Comparison of the Efficacy and Safety of *Z*otarolimus-*E*luting Stent versus *S*irolimus-Eluting Stent and Pacli*T*axel-Eluting Stent for Coronary Lesions:

The ZEST Trial

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on behalf of the ZEST investigators

ZEST Trial
-Disclosure Information-

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- Medtronic Vascular

Background

- Several clinical trials have documented that sirolimus-eluting stent (SES; Cypher) and paclitaxel-eluting stent (PES; Taxus) significantly reduce angiographic restenosis and repeat revascularization as compared to bare metal stents.
- However, the safety of the first-generation 2 drug-eluting stents (DES) (sirolimus- and paclitaxel-) has been concerned by numerous reports of increased late stent thrombosis, myocardial infarction, and death, especially in routine clinical practice.

Background

- Zotarolimus-eluting stent (ZES; Endeavor) is a second-generation DES comprising 3 components: (1) a low-profile, thin-strut, cobalt-alloy stent; (2) a biocompatible phosphorylcholine polymer; and (3) zotarolimus, an antiproliferative drug.
- Although second-generation DES, which may be theoretically less prone to thrombosis, is currently available, large randomized trial comparing first vs. second-generation DES in all-comer settings have been limited.

Objective

- To establish the safety and effectiveness of coronary stenting with zotarolimus-eluting stent (Endeavor, Medtronic) as compared with sirolimus-eluting stent (Cypher, Cordis Johnson & Johnson) and paclitaxel-eluting stent (Taxus, Boston Scientific) in a multicenter, randomized clinical trial for unselected patients in the real world.

Study Design

All Comer requiring PCI with DES for coronary lesions
in 19 Centers of Korea
(Total 2,640 patients)

Randomize 1:1:1
stratified by 1) Sites, 2) Diabetes, 3) Long lesions (≥ 28 mm)

ENDEAVOR®	**CYPER®**	**TAXUS Liberte™**
(N=880)	**(N=880)**	**(N=880)**

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

Major Inclusion Criteria

- Significant CAD (≥ 50% stenosis), amenable to stent-assisted PCI
- Silent ischemia, stable angina, and ACS (unstable angina, NSTEMI)

Major Exclusion Criteria

- Severe LV dysfunction (EF < 25%)
  or Cardiogenic Shock
- STEMI requiring primary PCI
- Organ damage (Creatinine ≥ 3.0 mg/dl or LFT > 3 times)
- Left Main Disease
- In-stent restenosis of DES
- Limited life expectancy < 1 year

Primary Study Endpoint

- The composite clinical outcome of
  - Death from any cause
  - Myocardial infarction (MI)
  - Ischemia-driven target-vessel revascularization (TVR)

  at 12 months after the index procedure.

Secondary Study Endpoint

- Death (all-cause or cardiac)
- MI
- Composite of death or MI
- TVR (all- and ischemia-driven)
- TLR (all- and ischemia-driven)
- Composite of death, MI, ischemia-driven TLR
- Stent thrombosis by ARC definition
- Late loss in both in-stent and in-segment at 9 months
- Restenosis in both in-stent and in-segment at 9 months
- Procedural success rate

Outcome Definitions

- Death was classified to cardiac vs. noncardiac
- MI: a new pathologic Q-wave or CK-MB > 3 times upper limit of the normal.
- TLR: any revascularization for a stenosis within the stent and adjacent 5-mm border.
- TVR: any revascularization for a stenosis at target vessel.
- Ischemia-driven: (1) >50% stenosis with ischemic signs or Sx. or (2) >70% stenosis even without ischemic signs or Sx.
- Stent thrombosis by the ARC criteria:
  (1) Definite, probable, or possible.
  (2) Acute, subacute, late, or very late.
- Procedural success: final diameter stenosis <30% without in-hospital death, Q-wave MI, or urgent revascularization of the target vessel.

Stenting Procedure

- Mixture of DES is not permitted by the protocol.
- If the patients have multiple lesions, all the lesions should be covered with the assigned study stent.
- If the assigned stent still fails to reach the lesion despite proper pre-dilation, another type of stent (either DES or BMS) may be considered.
- If the non-target vessel is too large (>4.5mm) to be stented with allocated DES, bare-metal stent can be accepted.
- Complete lesion coverage is recommended

Antiplatelet Regimen

Pre-Procedure

- Aspirin (≥ 100mg)
- Clopidogrel (loading dose) : 300 or 600 mg

During Procedure

- Heparin: IV bolus + boluses to maintain ACT > 250 s
- GP IIb/IIIa inhibitors: at physician's discretion

After Discharge

- Aspirin: 100-325 mg /day indefinitely
- Clopidogrel: 75 mg once daily for ≥ at least 12 months

Follow-up

Clinical Follow-up

- 1, 4, 9, and 12 months

Angiographic Follow-up

- 9 (±2) months
- All patients were asked to return for an angiographic follow-up.

ZEST Trial - Participants

“19 Centers in Korea”

1.	Asan Medical Center, Seoul	Seung-Jung Park
2.	Yonsei University Medical Center, Seoul	Yangsoo Jang
3.	Catholic Medical Center, Seoul	Ki Bae Seung
4.	Seoul National University Hospital, Seoul	Hyo-Soo Kim
5.	Ajou University Hospital, Suwon	Seung-Jae Tahk
6.	Chonnam National University Hospital, Gwangju	Myung Ho Jeong
7.	Chungnam National University Hospital, Daejeon	In-Whan Seong
8.	NHIC Ilsan Hospital, Ilsan	Joo-Young Yang
9.	Keimyung University Dongsan Medical Center, Daegu	Seung-Ho Hur
10.	Chonbuk National University Hospital, Jeonju	Jae-Gun Chae
11.	Asan Medical Center, GangNeung	Sang-Sig Cheong
12.	Ulsan University Hospital, Ulsan	Sang-Gon Lee
13.	Soonchunhyang University Bucheon Hospital, Bucheon	Nae-Hee Lee
14.	Hallym University Sacred Heart Hospital, PyeongChon	Young-Jin Choi
15.	Daegu Catholic University Medical Center, Daegu	Taeg Jong Hong
16.	Pusan Natioanal University Hospital, Pusan	Kee-Sik Kim
17.	Kyungpook National University Hospital, Daegu	Hun Sik Park
18.	Yonsei University Wonju Christian Hospital, Wonju	Junghan Yoon
19.	Korea University Hospital, Seoul	Do-Sun Lim

Clinical Trial Organization

Principal Investigators:	Seung-Jung Park, MD, PhD Asan Medical Center
Clinical Events Committee:	Jae-Joong Kim, MD, PhD Asan Medical Center
Data Safety Monitoring Board:	Moo-Song Lee, MD, PhD University of Ulsan Medical College
Data Coordination/Site Management:	Clinical Research Center Asan Medical Center
Angiographic Core Lab:	CVRF in Korea

