is increasingly used in complex patients and lesions.

KINETICS OF BVS RESORPTION SIGNIFICANTLY DISTURBS RADIAL STRENGTH @ 6 MONTHS





Garg S & Serruys PW, *J Am Coll Cardiol 2010;56:S43–78*

OBJECTIVE

To compare the efficacy of the everolimus-eluting bioresorbable vascular scaffold (BVS, Absorb) in all-comers with best-in-class new generation DES: everolimus- (EES, Promus Element), and biolimus-eluting (BES, Biomatrix Flex) stents

PRINCIPAL FEATURES OF THE 3 PLATFORMS

	EES PROMUS ELEMENT™	BES BIOMATRIX FLEX™	BVS ABSORB™
PLATFORM	Platinum Chromium	Stainless Steel	PLLA
strut thickness (um)	81	112	156
POLYMER polymer thickness (um)	7	10	6
	Durable fluoropolymer	Biodegradable PLLA	Biodegradable PLLA
DRUG	Everolimus	Biolimus A9	Everolimus
	1 ug/mm^2 - 87%, 90 days	15.6 ug/mm - 45%, 30 days	8.2 ug/mm - 80%, 30 days

Trial Design

Patients with stable CAD or ACS undergoing PCI

allocation ratio of 1:1:1 after lesion preparation

EES PROMUS ELEMENT™ (N=80)	BES BIOMATRIX FLEX™ (N=80)	BVS ABSORB™ (N=80)

Clinical follow-up @ 1, 6, 9, 12 months, 2 & 5 y; Angio @ 9 months

Primary endpoint - in-stent late lumen loss (LLL) at 9 months

Secondary endpoints

- in-segment LLL
- patient-oriented MACE (death, myocardial infarction and target-vessel revascularization)
- device-oriented MACE (cardiac death, myocardial infarction and target-lesion revascularization), stent thrombosis according to ARC at 9-month follow-up.

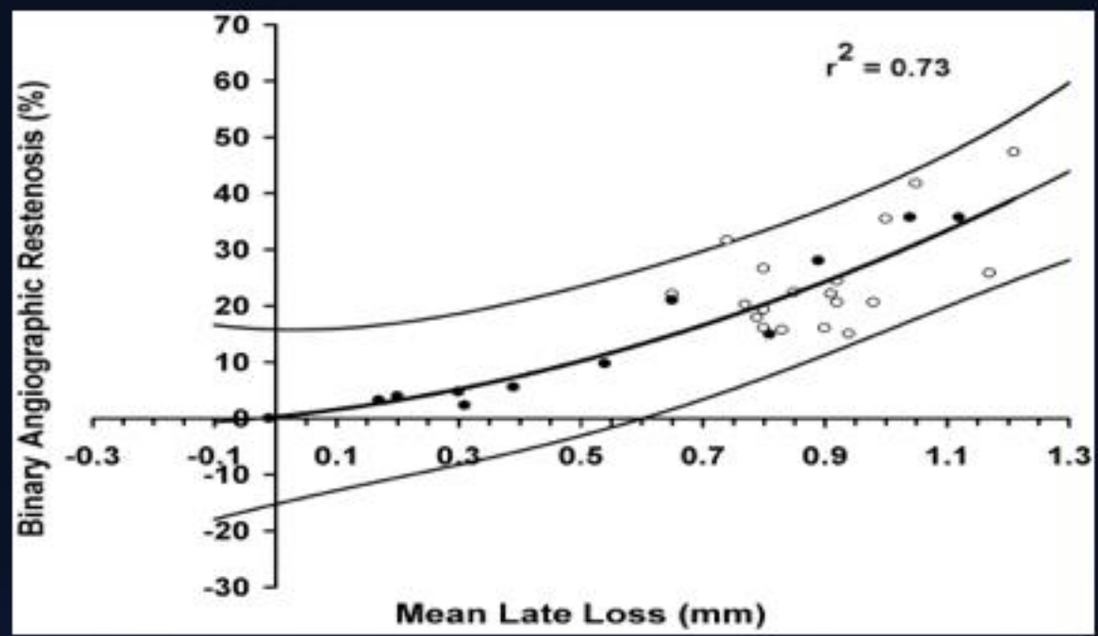
ii Study Organization

Sponsor	Fonds Scientifique Cardiovasculaire, Fribourg, Switzerland
Steering committee	Serban Puricel, Diego Arroyo, Stéphane Cook
Data monitoring	Sonja Lehmann, Estelle Boute, Hélène Villeneuve
Data coordination & analysis	Serban Puricel
QCA/OCT corelabs	University Fribourg (Noé Corpataux/Zacharenia Kallinikou)
Clinical adjudication committee	Olivier Müller, Lausanne -Switzerland (Chair), Juan-Fernando Iglesias , Lausanne -Switzerland
Funding	Educational/research grants from Abbott Vasc. and Biosensors Int., and a dedicated unrestricted grant from Boston Scientific (ISRCAR310040)

ELIGIBILITY FOR PATIENT ENROLLMENT

Inclusion criteria	Exclusion criteria
Age ≥18 y.o.	Inability to provide consent, participation in another trial
Coronary artery disease -Stable AP, silent ischemia -ACS: UA, NSTEMI, STEMI	Pregnancy, planned surgery within 6 months, intolerance to everolimus or biolimus
At least one lesion ≥50% in a native coronary artery or bypass graft (no limitation in number of vessels or lesions to be treated)	***Visual estimate of reference vessel size of >4.0mm***

SAMPLE SIZE CALCULATION



Late lumen loss (LLL) = MLD_{index} - $MLD_{follow\text{-}up}$

In-stent LLL is considered a particularly robust endpoint for discrimination of new coronary stents for which binary rates are anticipated to be low

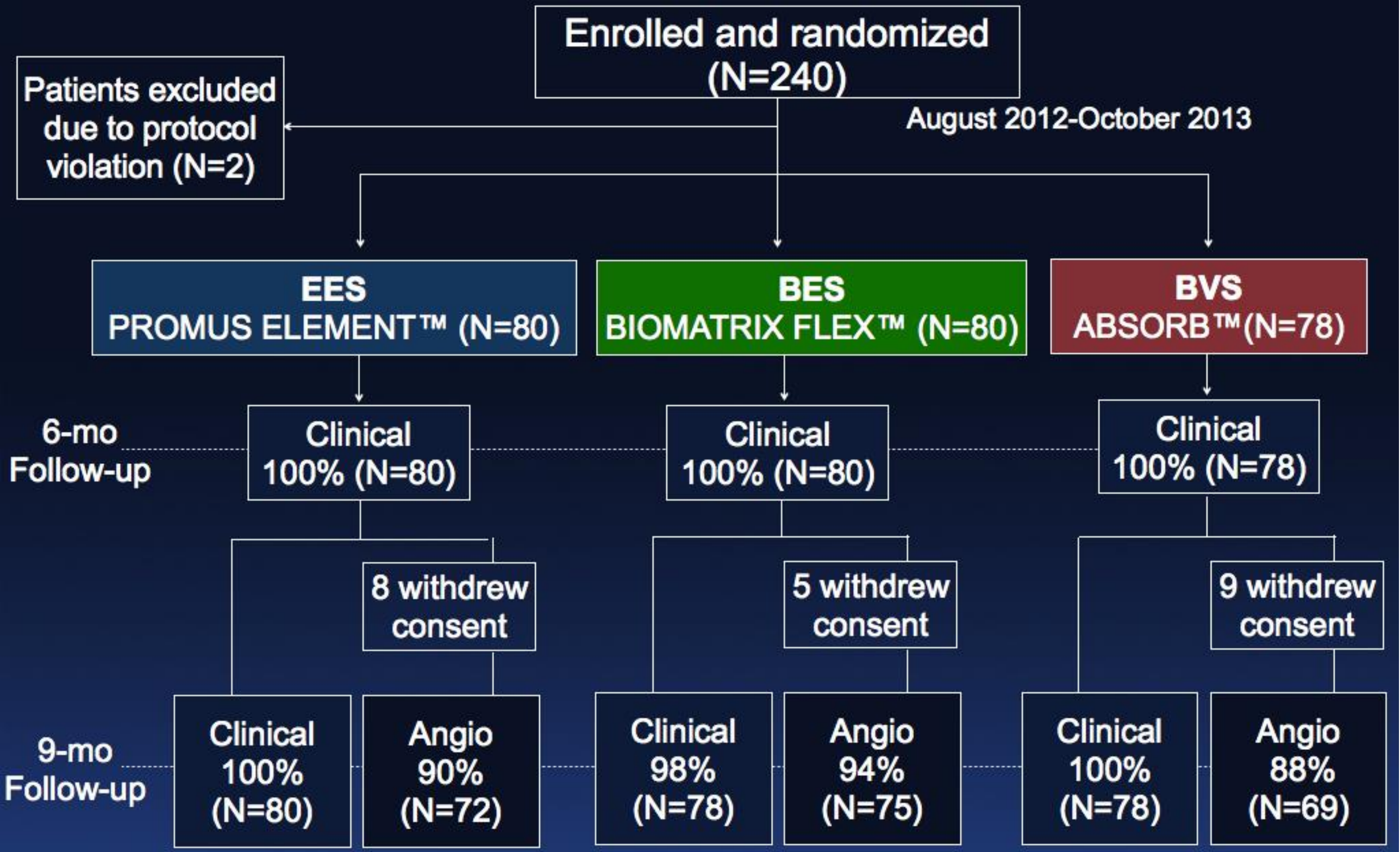
Mauri L et al. Circulation. 2005;111:3435-3442

