Impact of Diabetes on long-term outcomes of DES in Asian patients

-AMC Experience-

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General Concerns
about Diabetic Influence in Patients Undergoing PCI with DES

- Still higher restenosis rate and MACE in diabetics compare to non-diabetics
- Higher mortality after PCI with DES ?
- Higher incidence of stent thrombosis ?

Prognostic Influence of Diabetes Mellitus on Long-Term Clinical Outcomes and Stent Thrombosis Following DES Implantation in Asian Patients

Overall 3160 patients:

Diabetes (n=865) vs. Non-diabetes (n=2295) during 3-year follow-up.

Outcomes of study

- Primary end-point
  ; Composite of death, nonfatal MI, or TVR

- Secondary end-points
  ; Death, MI, TLR, TVR, and stent thrombosis
  (ARC criteria)

Baseline characteristics

Variable	Diabetes (n=865)	Non-diabetes (n=2295)	*P*
Age (years)	62.7±9.1	59.7±10.6	<0.001
Female	312 (36.1)	619 (27.0)	<0.001
Hypertension	533 (61.6)	1066 (46.4)	<0.001
Lipid profiles			
Total cholesterol (mg/dl)	178.2±53.3	172.2±48.5	0.003
Triglyceride (mg/dl)	161.2±102.8	147.0±93.5	0.005
HDL cholesterol (mg/dl)	41.9±17.3	43.2±15.1	0.10
Current smoking	201 (23.2)	719 (31.3)	<0.001
Renal failure	50 (5.8)	30 (1.3)	<0.001
Previous myocardial infarction	99 (11.4)	198 (8.6)	0.02
Previous coronary angioplasty	161 (18.6)	383 (16.7)	0.20
Previous coronary artery bypass graft	31 (3.6)	53 (2.3)	0.05

Baseline characteristics

Variable	Diabetes (n=865)	Non-diabetes (n=2295)	*P*
Clinical indication			<0.001
Stable angina	450 (52.0)	1074 (46.8)	
Unstable angina	334 (38.6)	865 (37.7)	
Myocardial infarction	81 (9.4)	356 (15.5)	
Multivessel disease	585 (67.6)	1280 (55.8)	<0.001
Left ventricular ejection fraction (%)	57.9±9.3	58.6±8.7	0.04
Medications at discharge			
Warfarin	10 (1.2)	21 (0.9)	0.54
Statin	498 (57.6)	1240 (54.0)	0.07
β-Blocker	631 (72.9)	1629 (71.0)	0.28
Calcium Channel Blocker	417 (48.2)	1129 (49.2)	0.62
ACE inhibitor	536 (62.0)	1271 (55.4)	0.001

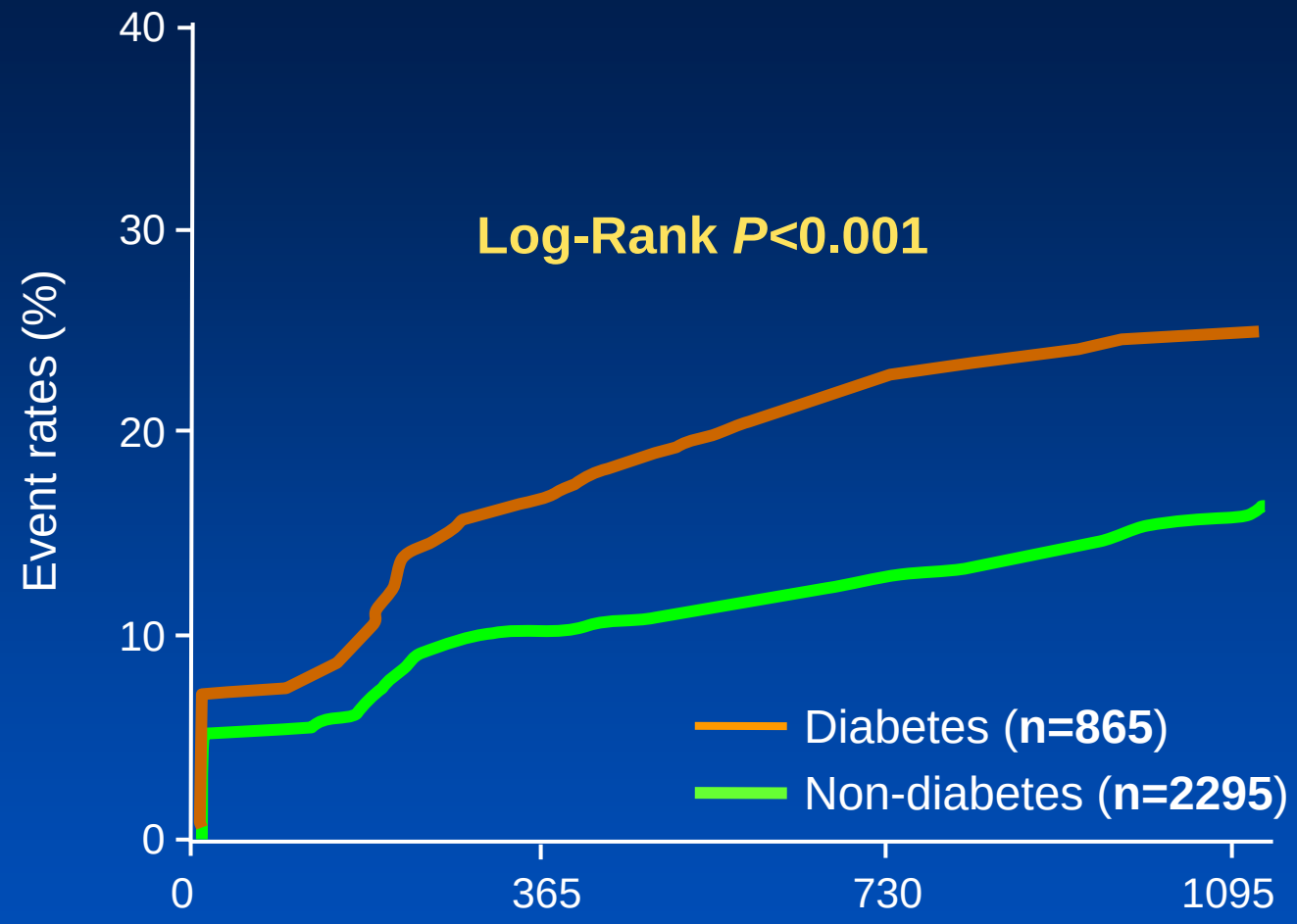
Baseline characteristics

Variable	Diabetes (n=865)	Non-diabetes (n=2295)	*P*
Treated lesions, No.	1301	3190	
Left anterior descending artery	637 (49.0)	1579 (49.5)	0.74
Left main artery	83 (6.4)	224 (7.0)	0.44
Lesion Characteristics			
ACC/AHA type B2 or C lesion	1008 (77.5)	2330 (73.0)	0.002
Ostial	84 (6.5)	271 (8.5)	0.02
Bifurcation	236 (18.1)	501 (15.7)	0.05
Total occlusion	70 (5.4)	181 (5.7)	0.70
Restenotic lesion	68 (5.2)	183 (5.7)	0.50

Procedural characteristics

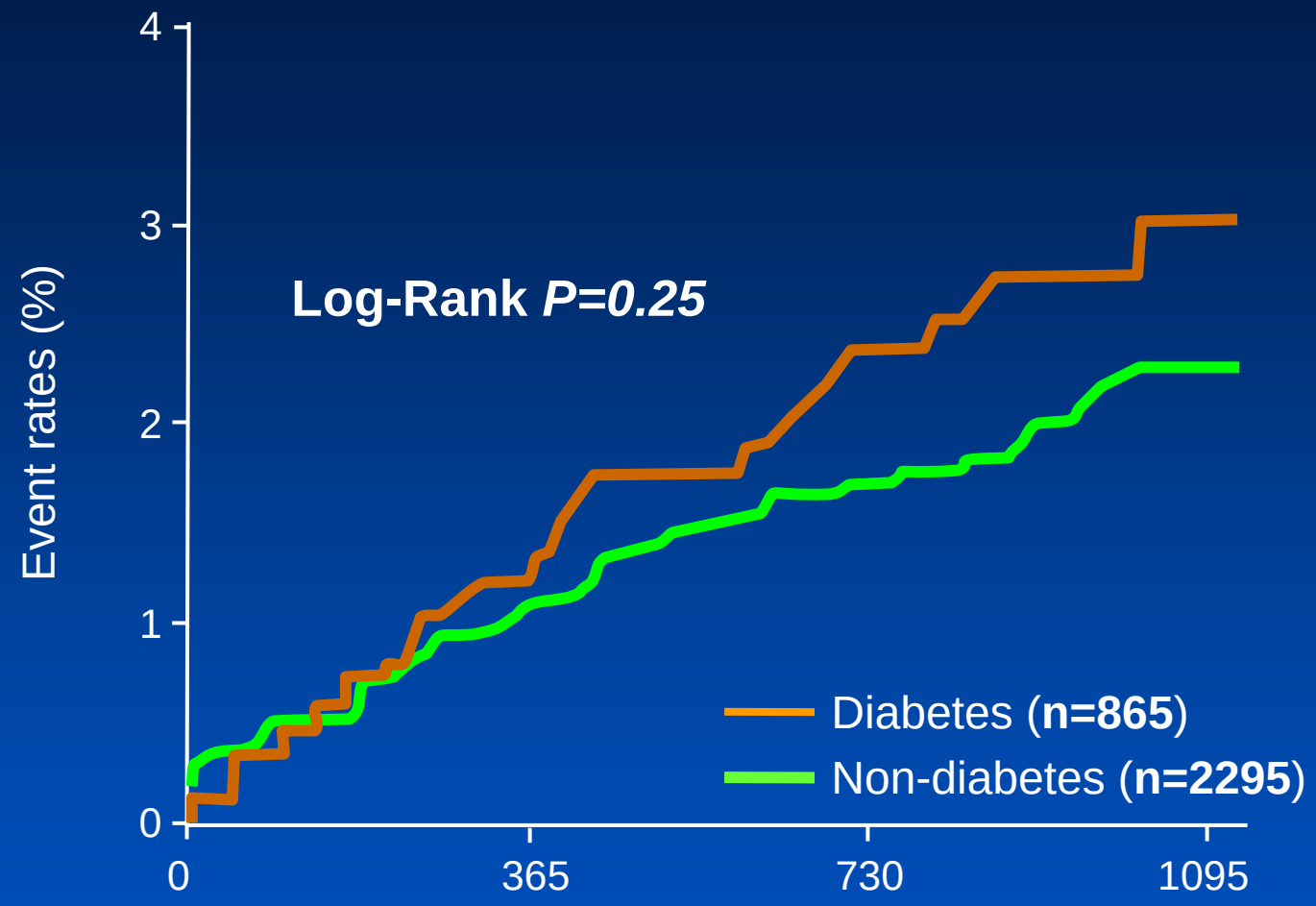
Variable	Diabetes (n=865)	Non-diabetes (n=2295)	*P*
Treated lesions, No.	1301	3190	
Direct stenting	174 (13.4)	553 (17.3)	0.001
IVUS guidance	798 (61.3)	2099 (65.8)	0.01
DES type			0.06
Sirolimus-eluting stent	976 (75.0)	2478 (77.7)	
Paclitaxel-eluting stent	325 (25.0)	712 (22.3)	
Number of stents per patient	2.1±1.2	1.8±1.1	<0.001
Total stent length per patient (mm)	53.5±33.3	46.0±29.8	<0.001
Average stent diameter per patient (mm)	3.1±0.3	3.2±0.3	<0.001
Use of Glycoprotein IIb/IIIa inhibitors	24 (2.8)	69 (3.0)	0.73