Http://www.zest-trial.com

- Randomization ; Computer-generating randomization (Web-based)
- Data collection ; Electric Case Report Form (CRF)
- DSMB (data safety monitoring board) ; Site Monitoring and AE/SAE reporting
- CEC (clinical event committee) ; Events adjudication
- Independent data analysis ; Statistical analysis and final results reporting

Sample Size Calculation and Statistical Analysis

- On the basis of early studies of DES, we assumed an incidence of primary endpoint of 6% in the SES, 11% in the ZES, and 17% in the PES group.
- We intended to give more than 90% power to the study and chose an α level of 0.025 (corrected by the Bonferroni method for the 2 planned comparison in the **primary analysis: non-inferiority for ZES vs. SES and superiority for ZES vs. PES**).
- A sample size of 2640 patients (880 patients per group) was calculated.
- All enrolled patients were included in the analyses of primary and secondary outcomes according to the intention-to-treat principle.
- A P value of <0.025 was considered statistically significant.

Results

Baseline Characteristics

Patients	ZES (n=883)	SES (n=878)	PES (n=884)	P value
Age (yr)	62±9	62±10	62±10	0.80
Male sex	586 (66)	591 (67)	582 (66)	0.80
Body mass index	25±3	25±3	25±3	0.88
Diabetes mellitus				
Any diabetes	268 (30)	247 (28)	245 (28)	0.42
Requiring insulin	32 (4)	33 (4)	36 (4)	0.88
Hypertension	552 (63)	517 (59)	540 (61)	0.29
Hyperlipidemia	466 (53)	451 (51)	446 (51)	0.62
Current smoker	236 (27)	256 (29)	243 (28)	0.51
Family history of CAD	48 (5)	44 (5)	52 (6)	0.72

n (%)

Baseline Characteristics

Patients	ZES (n=883)	SES (n=878)	PES (n=884)	P value
Previous PCI	75 (9)	82 (9)	83 (9)	0.76
Previous CABG	6 (1)	6 (1)	5 (1)	0.94
Previous MI	30 (3)	39 (4)	41 (5)	0.37
Previous CHF	9 (1)	4 (1)	7 (1)	0.39
Chronic lung disease	13 (2)	8 (1)	26 (3)	0.004
Cerebrovascular disease	65 (7)	55 (6)	53 (6)	0.47
Peripheral vascular disease	15 (2)	21 (2)	17 (2)	0.57
Renal insufficiency	7 (1)	7 (1)	6 (1)	0.95
Multi-vessel disease	414 (47)	430 (49)	410 (46)	0.51
Ejection fraction (%)	61±8	61±8	61±8	0.59

n (%)

Baseline Characteristics

Patients	ZES (n=883)	SES (n=878)	PES (n=884)	P value
Clinical indication (%)				0.73
Silent ischemia	48 (5)	44 (5)	56 (6)	
Chronic stable angina	348 (39)	343 (39)	343 (39)	
Unstable angina	410 (46)	424 (48)	403 (46)	
NSTEMI	77 (9)	67 (8)	82 (9)	
Electrocardiographic findings				0.99
Sinus rhythm	850 (96)	849 (97)	854 (97)	
Atrial fibrillation	21 (2)	18 (2)	17 (2)	
Other	12 (1)	11 (1)	13 (1)	

n (%)

Lesion Characteristics

Lesions	ZES (n=1190)	SES (n=1218)	PES (n=1205)	P value
Location				0.39
LAD	622 (52)	645 (53)	611 (51)	
LCX	252 (21)	225 (19)	253 (21)	
RCA	316 (27)	348 (29)	340 (28)	
Coronary graft	0	0	1 (0.1)	
ACC-AHA B2 or C type	858 (72)	921 (76)	895 (74)	0.14
Total occlusion	68 (6)	76 (6)	96 (8)	0.07
Thrombus-containing	32 (3)	37 (3)	38 (3)	0.78
Bifurcation lesion	181 (15)	151 (12)	168 (14)	0.14
Ostial lesion	85 (7)	72 (6)	82 (7)	0.45
Restenotic lesion	5 (0.4)	12 (1)	13 (1)	0.16

n (%)

Lesion Characteristics

Lesions	ZES (n=1190)	SES (n=1218)	PES (n=1205)	P value
Calcification				0.76
None or mild	1129 (95)	1145 (94)	1132 (94)	
Moderate	40 (3)	43 (4)	46 (4)	
Severe	21 (2)	30 (3)	27 (2)	
Lesion length				0.09
<10 mm	73 (6)	71 (6)	61 (5)	
10-20 mm	466 (39)	444 (37)	504 (42)	
>20 mm	651 (55)	703 (58)	640 (53)	

n (%)

Procedure Characteristics

Lesions	ZES (n=1190)	SES (n=1218)	PES (n=1205)	P value
No. of stents per lesion	1.2±0.4	1.2±0.4	1.2±0.4	0.35
No. of stents per patient	1.6±0.9	1.6±0.9	1.6±0.9	0.92
Length of stents per lesion	27.9±13.1	28.9±13.5	28.9±14.3	0.12
Length of stents per patients	39.7±26.8	38.3±24.3	38.9±25.2	0.45
Maximal stent diameter	3.4±0.7	3.4±0.7	3.5±0.6	0.03
Maximal pressure	16.3±4.2	16.3±4.1	16.2±4.2	0.95
Direct stenting	84 (7)	109 (9)	89 (7)	0.24
Use of IVUS	488 (41)	514 (42)	491 (41)	0.62
Use of glycoprotein IIb-IIIa inhibitors	19 (2)	15 (2)	14 (2)	0.64