Assumptions

- We assumed LLL of 0.5mm in BVS based on

  (a) LLL peaks at 6-12 months in humans (LLL of 0.7-0.9mm at 3-6 months in pigs)

  (b) LLL is greater in complex lesions than that in simple lesions such as in the ABSORB B Cohort (LLL of 0.2 at 6 months) due to a higher rate of scaffold recoil.
- Difference of 0.2mm in LLL at 9 months (BES/EES = 0.3mm vs. BVS 0.5mm; standard deviation 0.5mm).
- Sample size of *240 patients* will yield a power of 90%; [dropout rate of 20% power of 83%] to detect superiority of EES/BES at a two-tailed significance level of α=0.05.


Enrolled and randomized (N=240)
August 2012-October 2013
Patients excluded due to protocol violation (N=2)
EES PROMUS ELEMENT™ (N=80)
BES BIOMATRIX FLEX™ (N=80)
BVS ABSORB™(N=78)
6-mo Follow-up
Clinical 100% (N=80)
Clinical 100% (N=80)
Clinical 100% (N=78)
8 withdrew consent
5 withdrew consent
9 withdrew consent
9-mo Follow-up
Clinical 100% (N=80)
Angio 90% (N=72)
Clinical 98% (N=78)
Angio 94% (N=75)
Clinical 100% (N=78)
Angio 88% (N=69)

BASELINE PATIENT CHARACTERISTICS

					p-value		
	EES	BES	EES&BES	BVS	EES	BES	EES/BES
	N=80	N=80	N=160	N=78	vs. BVS	vs. BVS	vs. BVS
Male, n(%)	64 (80)	64 (80)	128 (80)	61 (78)	0.78	0.78	0.75
Age, years±SD	65±11	65±10	65±11	65±11	0.78	0.99	0.88
Hypertension, n(%)	51 (64)	50 (63)	101 (63)	43 (55)	0.27	0.35	0.24
Diabetes, n(%)	13 (16)	26 (33)	39 (24)	17 (22)	0.37	0.13	0.66
Non insulin-dependent, n(%)	8 (10)	21 (26)	29 (18)	17 (22)	0.04	0.51	0.5
Smoking, n(%)	30 (38)	25 (31)	55 (34)	28 (36)	0.83	0.54	0.82
Dyslipidemia, n(%)	50 (63)	52 (65)	102 (64)	44 (56)	0.44	0.27	0.28
Family History, n(%)	23 (29)	23 (29)	46 (29)	23 (30)	0.92	0.92	0.91
Previous PCI, n(%)	25 (31)	23 (29)	48 (30)	25 (32)	0.91	0.65	0.75
Previous CABG, n(%)	11 (14)	16 (20)	27 (17)	6 (8)	0.22	0.03	0.07
Previous MI, n(%)	14 (18)	16 (20)	30 (19)	11 (14)	0.56	0.33	0.37
Indication					0.74	0.14	0.72
UA, n(%)	5 (6)	9 (11)	14 (9)	6 (8)			
NSTEMI, n(%)	16 (20)	21 (26)	37 (23)	13 (17)			
STEMI, n(%)	6 (8)	8 (10)	14 (9)	9 (12)			
Stable Angina, n(%)	47 (59)	27 (34)	74 (46)	41 (53)			
Silent ischemia, n(%)	6 (8)	15 (19)	21 (13)	9 (12)			
LVEF* in %, median[IQR]	60 [55-65]	58 [45-65	60 [47.5-65]	61 [50-66]	0.74	0.19	0.35

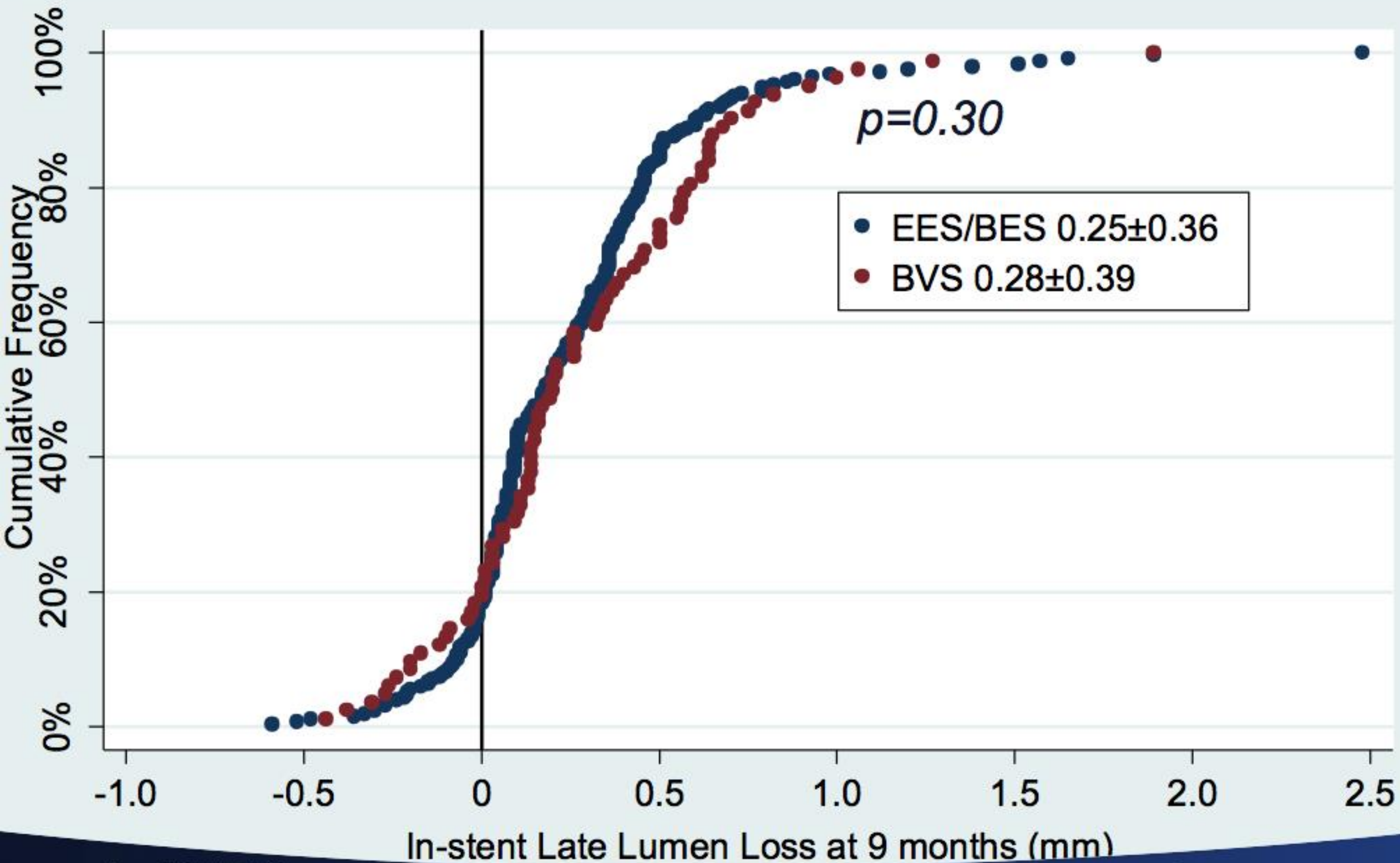
Procedural characteristics (I)