Composite of Death, MI, or TVR



No. at Risk				
Diabetes	865	730	457	195
Non-diabetes	2295	2057	1339	581

Stent Thrombosis



No. at Risk				
Diabetes	865	842	561	247
Non-diabetes	2295	2248	1521	674

Adjusted HRs of Clinical Outcomes
Diabetic vs. Non-diabetics

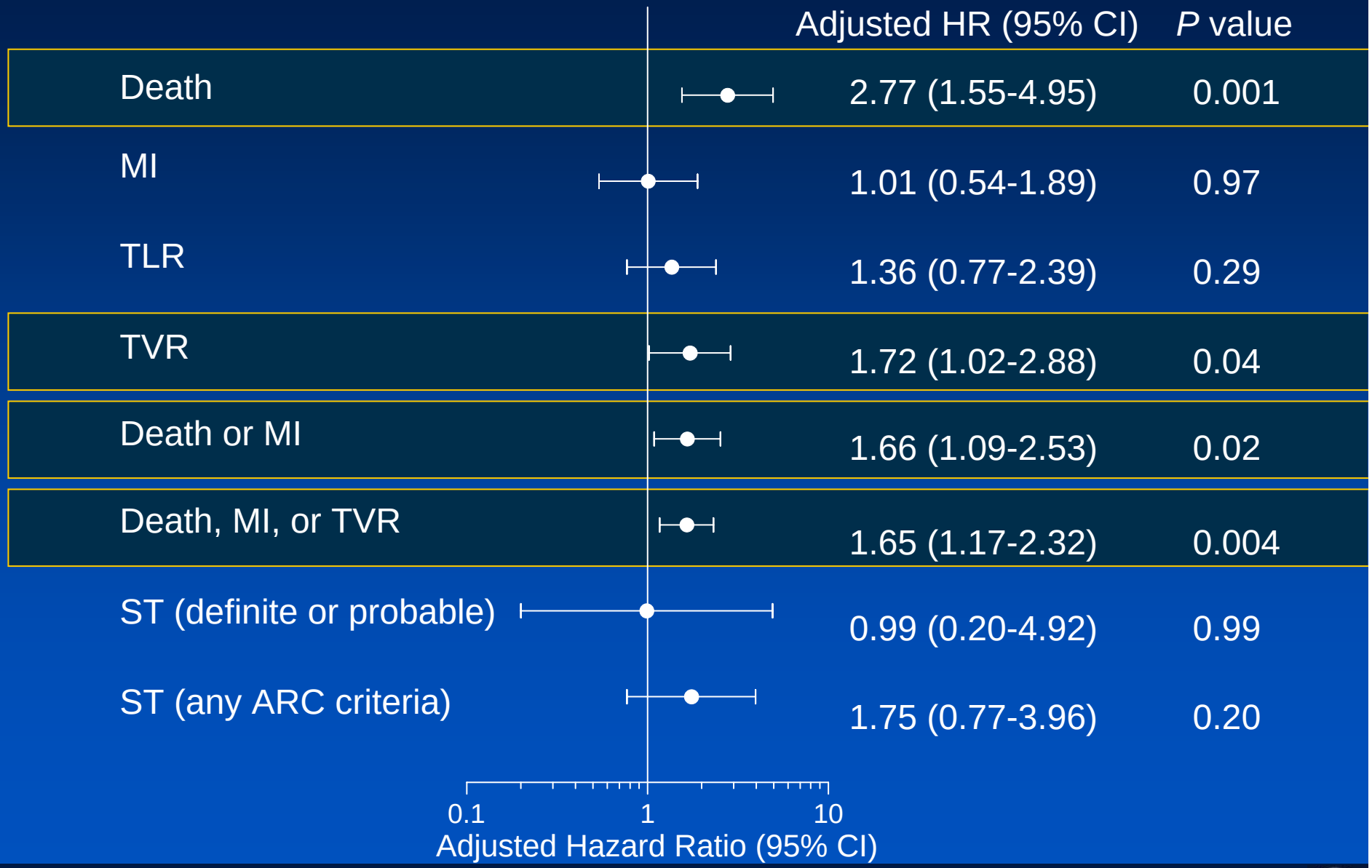
Outcome	HR	95% CI	P
Death	1.35	0.89-2.05	0.16
MI	1.08	0.78-1.50	0.63
TLR	1.06	0.78-1.43	0.71
TVR	1.37	1.04-1.81	0.03
Death/MI	1.18	0.92-1.53	0.20
Death/MI/TVR	1.24	1.02-1.51	0.03
Stent thrombosis			
Definite	0.62	0.20-1.84	0.41
Definite/probable	0.87	0.37-2.06	0.77
Any	1.14	0.69-1.99	0.64

Non-diabetes vs. **Non-insulin-treated diabetes**

	Adjusted HR (95% CI)	*P* value
Death	0.86 (0.52-1.45)	0.58
MI	1.05 (0.74-1.49)	0.79
TLR	0.94 (0.67-1.32)	0.72
TVR	1.23 (0.91-1.67)	0.18
Death or MI	0.99 (0.74-1.31)	0.92
Death, MI, or TVR	1.08 (0.87-1.35)	0.47
ST (definite or probable)	0.62 (0.21-1.88)	0.40
ST (any ARC criteria)	0.74 (0.36-1.52)	0.41

Adjusted Hazard Ratio (95% CI)

Non-diabetes vs. **Insulin-treated diabetes**



Independent predictors of clinical events

Predictors	Hazard Ratio	P Value
Death		
Insulin-treated diabetes	3.70 (2.21-6.21)	<0.001
Renal failure	2.63 (1.40-4.95)	0.003
Women	1.70 (1.09-2.65)	0.02
Age (per 1-year increase)	1.06 (1.04-1.08)	<0.001
LVEF (per 1%-increase)	0.97 (0.96-0.99)	0.003
Target-Vessel revascularization		
Insulin-treated diabetes	1.75 (1.10-2.78)	0.02
Previous coronary angioplasty	1.64 (1.22-2.19)	0.001
Paclitaxel-eluting stent	1.59 (1.19-2.11)	0.002
ACC/AHA type B2/C lesion	1.49 (1.02-2.19)	0.04
Number of stents (per 1-number increase)	1.23 (1.16-1.36)	<0.001
Age (per 1-year increase)	0.98 (0.96-0.99)	<0.001
Average stent diameter (per 1-mm increase)	0.57 (0.37-0.89)	0.01

Independent predictors of clinical events

Predictors	Hazard Ratio	P Value
Composite end point (death, MI, or TVR)		
Renal failure	2.14 (1.42-3.22)	<0.001
Insulin-treated diabetes	1.82 (1.33-2.50)	<0.001
Paclitaxel-eluting stent	1.40 (1.14-1.72)	0.001
ACC/AHA type B2/C lesion	1.32 (1.01-1.74)	0.04
Previous coronary angioplasty	1.31 (1.05-1.63)	0.02
Multivessel disease	1.29 (1.05-1.58)	0.02
Total stent length (per 1-mm increase)	1.007 (1.004-1.010)	<0.001
Average stent diameter (per 1-mm increase)	0.72 (0.52-0.98)	0.04

Independent predictors of Stent thrombosis

Predictors	Hazard Ratio	P Value
Definite		
Premature cessation of antiplatelet therapy	16.81 (5.26-53.79)	<0.001
Acute MI	5.32 (2.35-12.09)	<0.001
Restenotic lesion	3.99 (1.27-12.50)	0.02
Paclitaxel-eluting stent	2.26 (1.00-5.12)	0.05
Age (per 1year-increase)	0.95 (0.91-0.98)	0.001
Definite or probable		
Premature cessation of antiplatelet therapy	9.04 (3.04-26.88)	<0.001
Acute MI	6.64 (3.19-13.83)	<0.001
Restenotic lesion	4.55 (1.64-12.65)	0.004
Paclitaxel-eluting stent	2.22 (1.06-4.62)	0.03
Total stent length (per 1-mm increase)	1.01 (1.003-1.02)	0.01
Age (per 1year-increase)	0.96 (0.93-0.99)	0.01

Independent predictors of Stent thrombosis

Predictors	Hazard Ratio	P Value
Any ARC criteria		
Premature cessation of antiplatelet therapy	**7.12 (3.58-14.15)**	**<0.001**
Renal failure	**5.76 (2.79-11.92)**	**<0.001**
Acute MI	**2.54 (1.47-4.38)**	**0.001**
Total stent length (per 1-mm increase)	**1.01 (1.003-1.02)**	**0.004**
LVEF (per 1%-increase)	**0.96 (0.94-0.98)**	**0.001**

Summary:
Diabetic Impact in Asian Patients

- The overall mortality rate was similar in diabetic and non-diabetic patients
- Diabetic patients have a higher incidence of TVR, without a significantly increased rate of TLR
- There was no significant association between increased risk of stent thrombosis and diabetes, whether insulin-dependent or not
- Insulin-treated diabetes was independently associated with increased risk of death and TVR

A Randomized Comparison of SES vs. PES in Diabetic Patients

Lee et al, JACC 2008;52:727-33

A Randomized Comparison of triple antiplatelet therapy With dual antiplatelet therapy After drug-eluting stent implantation

:*D*rug-*E*luting stenting followed by *C*ilostazol treatment reduces *LA*te *Re*stenosis in Patients with *Diabetes* mellitus

The DECLARE-DIABETES Trial

Seong-Wook Park, Seung-Whan Lee, Duk-Woo Park, Young-Hak Kim, Cheol Whan Lee, Myeong-Ki Hong, Jae-Joong Kim, Seung-Jung Park
for the DECLARE-DIABETES Study investigators