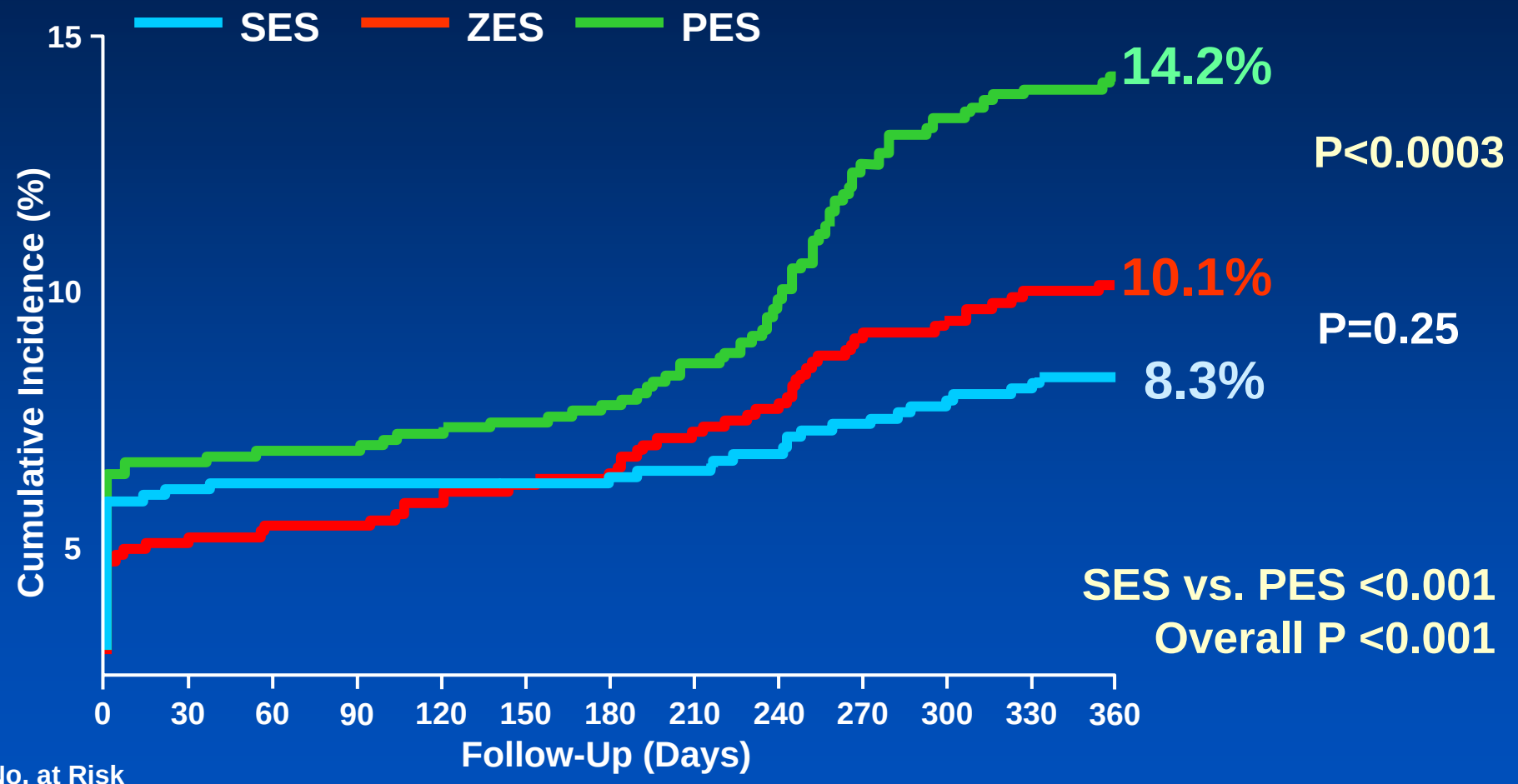
Discharge Medication

Patients	ZES (n=883)	SES (n=878)	PES (n=884)	P value
Aspirin	882 (99.9)	873 (99.4)	880 (99.5)	0.27
Clopidogrel	876 (99.2)	874 (99.5)	881 (99.7)	0.39
Cilostazol	251 (28.4)	230 (26.2)	244 (27.6)	0.54
Warfarin	3 (0.3)	7 (0.8)	6 (0.7)	0.44
Statin	698 (79.0)	720 (82.0)	715 (80.9)	0.29
ACE inhibitor	343 (38.8)	312 (35.5)	315 (35.6)	0.26
ARB	235 (26.6)	222 (25.3)	242 (27.4)	0.60
ß-blocker	581 (65.8)	562 (64.0)	594 (67.2)	0.37
Calcium channel blocker	460 (52.1)	481 (54.8)	439 (49.7)	0.10