						p-value	
	EES	**BES**	**EES&BES**	**BVS**	***EES***	***BES***	***EES/BES***
	N=80	**N=80**	**N=160**	**N=78**	***vs. BVS***	***vs. BVS***	***vs. BVS***
Vessels diseased per patient, mean±SD	1.9±0.8	1.9±0.8	1.9±0.6	1.9±0.7	*0.74*	*0.67*	*0.67*
Vessels treated per patient, mean±SD	1.2±0.4	1.1±0.4	1.1±0.4	1.1±0.3	*0.51*	*0.83*	*0.5*
Lesions per patient, mean±SD	2.1±1.3	2.2±1.4	2.2±1.3	2.1±1.4	*0.98*	*0.75*	*0.77*
Lesions treated per patient, mean±SD	1.5±0.8	1.4±0.6	1.4±0.7	1.3±0.5	*0.3*	*0.85*	*0.6*

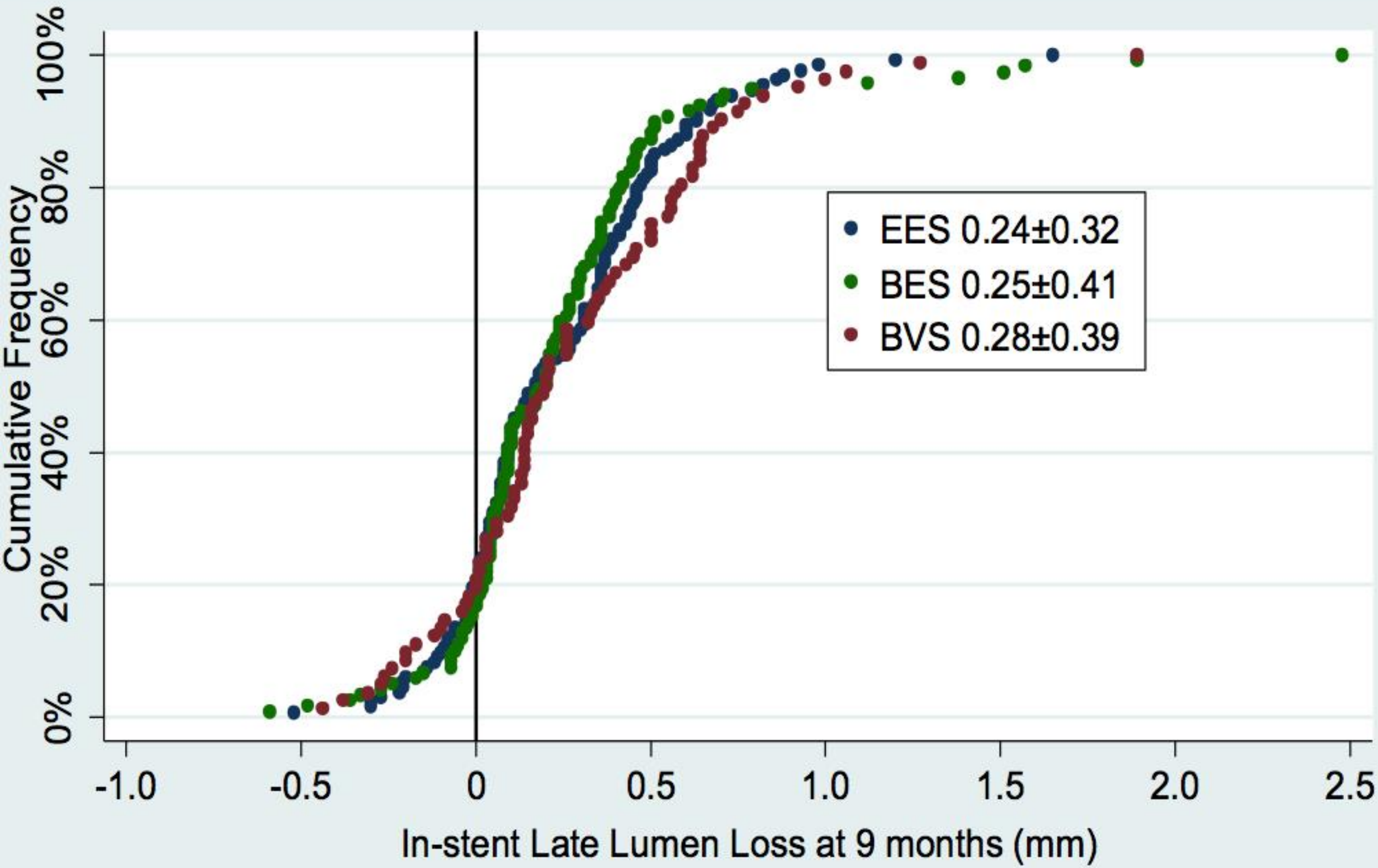
PROCEDURAL CHARACTERISTICS

	EES N=112	BES N=117	EES&BES N=229	BVS N=96	p-value EES vs. BVS	p-value BES vs. BVS	p-value EES/BES vs. BVS
Target coronary artery					0.31	0.05	0.19
LM, n(%)	1 (1)	1 (1)	2 (1)	0 (0)			
LAD, n(%)	44 (39)	34 (29)	78 (34)	44 (46)			
LCX, n(%)	21 (19)	27 (23)	48 (21)	24 (25)			
RCA, n(%)	40 (36)	48 (41)	88 (38)	24 (25)			
Arterial graft, n(%)	2 (2)	1 (1)	3 (1)	0 (0)			
Vein graft, n(%)	4 (4)	6 (5)	10 (4)	4 (4)			
Hybrid with DES, n(%)	**1 (1)**	**0 (0)**	**1 (1)**	**4 (4)**	**0.18**	**0.03**	**0.03**
TIMI Flow post, median [IQR]	3 [3-3]	3[3-3]	3 [3-3]	3 [3-3]	0.35	1	0.52
ISR, n(%)	2 (2)	3 (3)	5 (2)	1 (1)	1	0.63	0.5
CTO, n(%)	7 (6)	5 (4)	12 (5)	1 (1)	0.07	0.16	0.12
Number of stents per lesion, mean±SD	1.3±0.7	1.1±0.4	1.2±0.6	1.2±0.5	0.04	0.14	0.55
Stent length per lesion, mm ±SD	22.1±13.8	19.3±10.0	20.7±12.1	22.8±8.8	0.67	<0.01	0.08
Stent diameter per lesion, mm±SD	**3.0±1.0**	**3.0±0.6**	**3.0±0.8**	**3.1±0.4**	**0.31**	**<0.01**	**0.03**
Maximum pressure per lesion, atm±SD	14.6±2.9	13.8±3.0	14.2±3.0	13.6±2.8	0.04	0.67	0.09
Overlapping stents per lesion, n(%)	26 (23)	14 (12)	40 (17)	16 (17)	0.24	0.33	0.86
Postdilatation per lesion, n(%)	35 (31)	35 (30)	70 (31)	33 (34)	0.63	0.49	0.5
Acute recoil, %±SD	**6.2±4.2**	**7.2±5.4**	**6.7±4.8**	**9.3±6.5**	**<0.01**	**0.02**	**<0.01**