Asan Medical Center,
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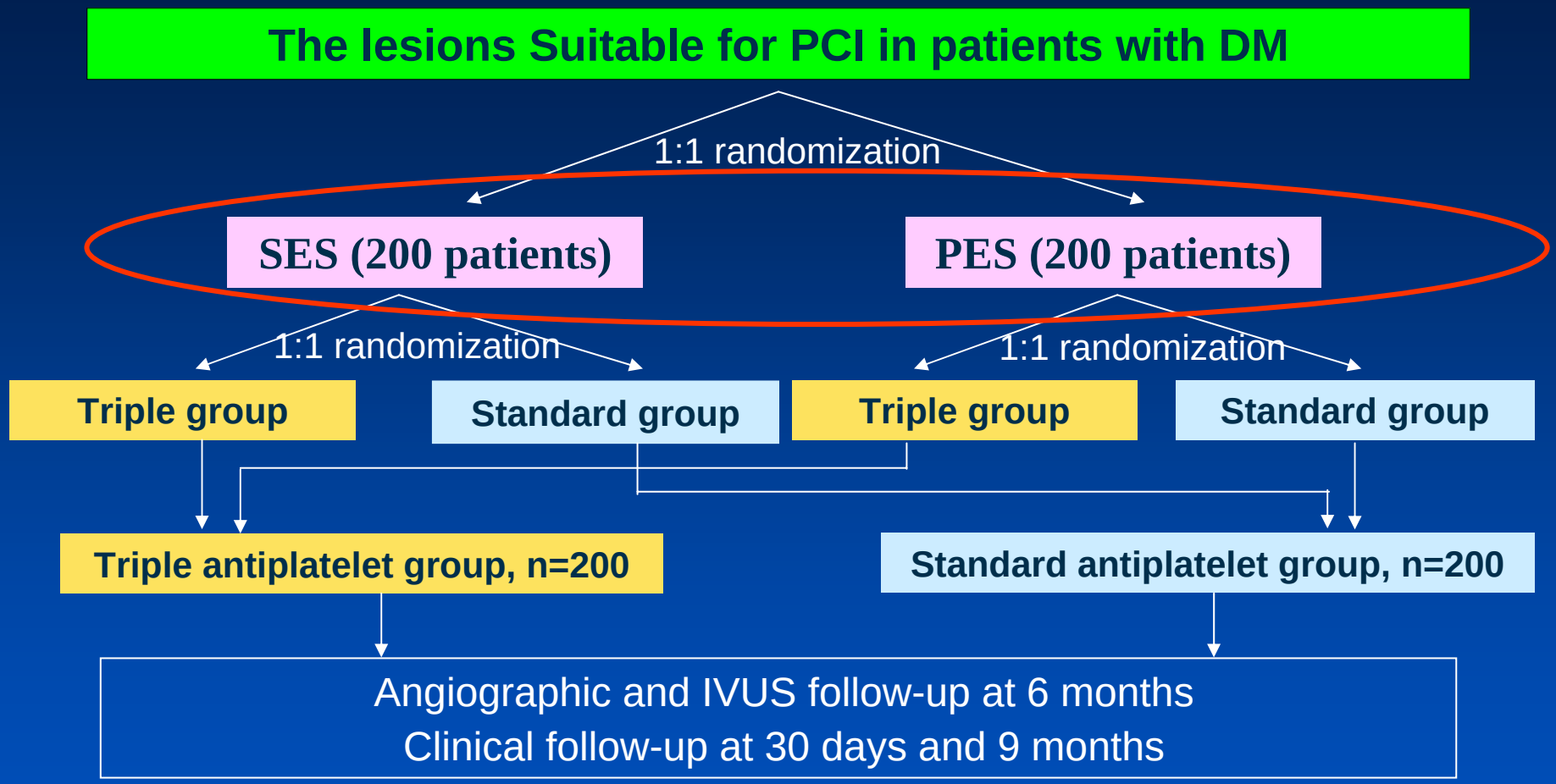
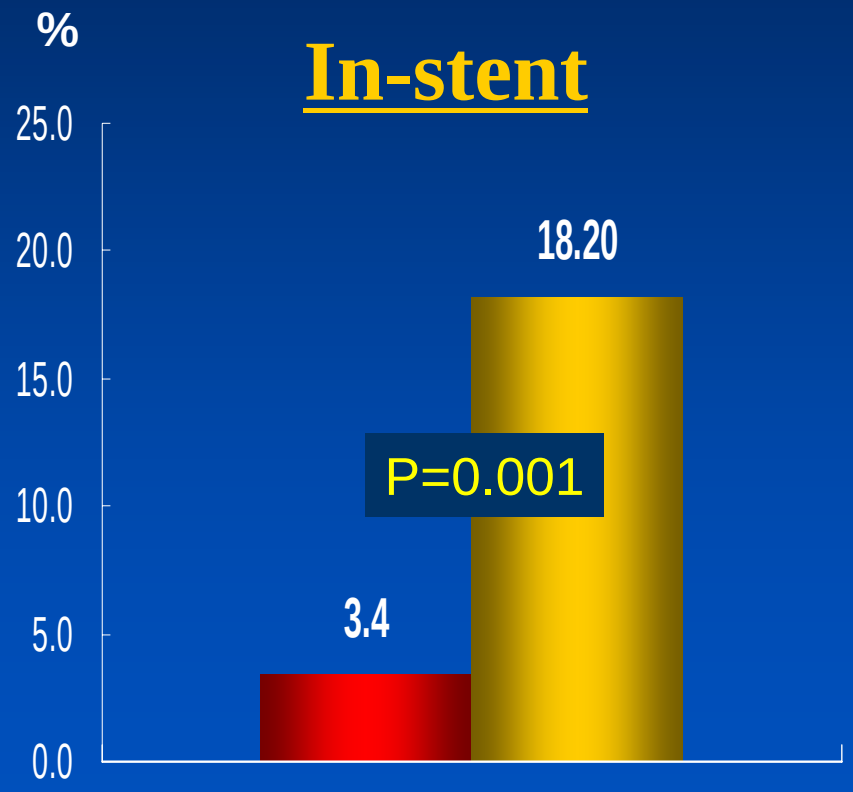
DECLARE-DIABETES Trial Design

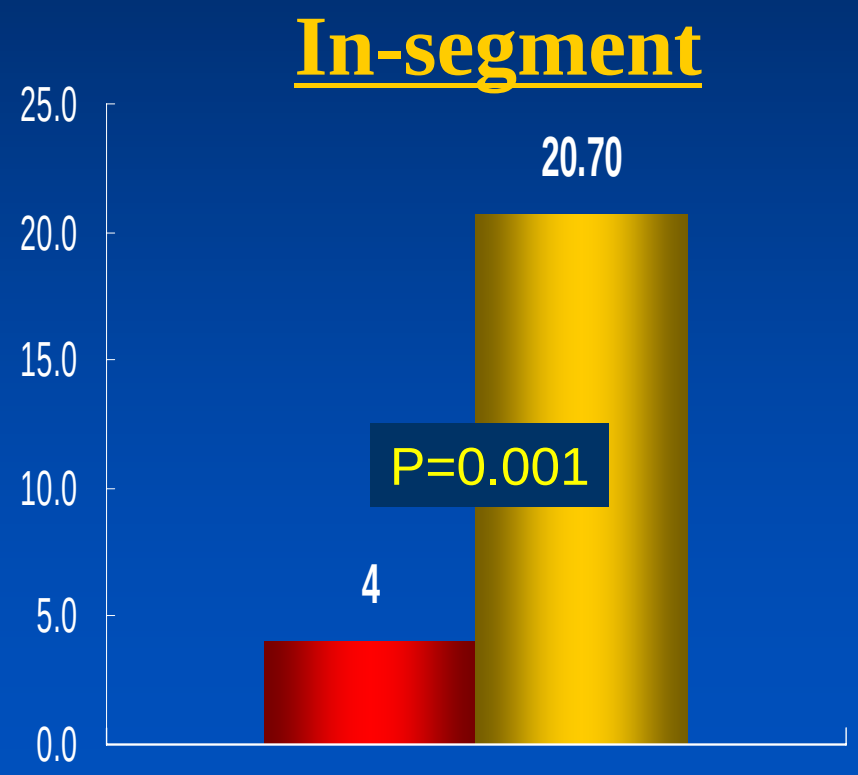


* Randomization – Stratification according to DES types
* Blinding – Patients, Outcome assessors
* Pre-specified angiographic primary endpoint
* Intention-to-treat analysis