Clinical Events During 12 Months of Follow-Up

Death, MI, Ischemia-driven TVR

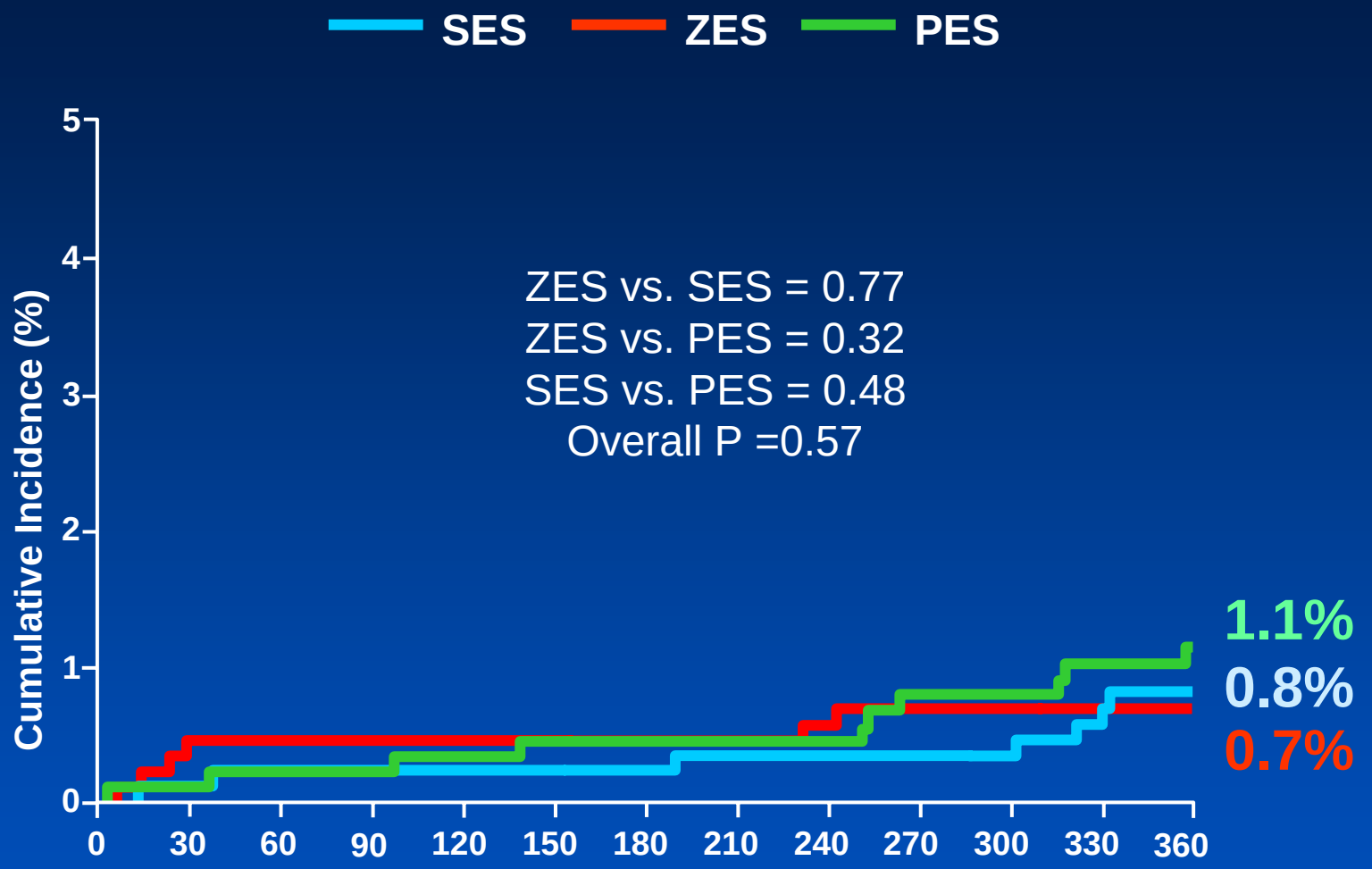
Primary End Point at 12 month



No. at Risk

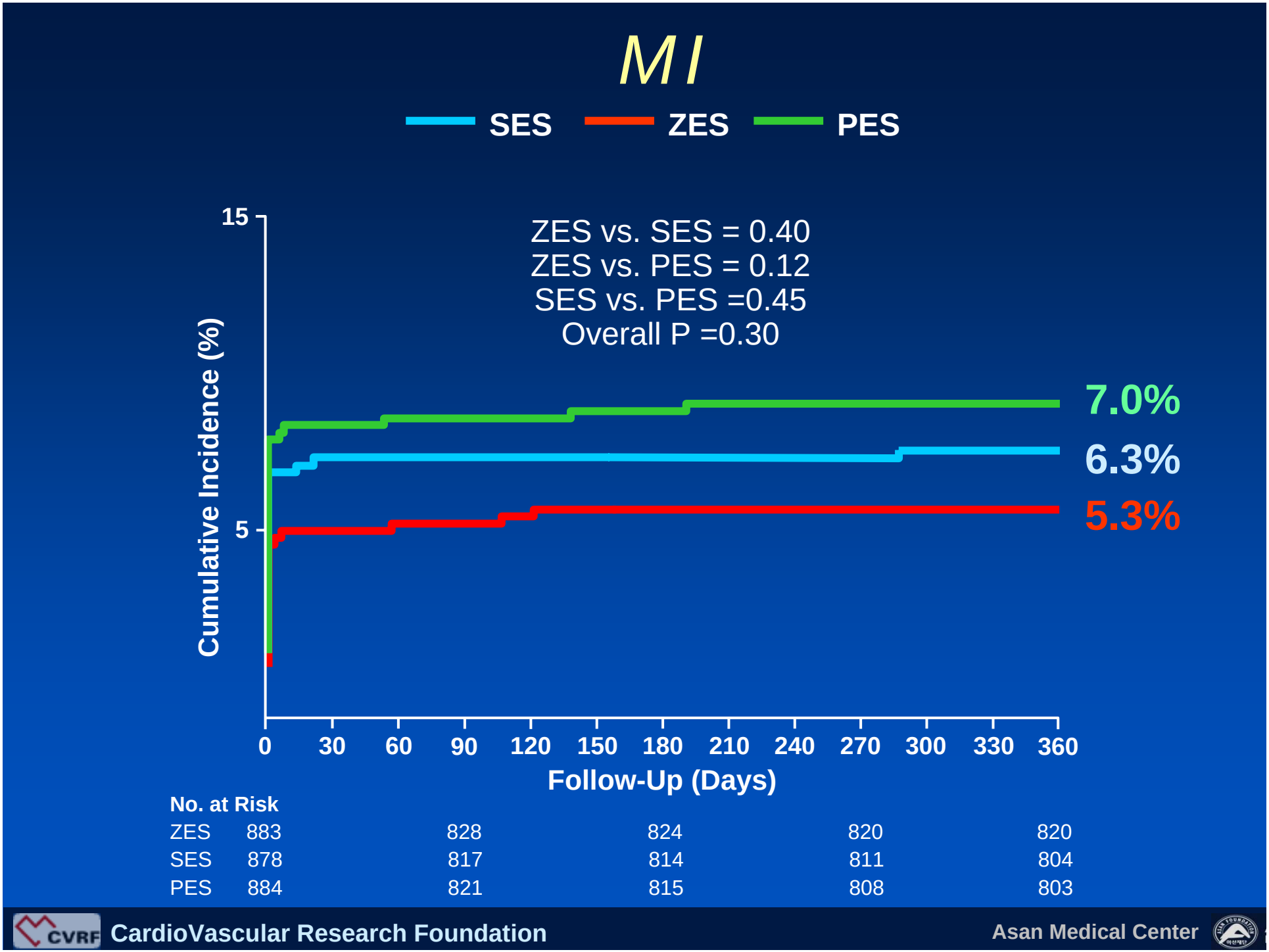
ZES	883	827	816	790	782
SES	878	816	813	802	792
PES	884	821	808	763	745

Death



No. at Risk					
ZES	883	871	869	864	864
SES	878	869	867	863	857
PES	884	880	873	865	859