PRIMARY ENDPOINT - IN-STENT LLL

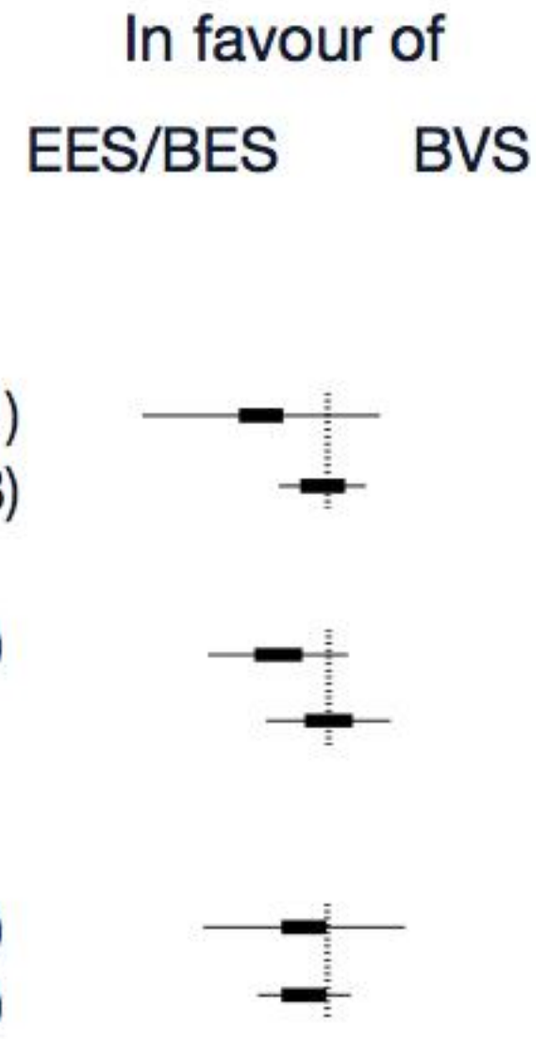


PRIMARY ENDPOINT - IN-STENT LLL

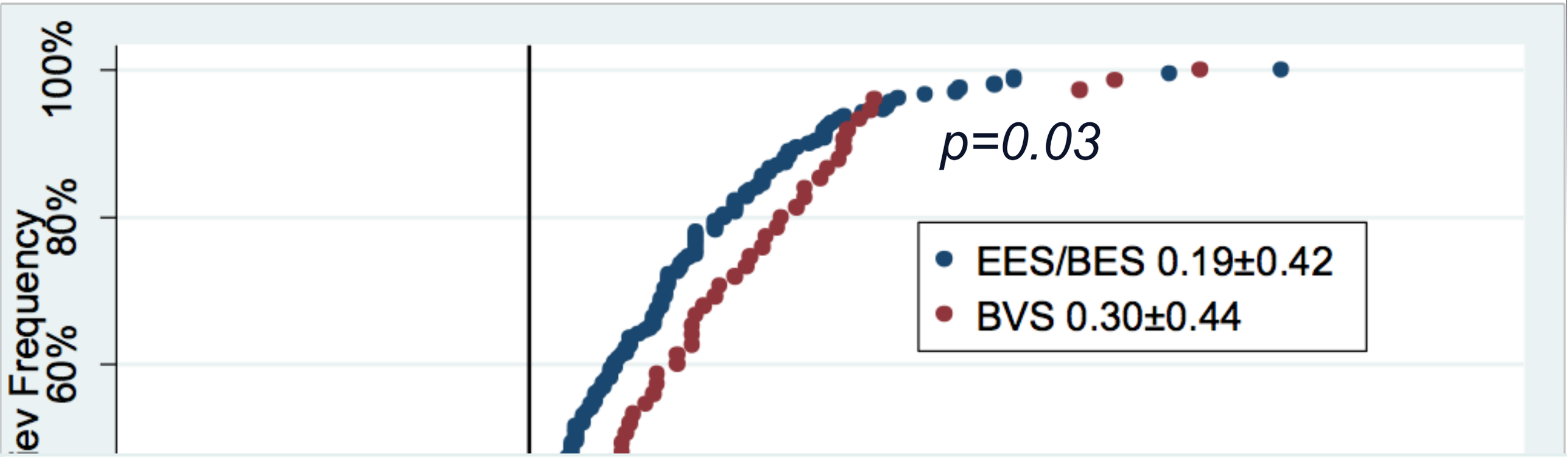


Stratified Analysis of Primary Endpoint

	EES&BES	BVS	Δ LLL (95%CI)	p-value	$p_{interaction}$
Diabetes					0.66
Yes	0.27±0.47	0.41±0.48	-0.14 (-0.38-0.11)	0.27	
No	0.24±0.32	0.25±0.35	-0.01 (-0.10-0.08)	0.81	
ACS					0.25
Yes	0.22±0.28	0.32±0.44	-0.10 (-0.23-0.04)	0.16	
No	0.26±0.40	0.26±0.35	0.00 (-0.12-0.12)	0.98	
Complex lesions (B2/C)					0.11
Yes	0.31±0.46	0.35±0.38	-0.05 (-0.25-0.16)	0.66	
No	0.21±0.29	0.26±0.39	-0.05 (-0.14-0.05)	0.35	