Restenosis rate
CYPHER vs. TAXUS in DM

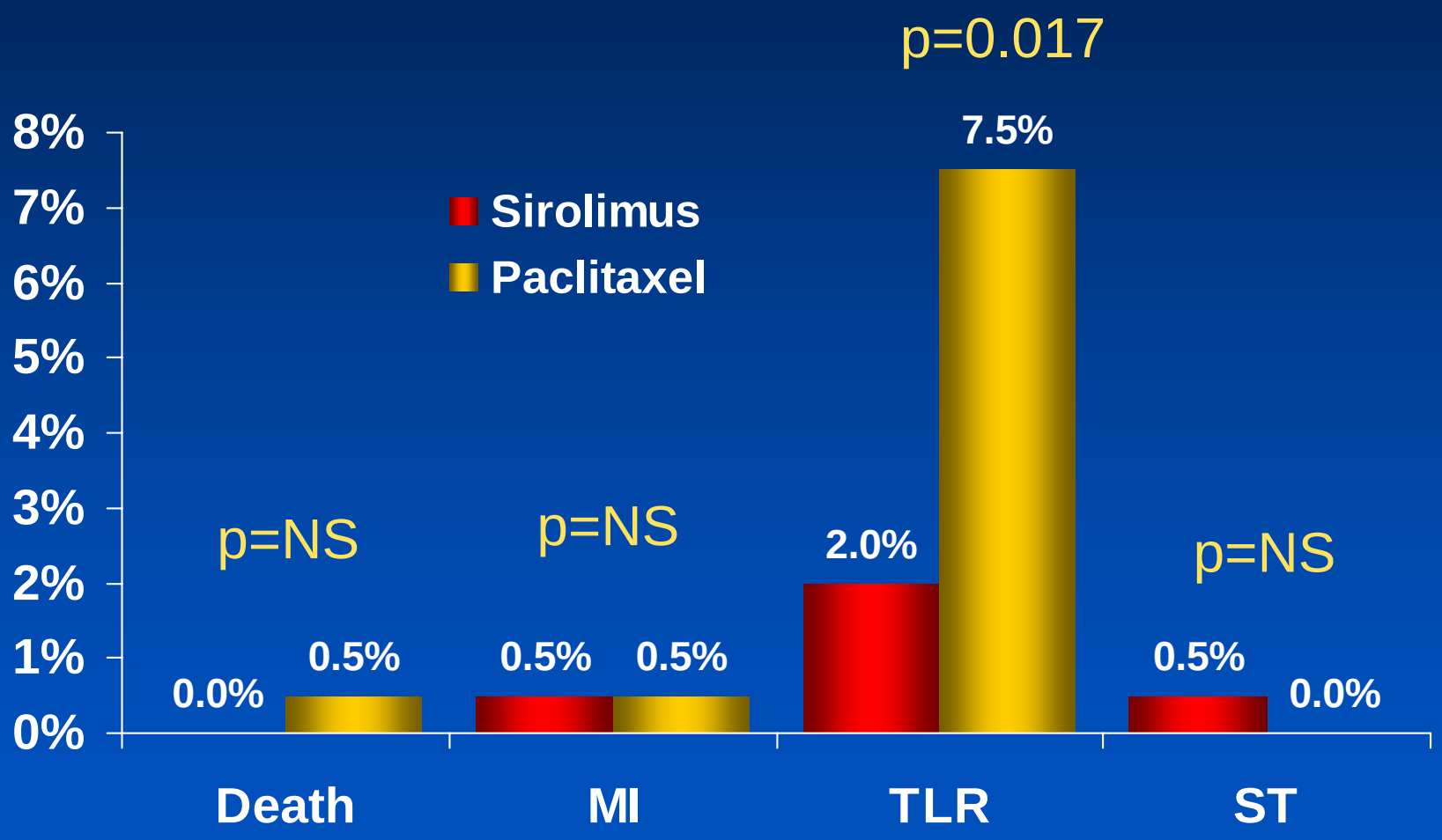
Sirolimus Paclitaxel





Lee et al, JACC 2008;52:727-33

Clinical Outcomes at 9-Months
CYPHER vs. TAXUS in DM



Lee et al, JACC 2008;52:727-33

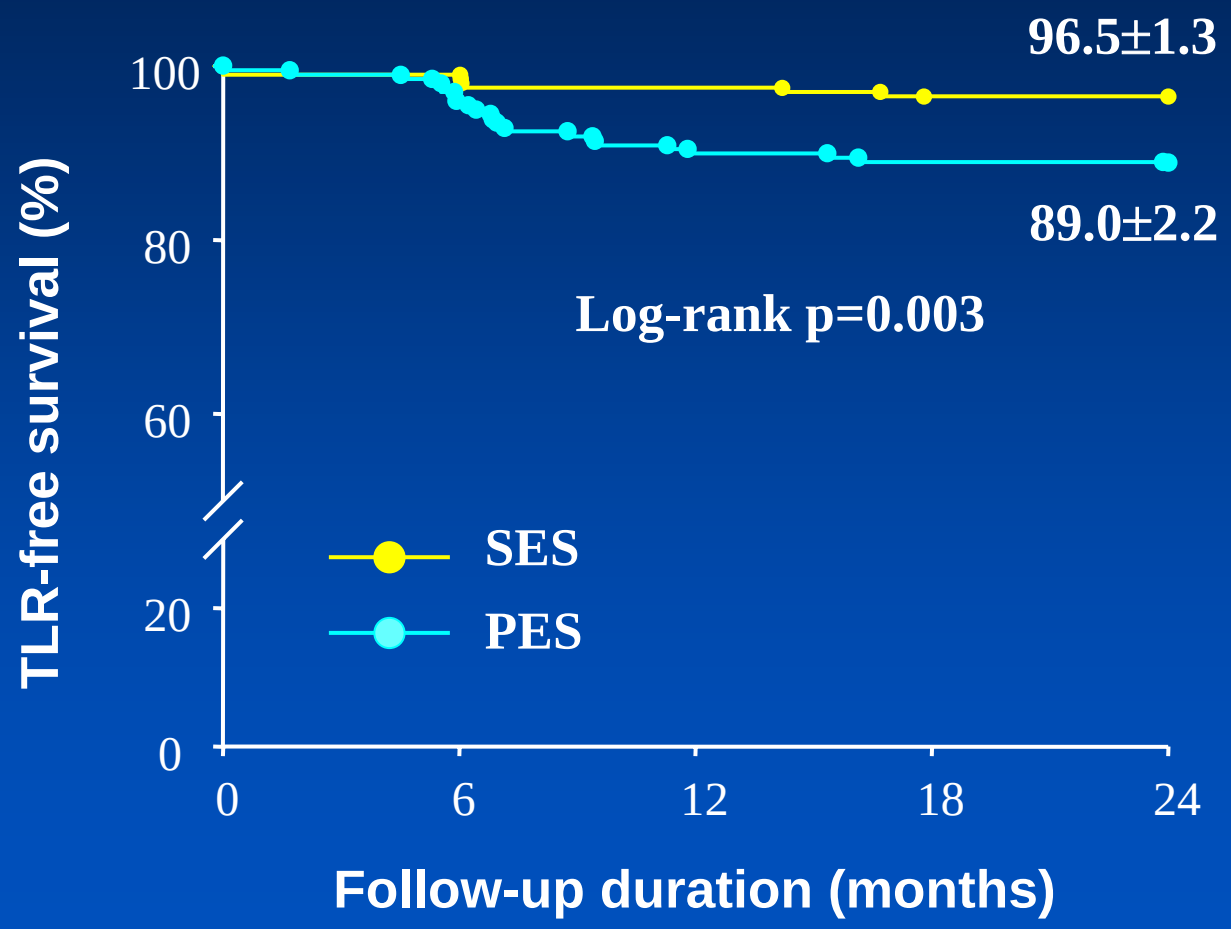
AMC data

Clinical Outcomes at 9 Months

Patients	SES (N=200)	PES (N=200)	P
Death	0	1 (0.5%)	0.999
Cardiac	0	1 (0.5%)	
Non-cardiac	0	0	
MI	1 (0.5%)	1 (0.5%)	0.999
TLR	4 (2.0%)	15 (7.5%)	0.017
TVR	7 (3.5%)	16 (8.0%)	0.053
Death/MI/TLR	4 (2.0%)	16 (8.0%)	0.010
Death/MI/TVR	7 (3.5%)	17 (8.5%)	0.035
Stent thrombosis	1 (0.5%)	0	0.999
Acute	1 (0.5%)	0	
Subacute & Late	0	0	

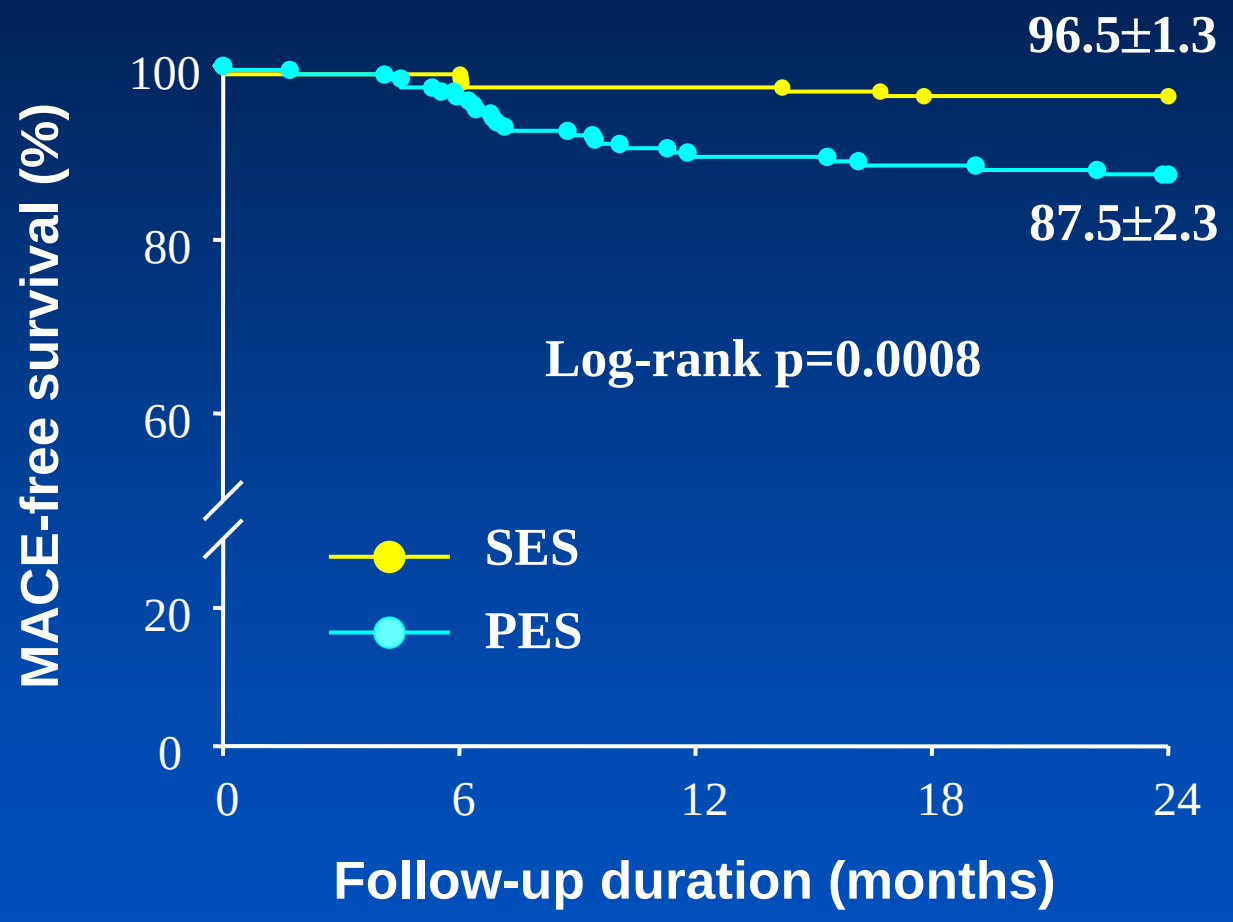
Lee et al, JACC 2008;52:727-33

Long-Term Outcomes: Two-year TLR-free survival



Lee et al, JACC 2009;53:812-813

Two-year MACE-free survival



MACE: Death/MI/TLR

Lee et al, JACC 2009;53:812-813

MACE at 2-years

	SES	PES	P
Patients	200	200	
Death	0	3(1.5%)	0.248
Cardiac	0	2(1.0%)	
Non-cardiac	0	1(0.5%)	
MI	1 (0.5%)	2 (1.0%)	0.999
Stent thrombosis	2 (1.0%)	0	0.499
Acute	1 (0.5%)	1	
Subacute	0	0	
Late	1 (0.5%)	0	
TLR	7 (3.5%)	22 (11.0%)	0.004
Death/MI/TVR	11 (5.5%)	28 (14.0%)	0.004
MACE (Death/MI/TLR)	7 (3.5%)	25 (12.5%)	0.001

Lee et al, JACC 2009;53:812-813

Conclusions

- SES implantation is associated with reduced angiographic restenosis and 9-month TLR and MACE, and showed sustained reduction of 2-year TLR and MACE compared to PES implantation with no difference of death or MI

- The use of SES was negative independent predictors of angiographic restenosis, 2-year risks of TLR and MACE.