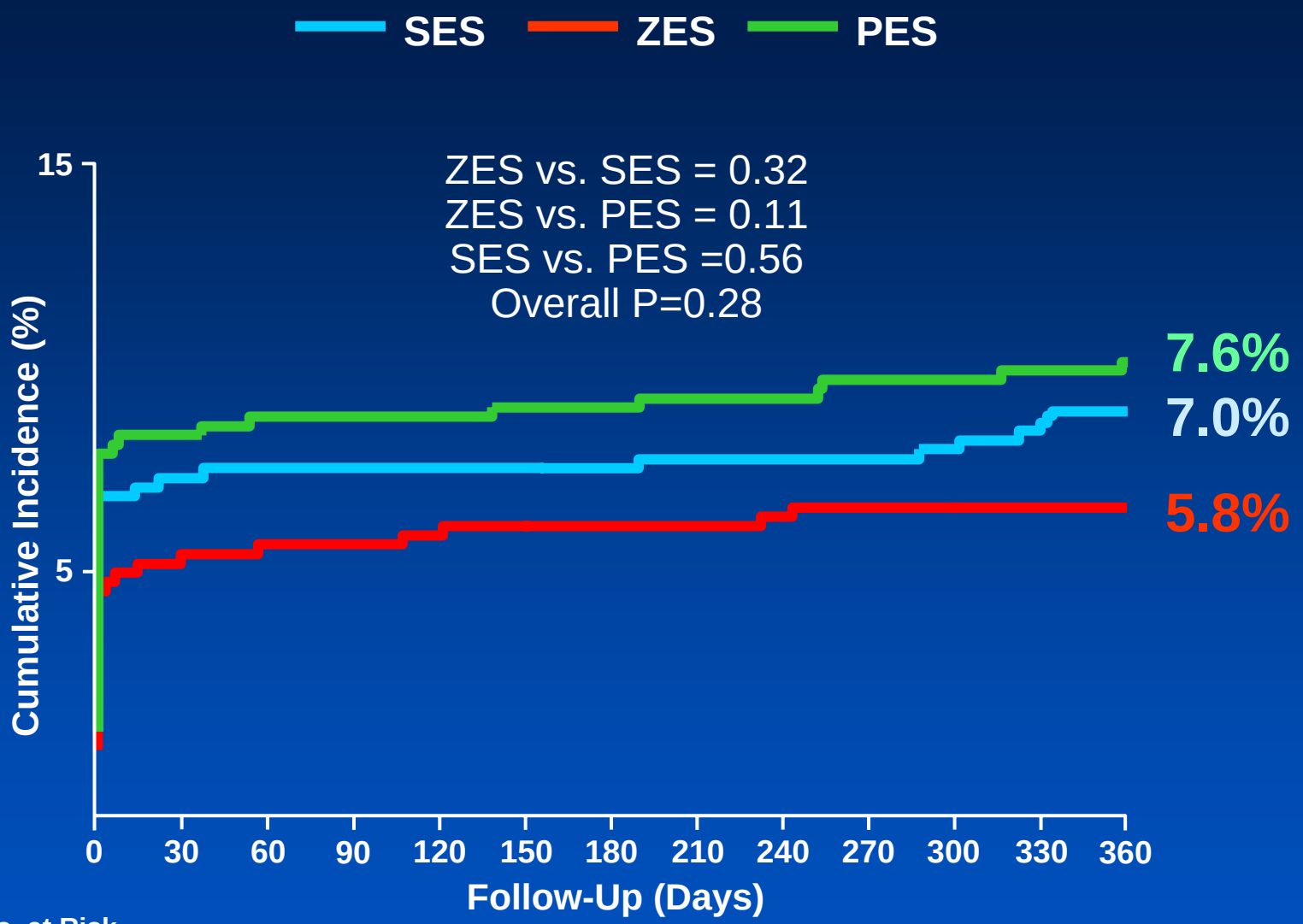
MI



No. at Risk

ZES	883	828	824	820	820
SES	878	817	814	811	804
PES	884	821	815	808	803

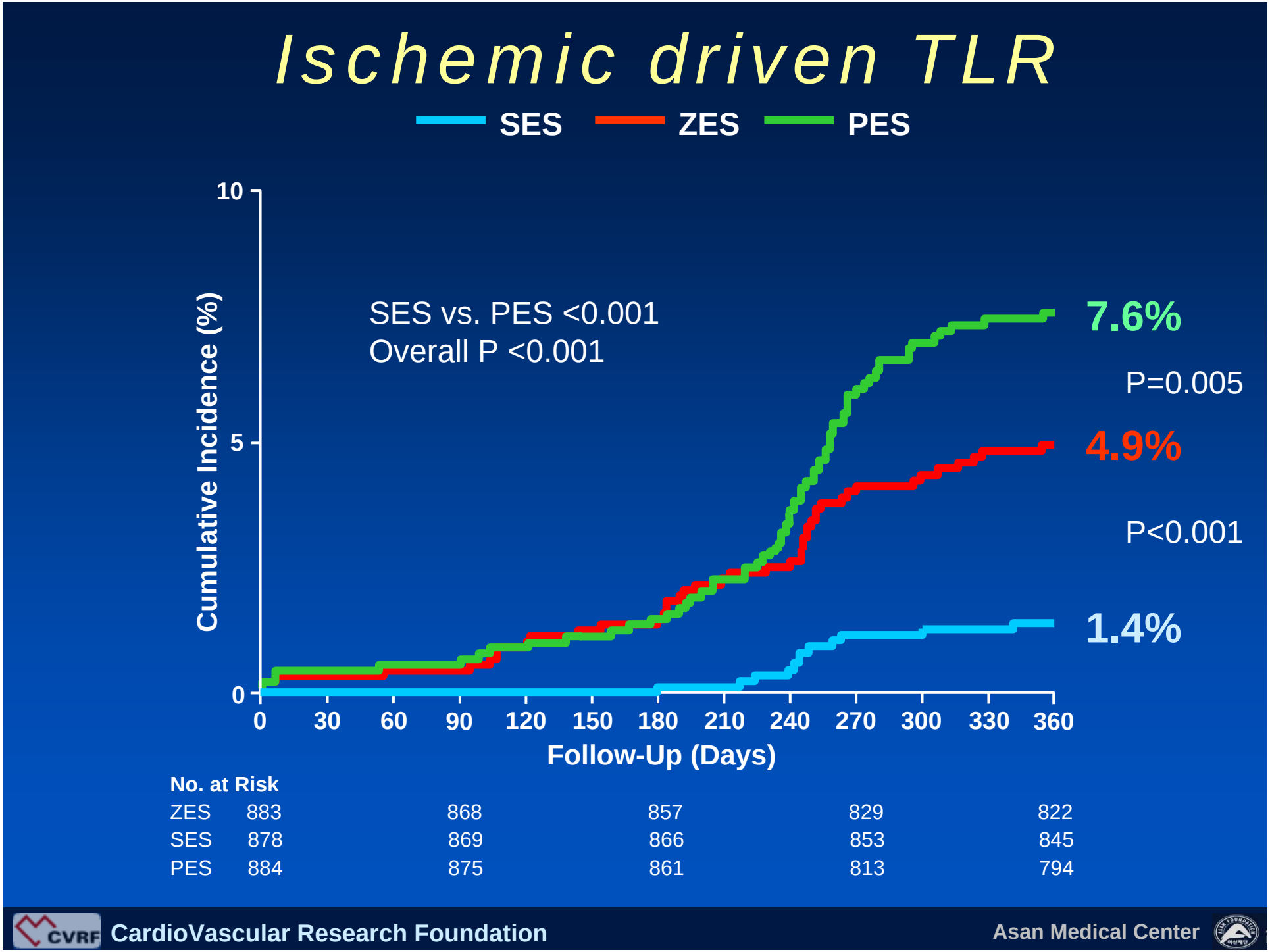
Death or MI



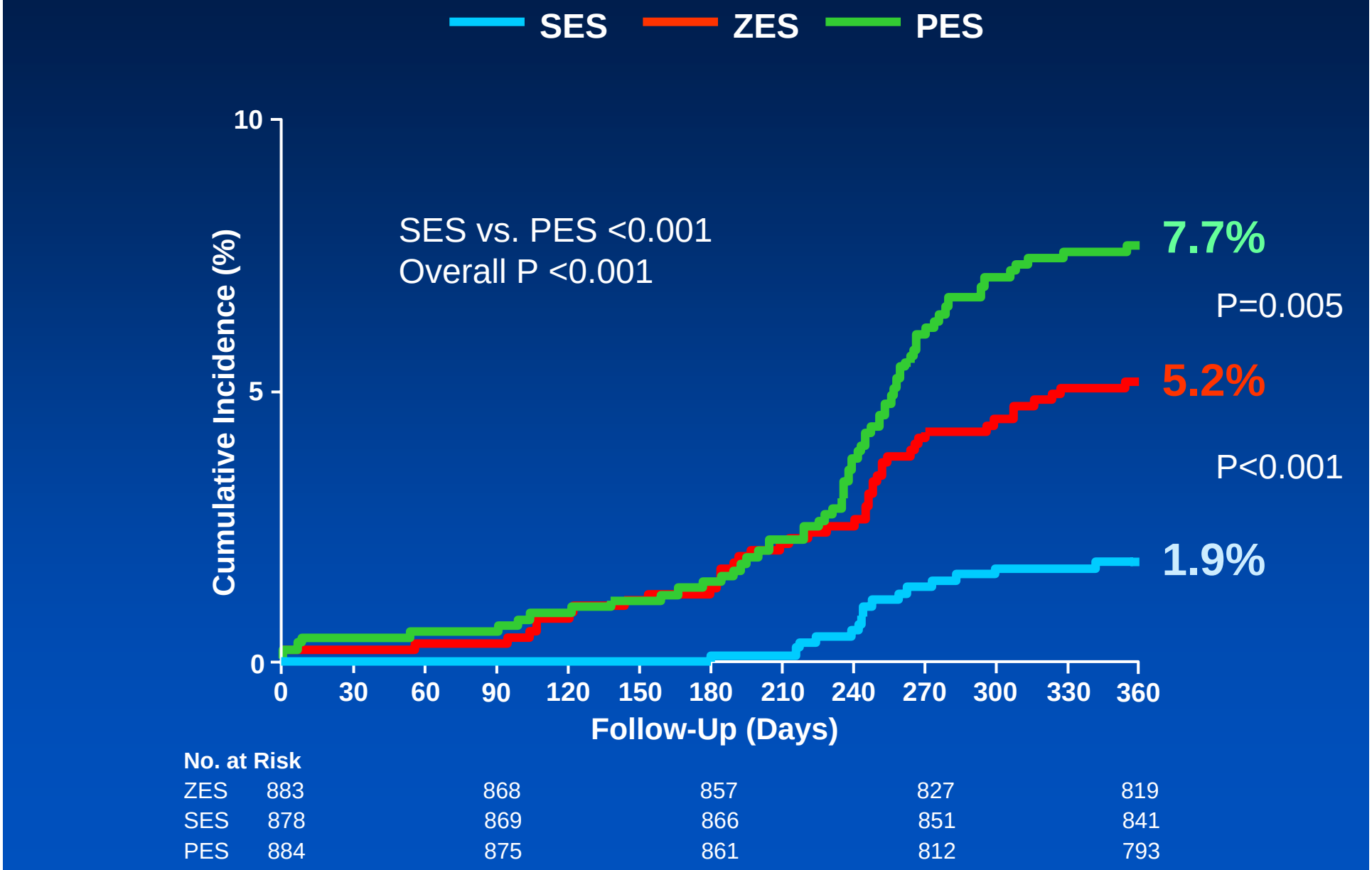
No. at Risk