SECONDARY ENDPOINT - IN-SEGMENT LLL



In favour of

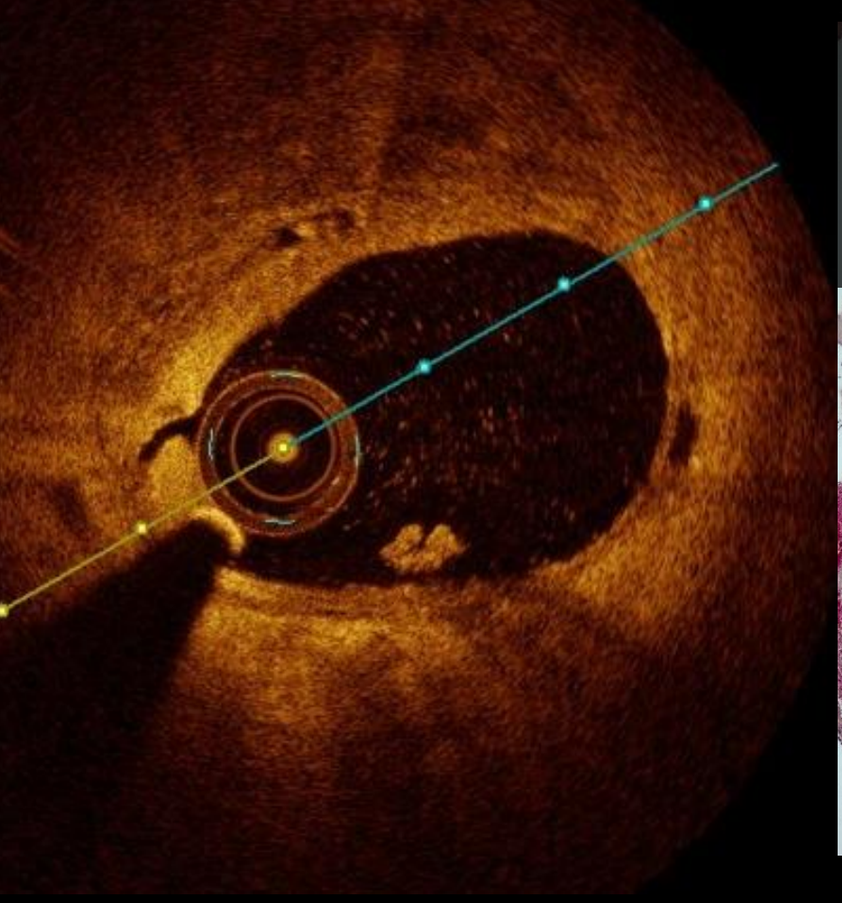
	EES&BES	BVS	Δ LLL (95%CI)	EES/BES BVS	p-value	$p_{interaction}$
Diabetes						0.06
Yes	0.12±0.45	0.36±0.46	-0.23 (-0.48-0.01)		0.06	
No	0.21±0.40	0.29±0.44	-0.07 (-0.20-0.05)		0.22	
ACS						0.18
Yes	0.16±0.37	0.41±0.51	-0.24 (-0.43-[-0.07])		<0.01	
No	0.20±0.44	0.24±0.40	-0.04 (-0.19-0.10)		0.54	
Complex lesions (B2/C)						0.05
Yes	0.30±0.47	0.45±0.46	-0.15 (-0.37-0.08)		0.20	
No	0.12±0.37	0.24±0.42	-0.23 (-0.24-0.01)		0.07	

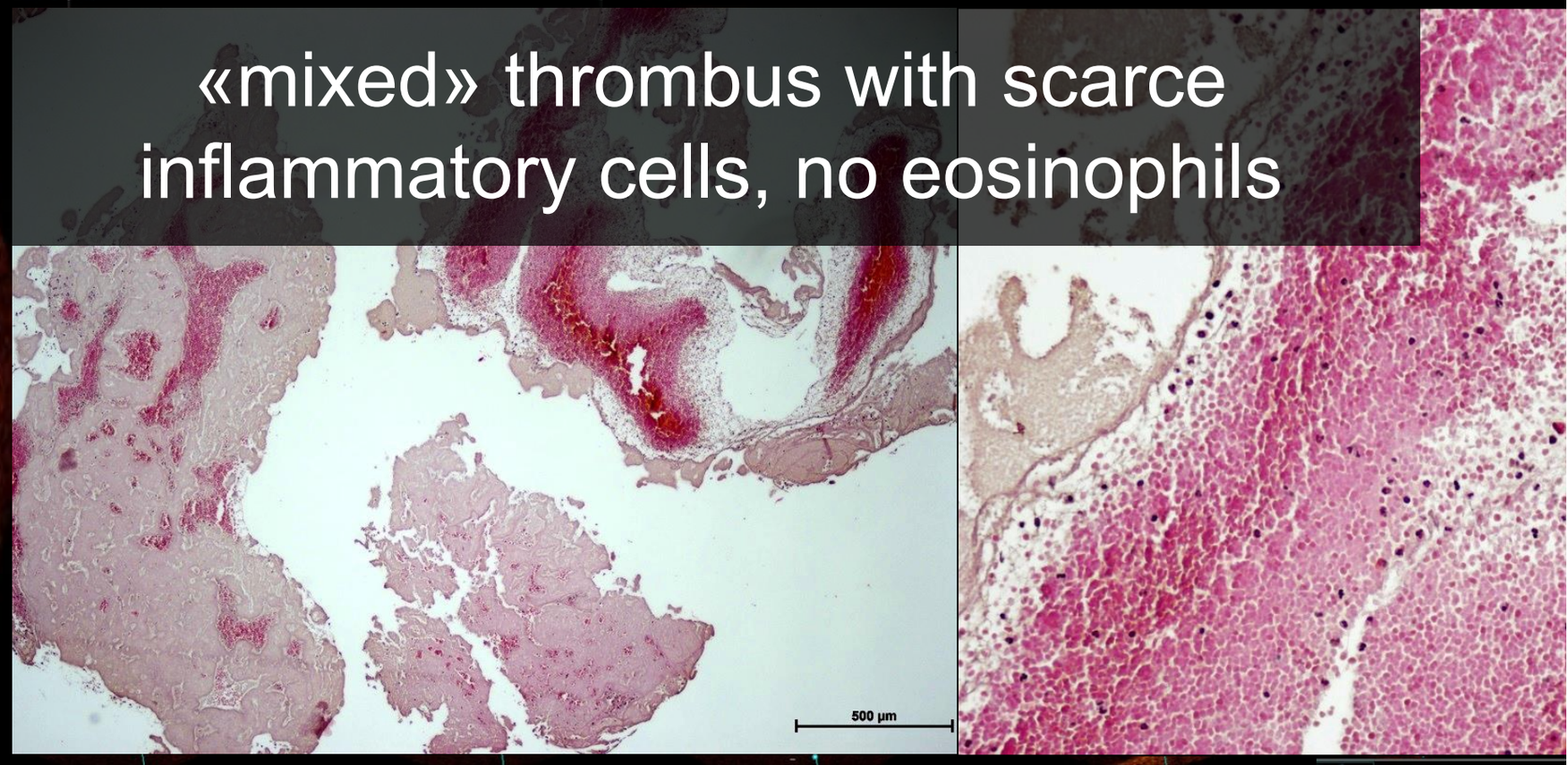
DAPT

	EES N=80	BES N=80	EES/BES N=160	BVS N=78	p-value EES vs. BVS	p-value BES vs. BVS	p-value EES/BES vs. BVS
In-hospital							
Any P2Y12 In	80 (100)	80 (100)	160 (100)	78 (100)	-	-	-
Clopidogrel	36 (45)	35 (44)	71 (44)	31 (40)	0.52	0.63	**0.58**
Prasugrel	41 (51)	40 (50)	81 (51)	44 (56)	0.53	0.43	**0.41**
Ticagrelor	3 (4)	5 (6)	8 (5)	3 (4)	1	0.72	**1**
6 Months							
Any P2Y12 In	77 (96)	75 (94)	152 (95)	72 (92)	0.33	0.76	**0.37**
Clopidogrel	34 (43)	30 (38)	64 (40)	26 (33)	0.26	0.62	**0.39**
Prasugrel	40 (50)	38 (48)	78 (49)	42 (54)	0.64	0.43	**0.49**
Ticagrelor	3 (4)	7 (9)	10 (6)	4 (5)	0.72	0.53	**1**
9 months							
Any P2Y12 In	66 (83)	66 (83)	132 (83)	61 (78)	0.55	0.55	**0.48**
Clopidogrel	27 (34)	25 (31)	52 (33)	21 (27)	0.39	0.6	**0.45**
Prasugrel	37 (46)	36 (45)	73 (46)	38 (49)	0.87	0.75	**0.68**
Ticagrelor	2 (3)	5 (6)	7 (4)	2 (3)	1	0.43	**0.72**