Lee et al, JACC 2008;52:727-33
Lee et al, JACC 2009;53:812-813

SES vs. PES

- There has been heterogeneous clinical outcomes, but SES showed consistent superiority of late loss and angiographic restenosis, which is translated to improved clinical outcomes (SIRTAX, DECLARE-DIABETES) without difference of death, MI, and stent thrombosis.

- Network meta-analysis showed similar TLR up to 4 years (HR 0.78, 95% CI,0.50 to 1.14), but HR favoring SES explained possible superiority of SES over PES, which was demonstrated in randomized trial (DECLARE-DIABETES) dedicated for diabetic patients

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

ZEST-Diabetic Subgroup

Seung-Jung Park, MD, PhD
on behalf of the ZEST investigators

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®
(N=880)

CYPER®
(N=880)

TAXUS Liberte™
(N=880)

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

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.

Study Endpoints

- Secondary 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

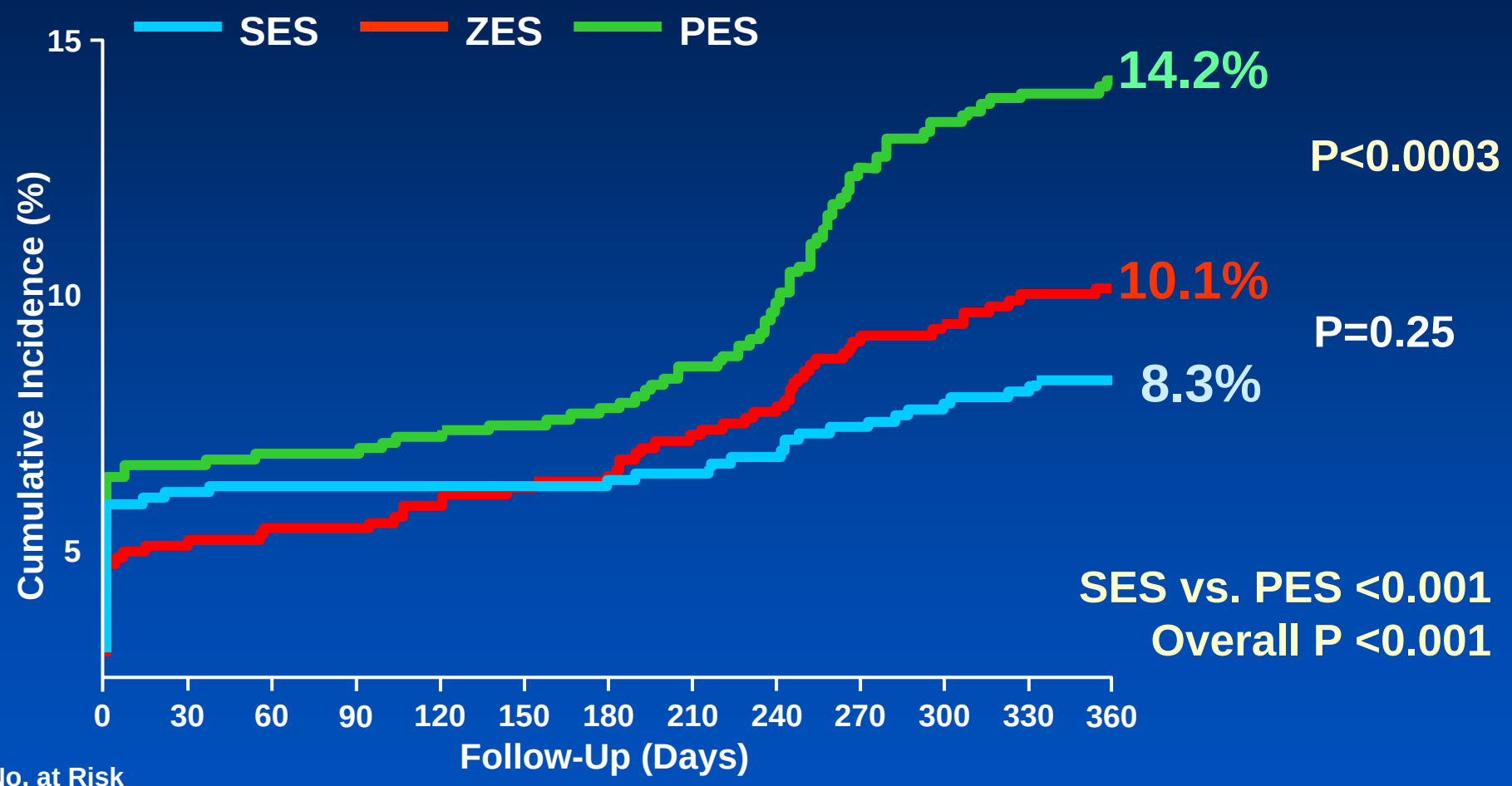
Baseline Characteristics

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 (%)

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

Baseline Characteristics

Patients	ZES (n=268)	SES (n=247)	PES (n=245)	P value
Age (yr)	63±9	63±8	62±10	0.65
Male sex	157 (59)	148 (60)	157 (64)	0.42
Body mass index	25±3	25±3	25±3	0.89
Insulin-requiring	32 (12)	33 (13)	36 (15)	0.66
Hypertension	199 (74)	176 (71)	174 (71)	0.66
Hyperlipidemia	133 (50)	119 (48)	117 (48)	0.91
Current smoker	59 (22)	59 (24)	70 (29)	0.21
Family history of CAD	12 (5)	9 (4)	13 (5)	0.67

n (%)

Lesion Characteristics

Lesions	ZES (n=435)	SES (n=448)	PES (n=441)	P value
Location				0.39
LAD	52%	53%	51%	
LCX	21%	19%	21%	
RCA	27%	29%	28%	
ACC-AHA B2 or C type	72%	76%	74%	0.24
Total occlusion	6%	6%	8%	0.17
Thrombus-containing	3%	3%	3%	0.78
Bifurcation lesion	20%	18%	16%	0.24
Ostial lesion	7%	6%	7%	0.56
Restenotic lesion	1%	1%	1%	0.86

n (%)

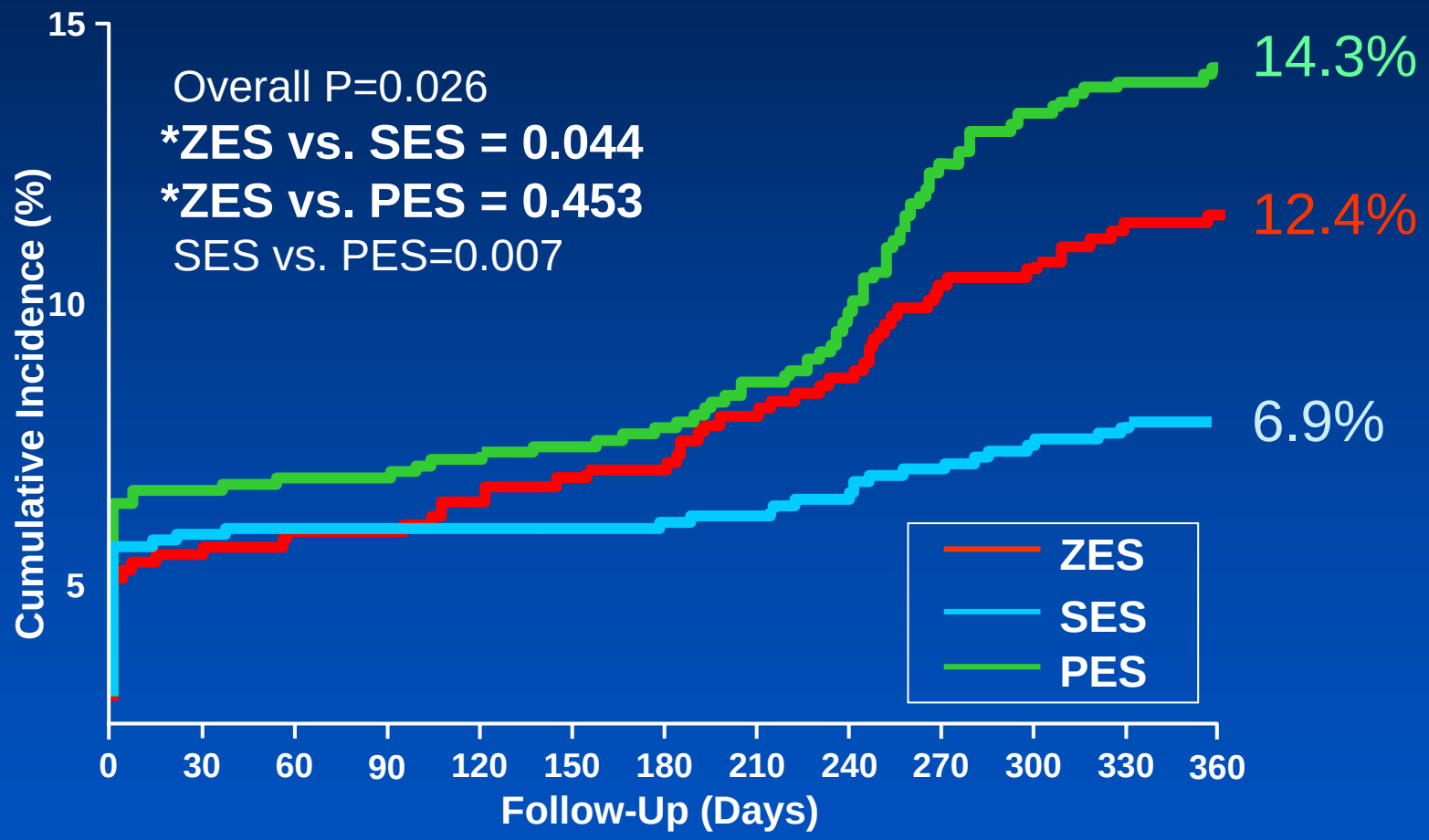
Procedural Characteristics

Lesions	ZES (n=435)	SES (n=448)	PES (n=441)	P value
No. of stents per lesion	1.3±0.4	1.3±0.4	1.3±0.4	0.45
No. of stents per patient	1.8±0.9	1.8±0.9	1.8±0.9	0.92
Length of stents per lesion	30.9±13.1	31.9±13.5	30.9±14.3	0.22
Length of stents per patients	42.7±26.8	41.3±24.3	41.9±25.2	0.55
Maximal stent diameter	3.4±0.7	3.4±0.7	3.5±0.6	0.29
Maximal pressure	16.3±4.2	16.3±4.1	16.2±4.2	0.95
Direct stenting	7%	9%	7%	0.34
Use of IVUS	40%	42%	41%	0.62