ZES	883	828	824	820	820
SES	878	817	814	811	804
PES	884	821	815	808	803

Ischemic driven TLR

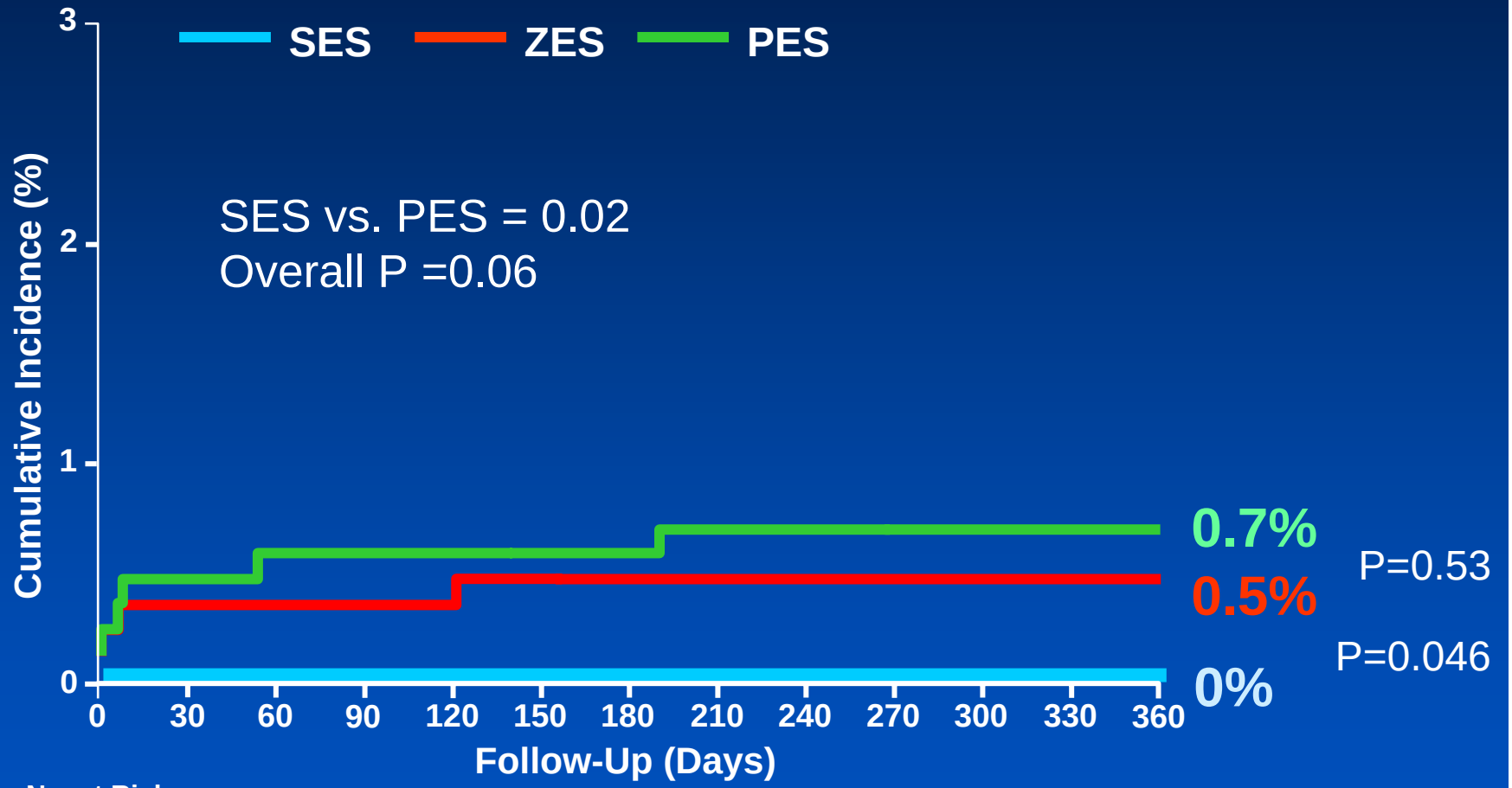


Ischemic driven TVR



No. at Risk					
ZES	883	868	857	827	819
SES	878	869	866	851	841
PES	884	875	861	812	793