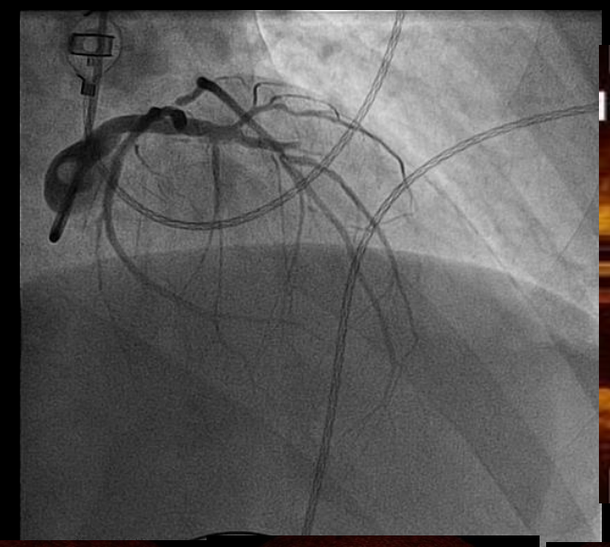
CLINICAL OUTCOME AT 9 MONTHS

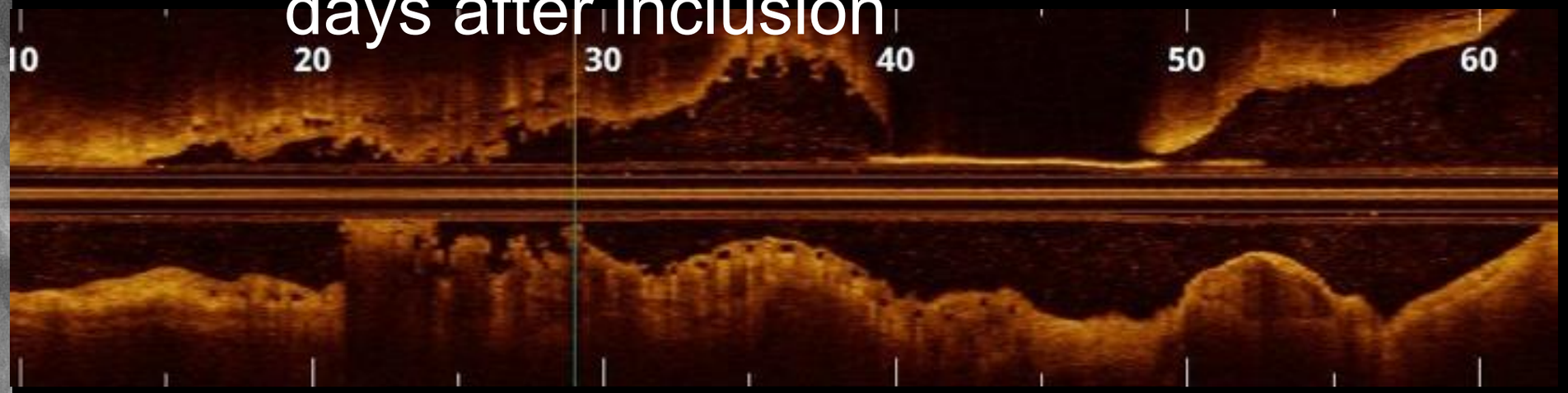
					p-value		
	EES	BES	EES&BES	BVS	*EES*	*BES*	*EES/BES*
	N=80	N=80	N=160	N=78	*vs. BVS*	*vs. BVS*	*vs. BVS*
Device-oriented MACE	11 (14)	4 (5)	15 (9)	9 (12)	*0.68*	*0.14*	*0.6*
Cardiac death, n(%)	0 (0)	0 (0)	0 (0)	1 (1)	*0.49*	*0.49*	*0.33*
MI of TV n(%)	0 (0)	0 (0)	0 (0)	0 (0)			
TLR, n(%)	11 (14)	4 (5)	15 (9)	8 (10)	*0.5*	*0.21*	*0.83*
clinically indicated, n(%	7 (9)	2 (3)	9 (6)	6 (8)	*0.81*	*0.16*	*0.54*
Patient-oriented MACE	26 (33)	15 (19)	41 (26)	21 (27)	*0.44*	*0.22*	*0.83*
All cause mortality, n(%)	3 (4)	0 (0)	3 (2)	1 (1)	*0.62*	*0.49*	*1*
Any MI, n(%)	1 (1)	0 (0)	1 (1)	1 (1)	*1*	*0.49*	*0.55*
Any Revasc., n(%)	24 (30)	15 (19)	39 (24)	19 (24)	*0.43*	*0.39*	*0.99*
TVR, n(%)	14 (18)	8 (10)	22 (14)	11 (14)	*0.56*	*0.43*	*0.94*
clinically indicated, n(%)	8 (10)	5 (6)	13 (8)	8 (10)	*0.96*	*0.36*	*0.59*
ST (definite/probable), n(%	0 (0)	0 (0)	0 (0)	0 (0)			
ST (possible), n(%)	0 (0)	0 (0)	0 (0)	1 (1)	*0.49*	*0.49*	*0.33*

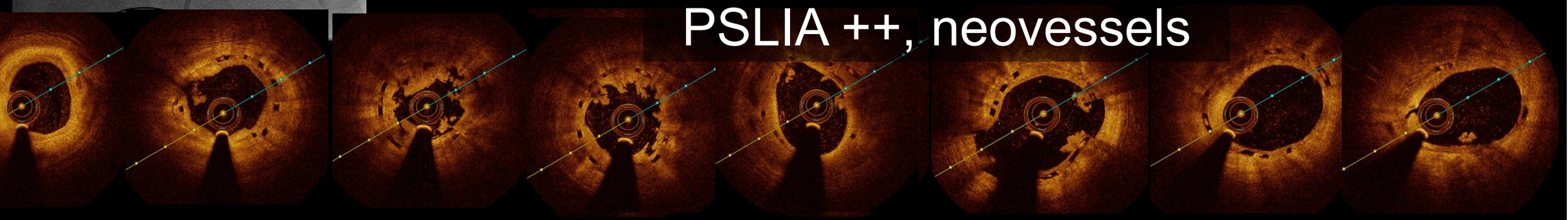




Scaffold thrombosis @ 263 days after BVS implantation and 743 days after inclusion







Limitations

- This study was not powered for non-inferiority or to detect differences in clinical event rates.
- This study was performed in a single center with uniform procedural strategies that makes generalizations to other centers limited.
- We did not address whether BVS modified the thrombotic risk.

Conclusions

- In a patient population with minimal exclusion criteria and using LLL as an early and robust marker for restenosis, BVS demonstrated satisfactory angiographic and clinical outcomes compared to EES/BES.

- In-segment LLL was slightly but significantly higher in BVS compared to EES/BES. A possible explanation to this difference may be due to the modest and transient constrictive effect found at scaffold edges.