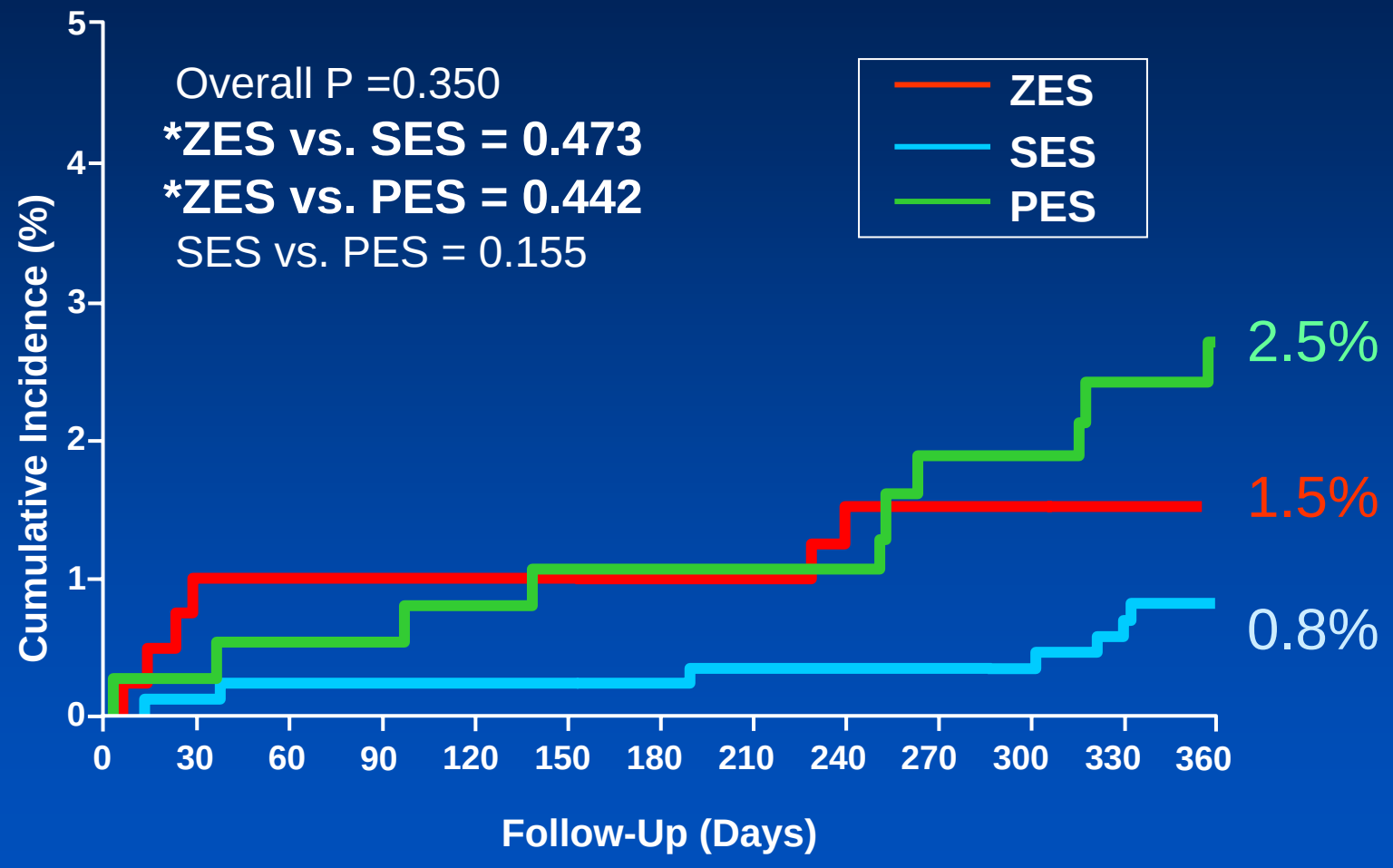
Clinical Events During 12 Months of Follow-Up