Stent Thrombosis
: ARC Definite Criteria

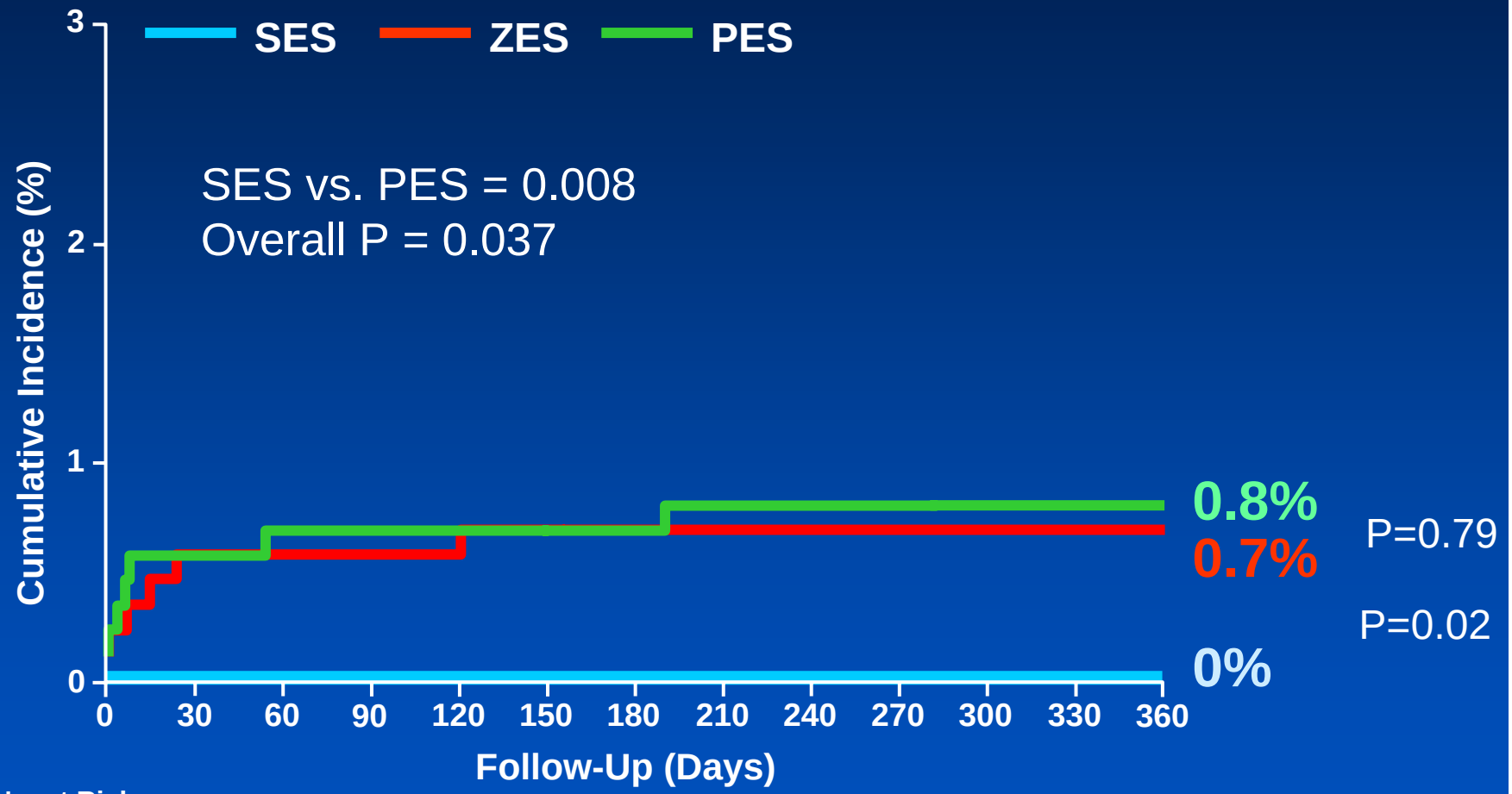


No. at Risk

ZES	883	869	866	861	861
SES	878	869	867	863	857
PES	884	875	868	859	853

Stent Thrombosis

: ARC Definite or Probable Criteria

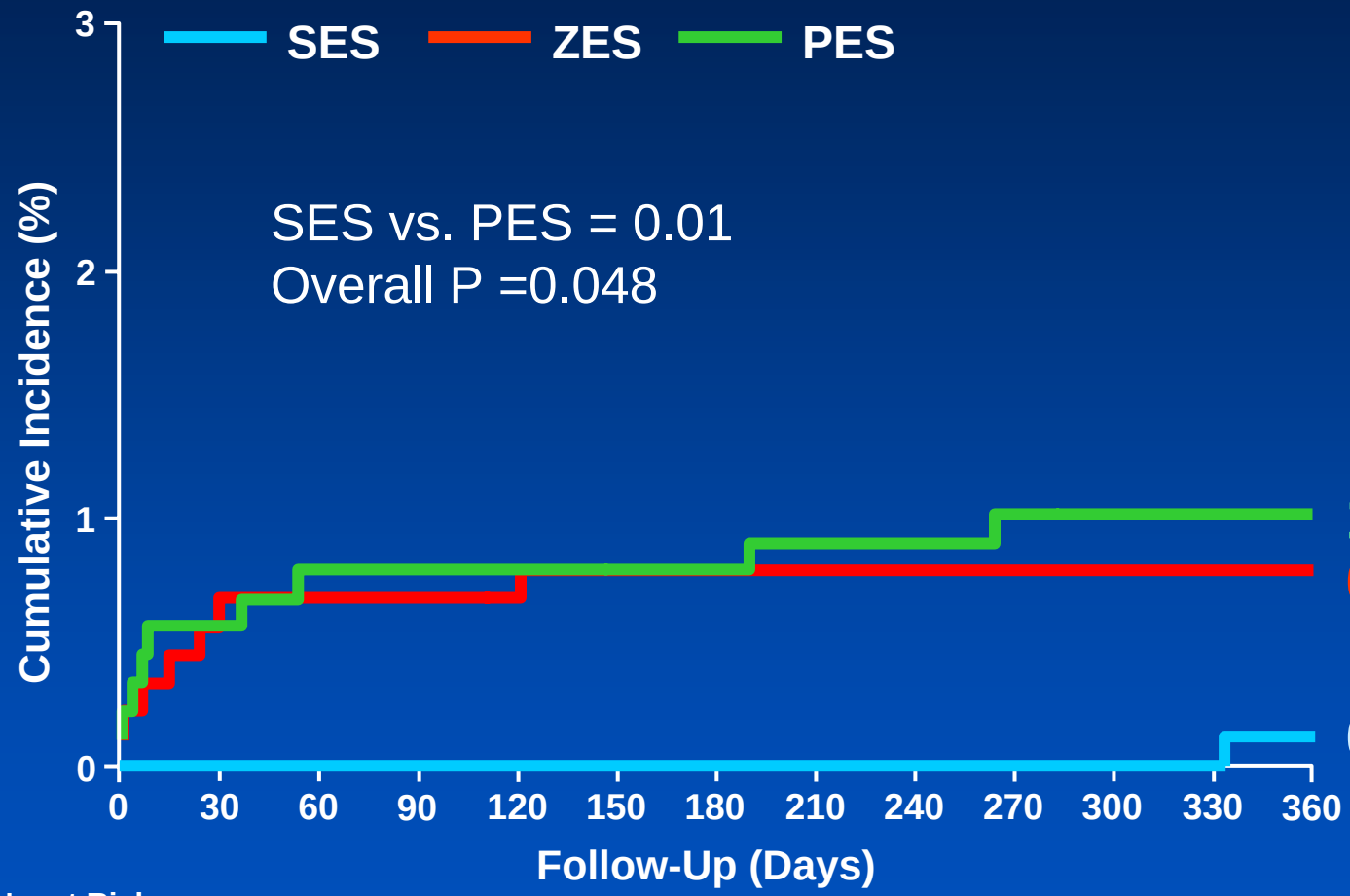


No. at Risk

ZES	883	869	866	861	861
SES	878	869	867	863	857
PES	884	875	868	859	853

Stent Thrombosis

: ARC Any Criteria



No. at Risk

ZES	883	869	866	861	861
SES	878	869	867	863	857
PES	884	875	868	859	853

Major Clinical Events at 1 Months

N (%)	ZES (n=883)	SES (n=878)	PES (n=884)	P
Death	3 (0.3)	1 (0.1)	1 (0.1)	0.55
Cardiac	3 (0.3)	1 (0.1)	1 (0.1)	0.55
Noncardiac	0	0	0	NA
MI	44 (5.0)	54 (6.2)	60 (6.8)	0.27
Q-wave	3 (0.3)	3 (0.3)	3 (0.3)	1.00
Non-Q-wave	41 (4.6)	51 (5.8)	57 (6.4)	0.25
Death or MI	45 (5.1)	54 (6.2)	60 (6.8)	0.32
TLR	3 (0.3)	0	4 (0.5)	0.23
Percutaneous	3 (0.3)	0	4 (0.5)	0.23
Surgical	0	0	0	NA
TVR	3 (0.3)	0	4 (0.5)	0.23
Percutaneous	3 (0.3)	0	4 (0.5)	0.23
Surgical	0	0	0	NA
MACE*	45 (5.1)	54 (6.2)	60 (6.8)	0.32

*MACE: composite of death, MI, or ischemia-driven TVR

Major Clinical Events at 12 Months

	ZES (n=883)	SES (n=878)	PES (n=884)	P
Death	6 (0.7)	7 (0.8)	10 (1.1)	0.57
Cardiac	5 (0.6)	3 (0.3)	5 (0.6)	0.74
Noncardiac	1 (0.1)	4 (0.5)	5 (0.6)	0.27
MI	47 (5.3)	55 (6.3)	62 (7.0)	0.30
Q-wave	5 (0.6)	3 (0.3)	5 (0.6)	0.74
Non-Q-wave	42 (4.8)	52 (5.9)	57 (6.4)	0.26
Death or MI	51 (5.8)	61 (6.9)	67 (7.6)	0.28
TLR	43 (4.9)	12 (1.4)	66 (7.5)	<0.001