Gogas B. et al, J Am Coll Cardiol Intv 2012;5:656–65

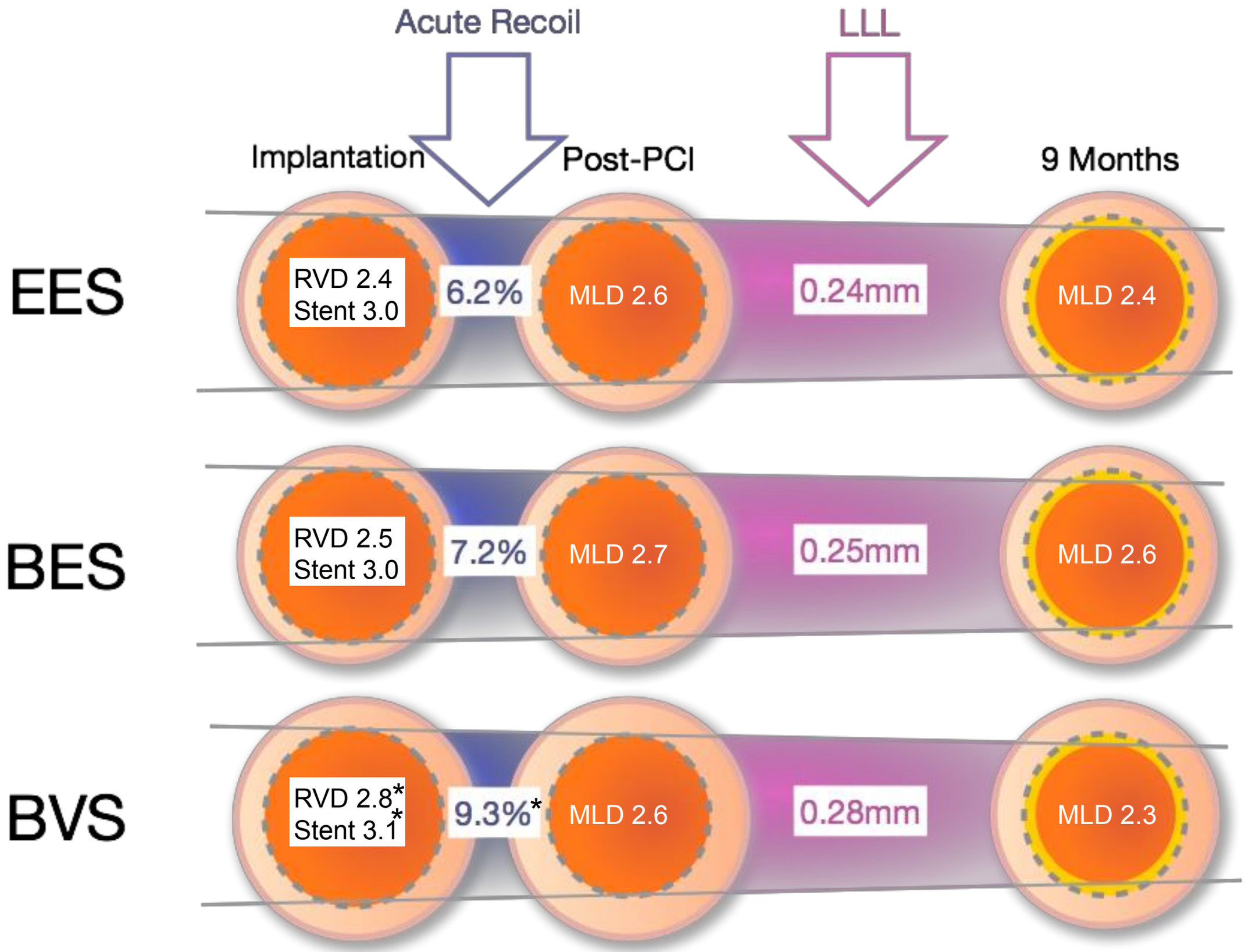
This reinforces our primary hypothesis of DES superiority within the 6-12 months timeframe.

- Optimal DAPT duration after BVS is unknown.

Thank you!