Primary End Point at 12 month

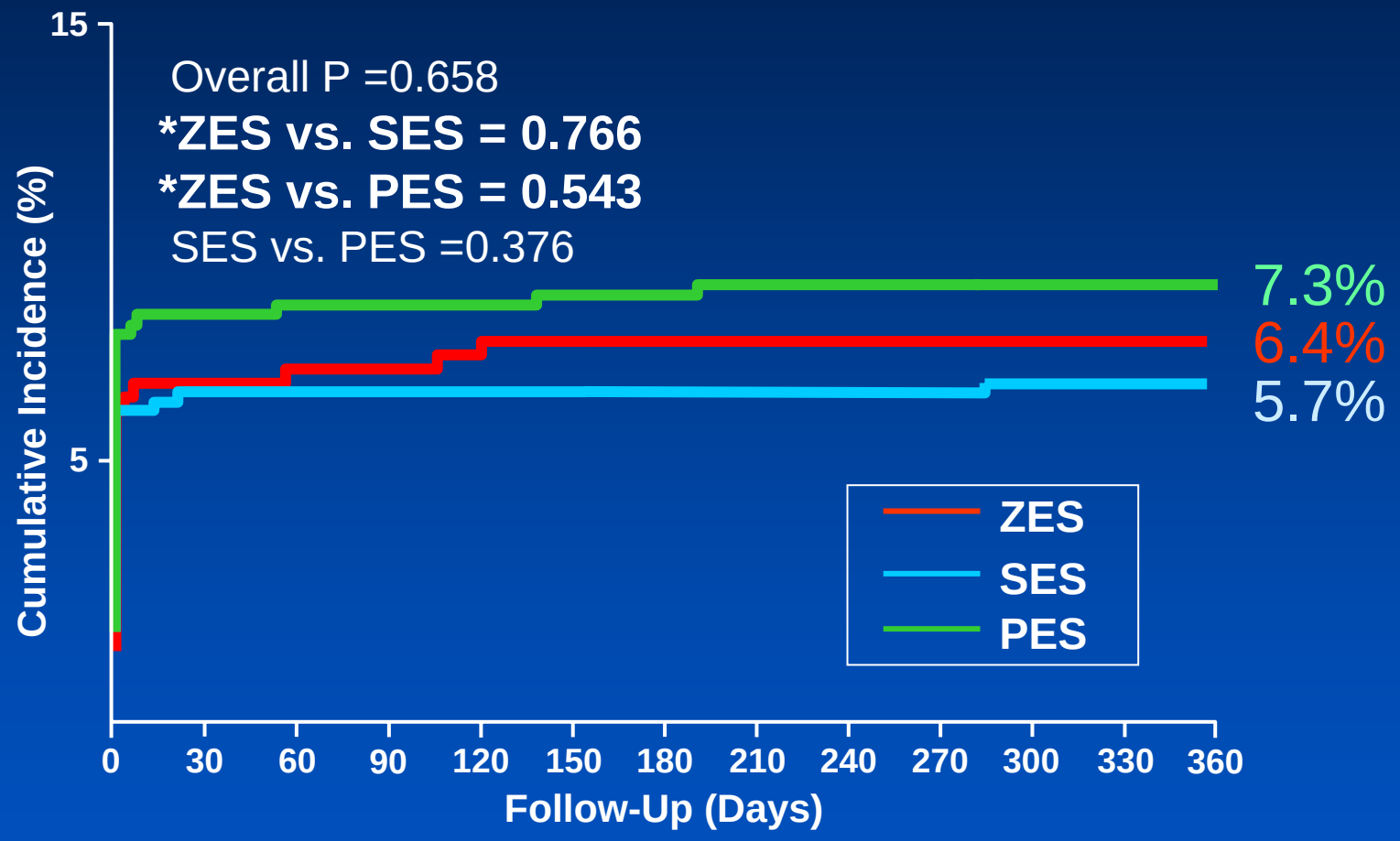
: Death, MI, Ischemia-driven TVR



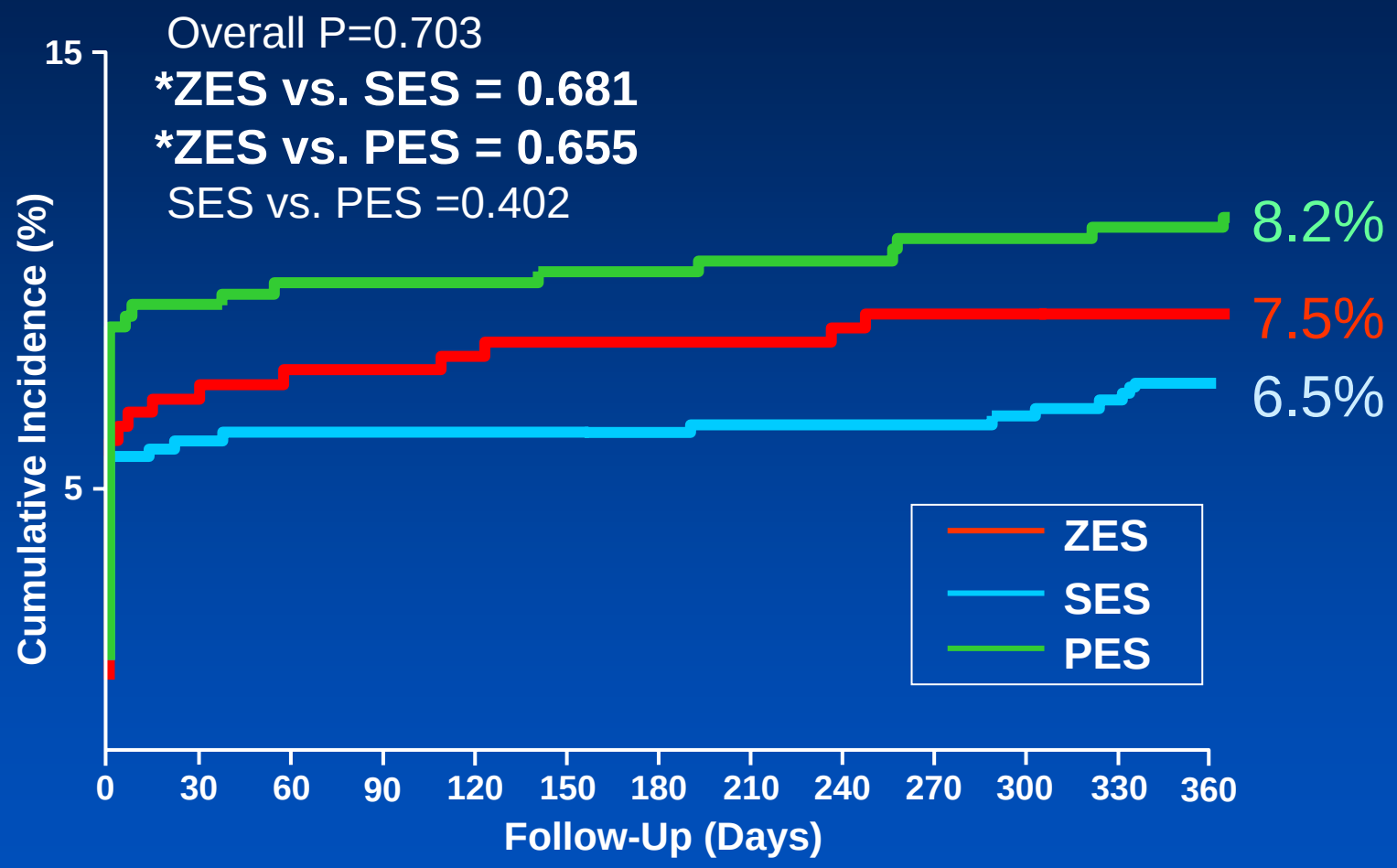
Death at 12 month



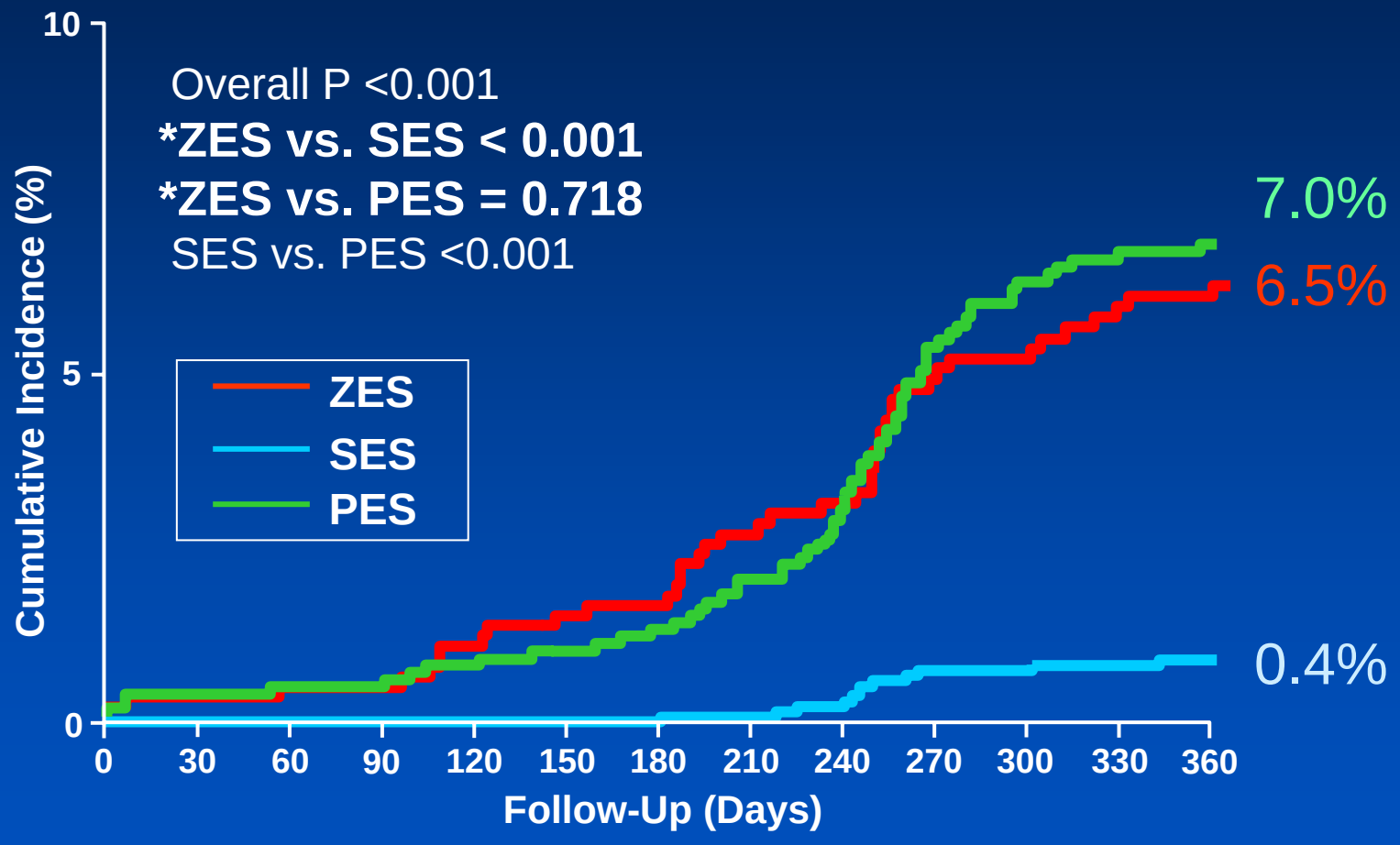
MI at 12 month



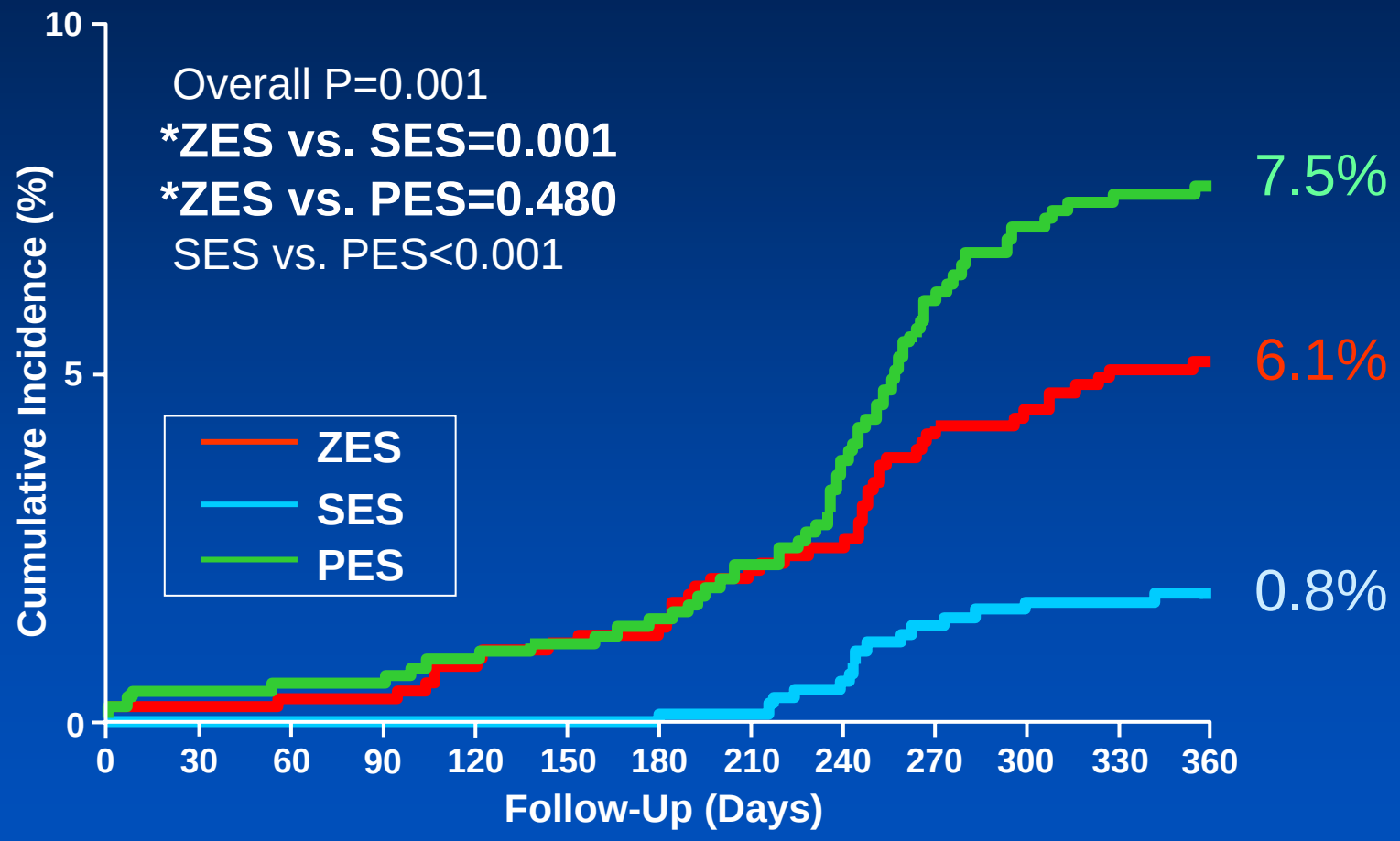
Death or MI at 12 month



Ischemia-Driven TLR at 12 month

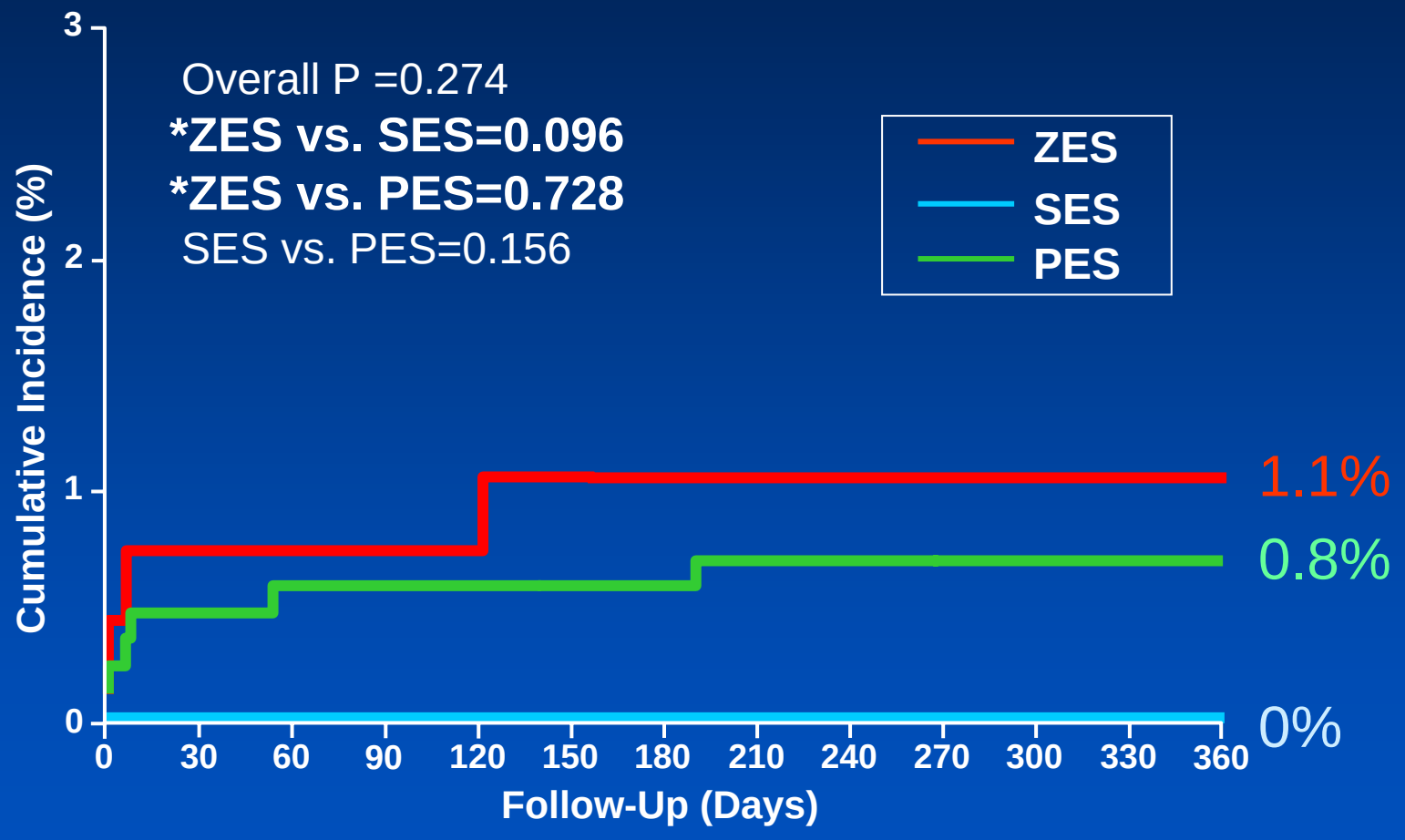


Ischemia-Driven TVR at 12 month



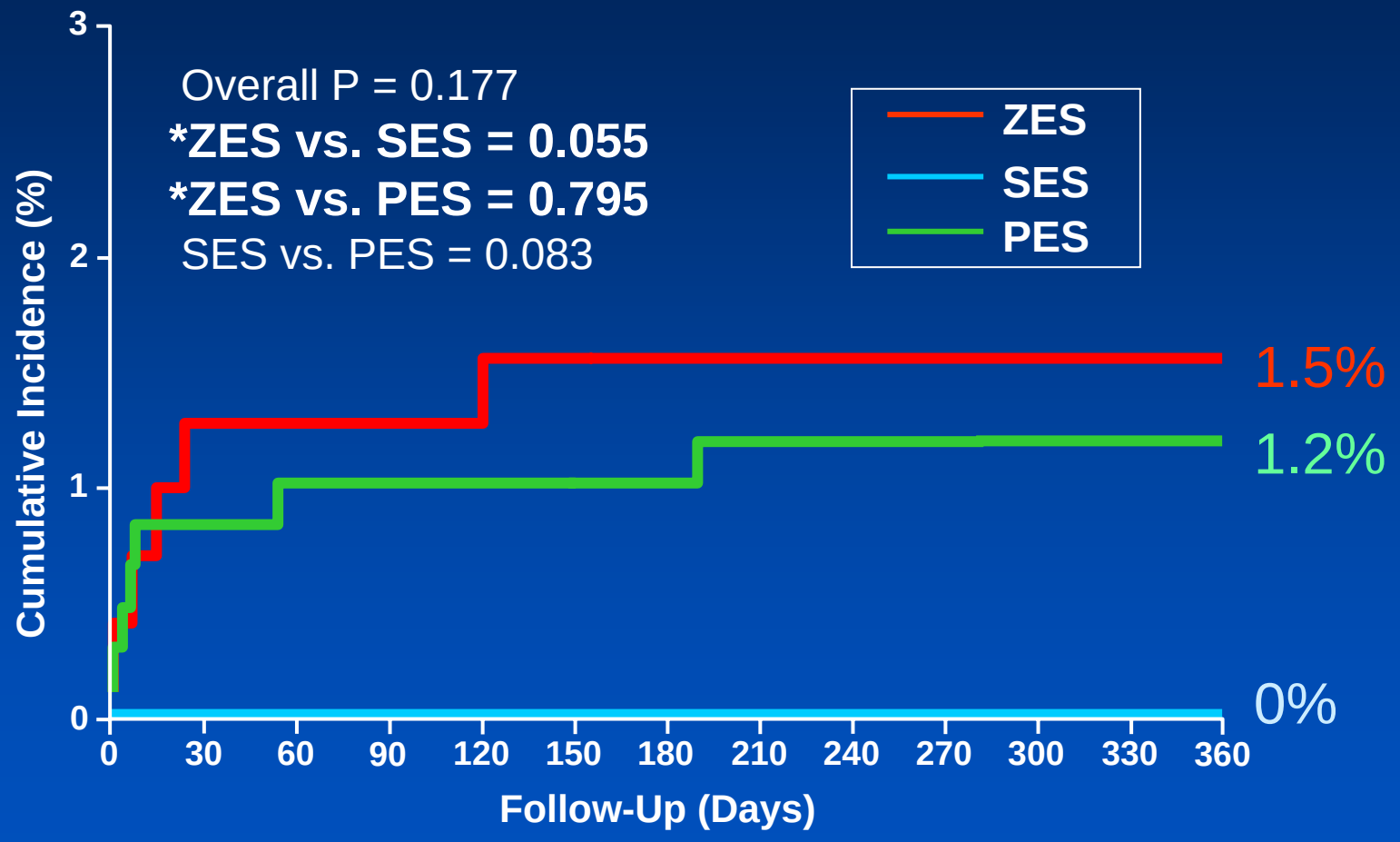
Stent thrombosis at 12 month

: ARC Definite Criteria



Stent thrombosis at 12 month

: ARC Definite or Probable Criteria



Summary:
ZEST Diabetic Subgroup

- The use of Cypher stent resulted in fewer major adverse cardiac events as compared with Taxus Liberte or Endeavor stent, mainly due to significant reduction of TLR and TVR.

- There were no significant differences in terms of death, MI, or stent thrombosis.

Evaluation of *D*iabetic *E*ffects on Clinical Outcomes After *S*irolimus-Eluting *S*tents in As*IAN* Population

The **DESSIAN** Registry

1. Prospective Enrollment of Consecutive **Diabetic Patients** Receiving Sirolimus-Eluting Stents (SES) in Routine Clinical Practice.
2. For Comparison, Concomitant Enrollment of **Non-diabetic Patients** Receiving SES

↓

Consecutive Enrollment
Of Patients Treated With SES
Up to 3600 Patients

Approximately DM vs. Non-DM = 30% vs. 70%

Diabetic Patients (n=1100)	Nondiabetic patients (n=2500)

Clinical follow-up at 1-, 6-, and 12-months

***Primary end point:** Composite of Death, MI, and TVR at 12-months `

ESSENCE-DIABETES Trial

AMC data

Patients with de novo coronary lesions requiring single or multiple stents in diabetic patients (Total patients, N=280)

18 Centers in Korea