Percutaneous	43 (4.9)	11 (1.3)	65 (7.4)	<0.001
Surgical	0	1 (0.1)	1 (0.1)	0.61
TVR	46 (5.2)	16 (1.8)	67 (7.6)	<0.001
Percutaneous	46 (5.2)	15 (1.7)	66 (7.5)	<0.001
Surgical	0	1 (0.1)	1 (0.1)	0.61
Primary end point*	90 (10.2)	73 (8.3)	125 (14.1)	<0.001

*Primary end point: composite of death, MI, or ischemia-driven TVR

N (%)

Stent Thrombosis at 12 Months

	ZES (n=883)	SES (n=878)	PES (n=884)	P
Type of ST				
Definite	4 (0.5)	0	6 (0.7)	0.06
Probable	2 (0.2)	0	1 (0.1)	0.37
Possible	1 (0.1)	1 (0.1)	2 (0.2)	0.78
Definite or Probable	6 (0.7)	0	7 (0.8)	0.04
Any Criteria	7 (0.8)	1 (0.1)	9 (1.0)	0.048
Timing of ST				
Definite or Probable	6 (0.7)	0	7 (0.8)	0.04
Acute	1 (0.1)	0	1 (0.1)	1.00
Subacute	4 (0.5)	0	4 (0.5)	0.14
Late	1 (0.1)	0	2 (0.2)	0.78

Results of Quantitative Coronary Analysis are being in the finalizing process and will be reported in the final study outcome.

Conclusion

- As compared with first-generation DES (SES and PES), the use of ZES results in similar major adverse cardiac events with reference to SES, but in fewer major adverse cardiac events with reference to PES.

Conclusion

- There was a trend toward lower rates of death or MI in the ZES group as compared with the SES and PES group.
- The rates of Ischemia-driven TLR and TVR in the ZES group was significantly lower than the PES group, but higher than in the SES group.
- The rate of stent thrombosis in the ZES group was similar with the PES group, but higher than in the SES group.