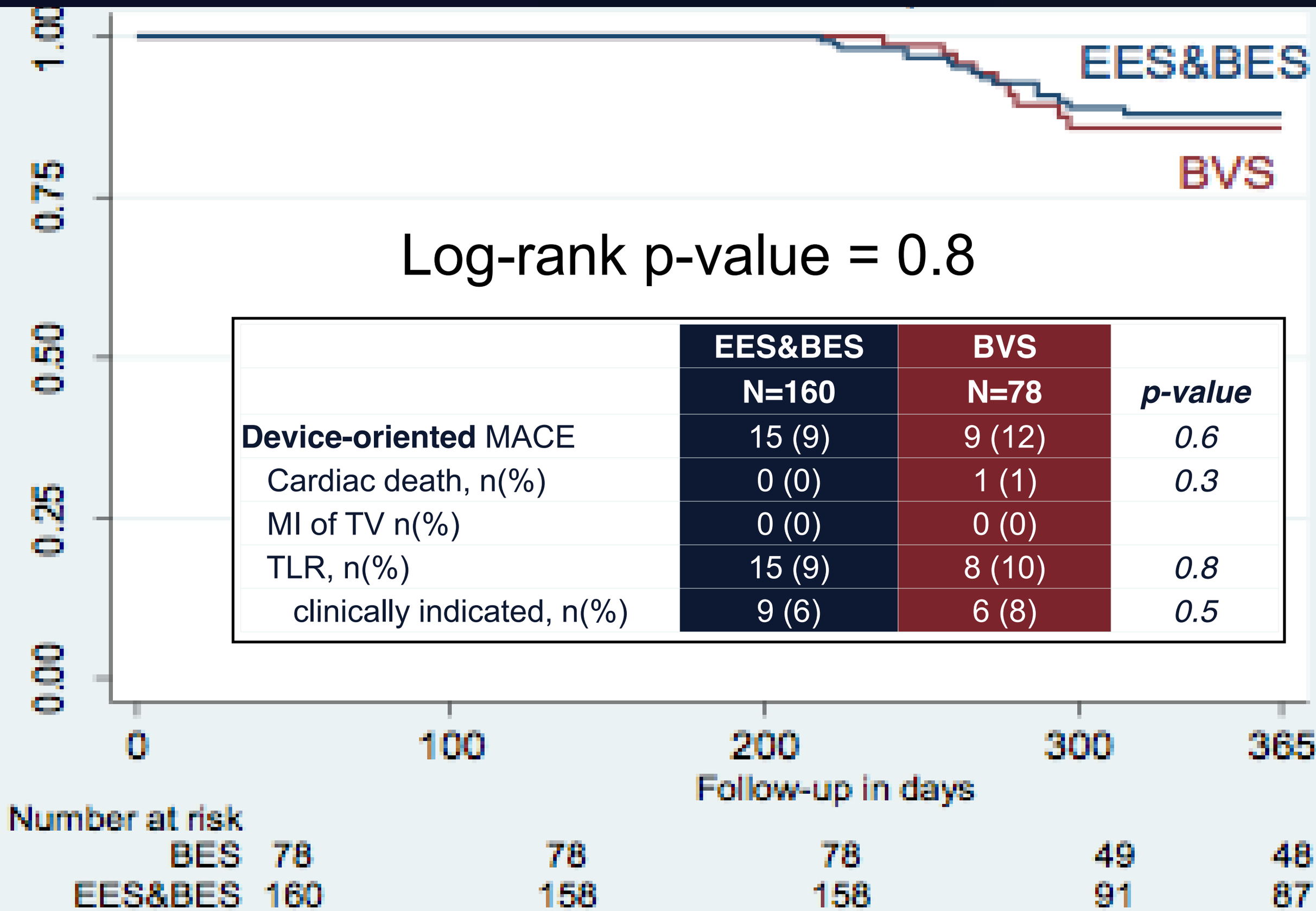
Results-Angiographic Outcome

						p-value	
	EES	BES	EES&BES	BVS	EES	BES	EES/BES
	N=72	N=75	N= 147	N=69	vs. BVS	vs. BVS	vs. BVS
Pre-procedure							
MLD, mm±SD	0.52±0.42	0.59±0.5	0.55±0.46	0.60±0.58	0.58	0.99	0.75
Diameter stenosis, %±SD	7978±15.3	78.7±15.3	79.2±15.7	81.3±16.2	0.48	0.3	0.33
RVD, mm±SD	**2.39±0.70**	**2.53±0.84**	**2.46±0.78**	**2.77±0.60**	**<0.01**	**0.04**	**<0.01**
Post-procedure							
MLD, in-stent, mm±SD	2.62±0.40	2.72±0.53	2.67±0.47	2.56±0.43	0.36	0.08	0.18
MLD, in-segment, mm±SD	2.11±0.45	2.24±0.60	2.17±0.53	2.35±0.51	<0.01	0.2	0.01
Diameter stenosis, in-stent, %±SD	8.1±4.8	7.1±5.8	7.6±5.3	9.3±5.7	0.28	<0.01	0.04
Diameter stenosis, in-segment, %±SD	12.9±10.4	12.3±9.4	12.6±9.9	11.8±7.4	0.44	0.5	0.41
Acute gain, in-stent, mm±SD	2.09±0.49	2.12±0.53	2.11±0.51	1.97±0.66	0.47	0.21	0.35
Acute gain, in-segment, mm±SD	1.59±0.49	1.65±0.58	1.62±0.53	1.76±0.73	0.07	0.41	0.12
9 months							
MLD, in-stent, mm±SD	**2.38±0.47**	**2.57±0.65**	**2.42±0.56**	**2.28±0.51**	**0.17**	**0.02**	**0.07**
MLD, in-segment, mm±SD	1.91±0.48	2.06±0.63	1.99±0.58	2.05±0.51	0.19	0.86	0.42
Diameter stenosis, in-stent, %±SD	**11.3±9.8**	**12.6±14.94**	**11.9±12.5**	**16.9±11.6**	**<0.01**	**<0.01**	**<0.01**
Diameter stenosis, in-segment, %±SD	**15.5±11.0**	**16.1±17.2**	**15.8±14.3**	**17.8±11.7**	**0.17**	**0.01**	**0.03**
RVD, mm±SD	**2.68±0.51**	**2.66±0.48**	**2.67±0.37**	**2.83±0.51**	**0.07**	**0.04**	**0.03**
Late loss, in-stent, mm±SD	0.24±0.32	0.25±0.41	0.25±0.36	0.28±0.39	0.4	0.31	0.3
Late loss, in-segment, mm±SD	**0.20±0.43**	**0.17±0.40**	**0.19±0.42**	**0.30±0.44**	**0.08**	**0.03**	**0.03**



* for p<0.05 versus DES

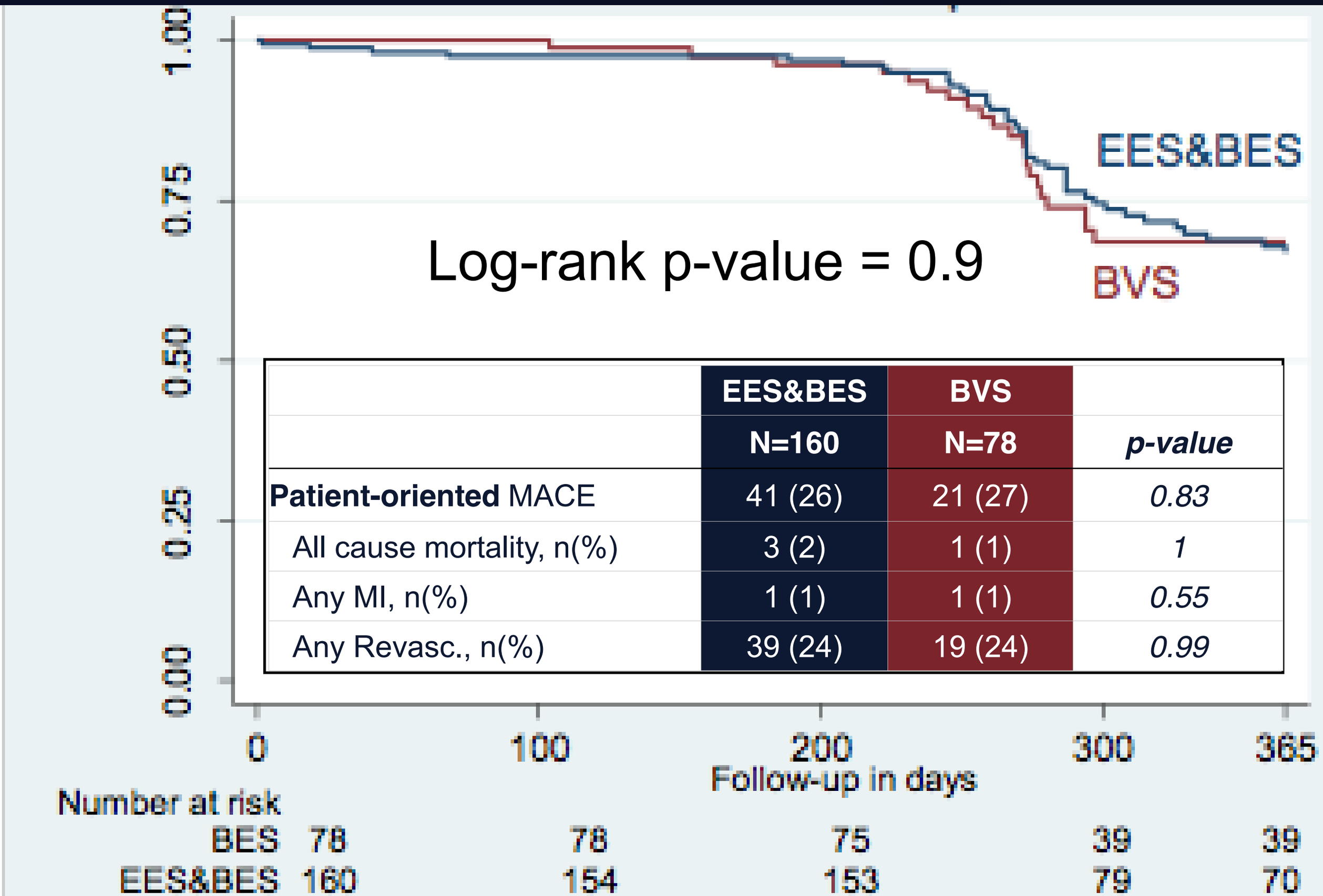
Secondary outcome - d.o. MACE



Log-rank p-value = 0.8

	EES&BES	BVS	
	N=160	N=78	*p-value*
Device-oriented MACE	15 (9)	9 (12)	*0.6*
Cardiac death, n(%)	0 (0)	1 (1)	*0.3*
MI of TV n(%)	0 (0)	0 (0)	
TLR, n(%)	15 (9)	8 (10)	*0.8*
clinically indicated, n(%)	9 (6)	6 (8)	*0.5*

Secondary outcome - p.o. MACE



	EES&BES	BVS	
	N=160	N=78	*p-value*
Patient-oriented MACE	41 (26)	21 (27)	*0.83*
All cause mortality, n(%)	3 (2)	1 (1)	*1*
Any MI, n(%)	1 (1)	1 (1)	*0.55*
Any Revasc., n(%)	39 (24)	19 (24)	*0.99*

Narratives of BVS failures

#ID	*History*	Lesions	Time (days)/DAPT	Manifestation
3.55	*55 y.o. ♂ with stable AP. PCI LAD (1BVS: 3.0/18), 1* aberrant LCx (hybrid 1BVS 2.5/28)	Prox. LAD Aberrant LCx (hybrid)	307 (Aspirin alone)	Cardiac death (possible ST): chest pain and sudden cardiac death while skiing
3.79	*48 y.o. ♂ with stable AP. PCI CTO RCA (3BVS: 3.0/28; 3.0/28, 3.5/28mm) and LCx (2BVS: 2.5/18; 3.0/18mm)*	Mid RCA	212 (Aspirin/prasugrel)	Unstable angina
3.41	*58 y.o. ♂ with STEMI inferoposterior with PCI RCA (1BVS) and staged PCI LAD (3 BVS) and LCx (2 BVS) @ 9-months angio FUP*	Mid LAD	263 (Aspirin alone) - 743 after index	Definite ST with anterior MI