1:1 randomization

XIENCE V (n=140)

CYPHER (n=140)

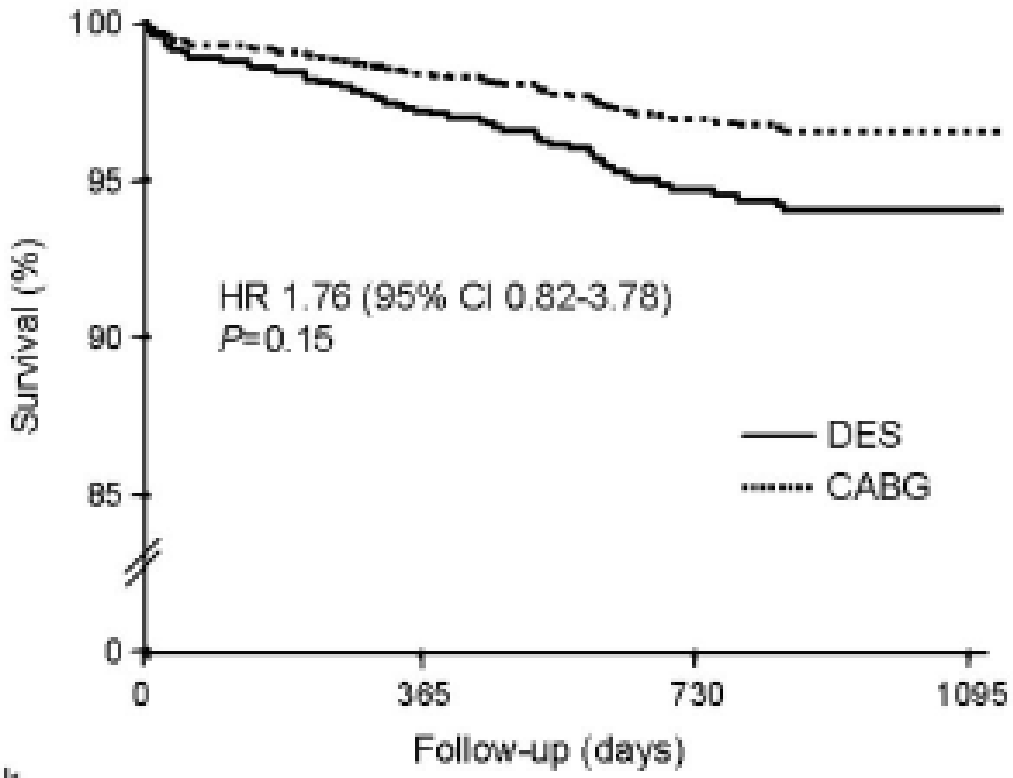
8 month angiographic follow-up
1-year clinical follow-up

Primary end-point: Angiographic in-segment late loss at 8-month angiography
Secondary end-point: Clinical outcomes at 12 month follow-up
IVUS results at 8 month angiographic follow-up (selected center)

PI: Seong-Wook Park, MD, PhD, FACC

DES vs. CABG
in Diabetic Patients

DES vs. CABG
Three-year mortality in Diabetes



No. at Risk				
DES	482	471	317	147
CABG	395	375	251	105

Park DW et al., Circulation 2008;117:2079-2086

Adjusted HRs of 3-year Outcomes

	HRs	95% CI	P	Interaction P
Oveall Patients				
Death	0.95	0.62,1.46	0.83	0.16
Death, QMI, CVA	0.96	0.65,1.42	0.85	0.93
TVR	4.31	2.28,8.15	<0.001	0.92
Diabetic Patients				
Death	0.55	0.24,1.25	0.15	
Death, QMI, CVA	0.78	0.38,1.62	0.51	
TVR	7.67	2.76,21.32	<0.001	
Non-Diabetic Patients				
Death	1.00	0.59,1.72	0.99	
Death, QMI, CVA	0.96	0.57,1.58	0.88	
TVR	2.94	1.36,6.38	0.006	

Summary (1)
DES in Diabetics

- Diabetics still have higher TVR and Death/MI/TVR especially, insulin treated diabetics have a clear trend of poor clinical outcomes (Death, TVR and Death/MI/TVR) compared to non-diabetics even in the era of DES

- According to the DECLARE-DIABETES Trial and ZEST diabetics subgroup analysis, SES appears to be more effective than PES and Endeavor stents in primary end point of study

Summary (2)
DES in Diabetics

- Adjunctive pharmacologic therapy (Cilostazol) is likely to further improve PCI outcomes
- Efficacy concerns of DES compare to surgery should be evaluated in the future.

Thank You !!

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