A Randomized Comparison of Sirolimus-versus Paclitaxel-eluting stent implantation in Patients with Diabetes Mellitus

:*D*rug-*E*luting *S*tenting for Patients with *Diabetes* mellitus

The DES-DIABETES Trial

Seong-Wook Park,

for the DES-DIABETES Study investigators

Asan Medical Center,
University of Ulsan College of Medicine, Seoul, Korea

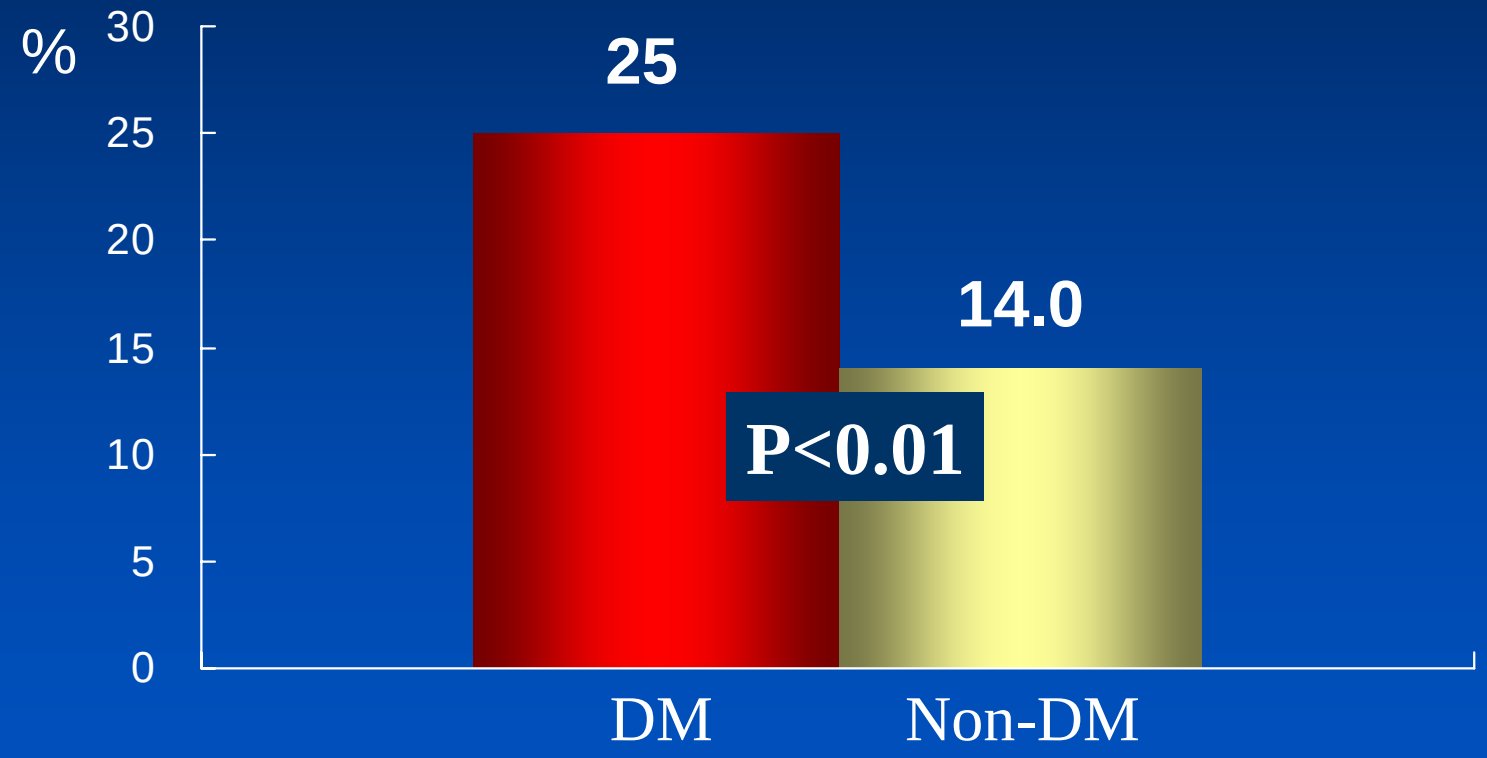
Lee SW, Park SW, et al. J Am Coll Cardiol 2008;52:727–33

Diabetes on Coronary Artery Disease

- Diabetic patients often present unfavorable coronary anatomy with small and diffusely diseased vessels and exhibit exaggerated neointimal hyperplasia after DES implantation as compared with nondiabetics.
- Presence of DM has been still associated with an increased risk of restenosis and unfavorable clinical outcomes in the era of DES.

Impact of DM on Restenosis after DES Implantation

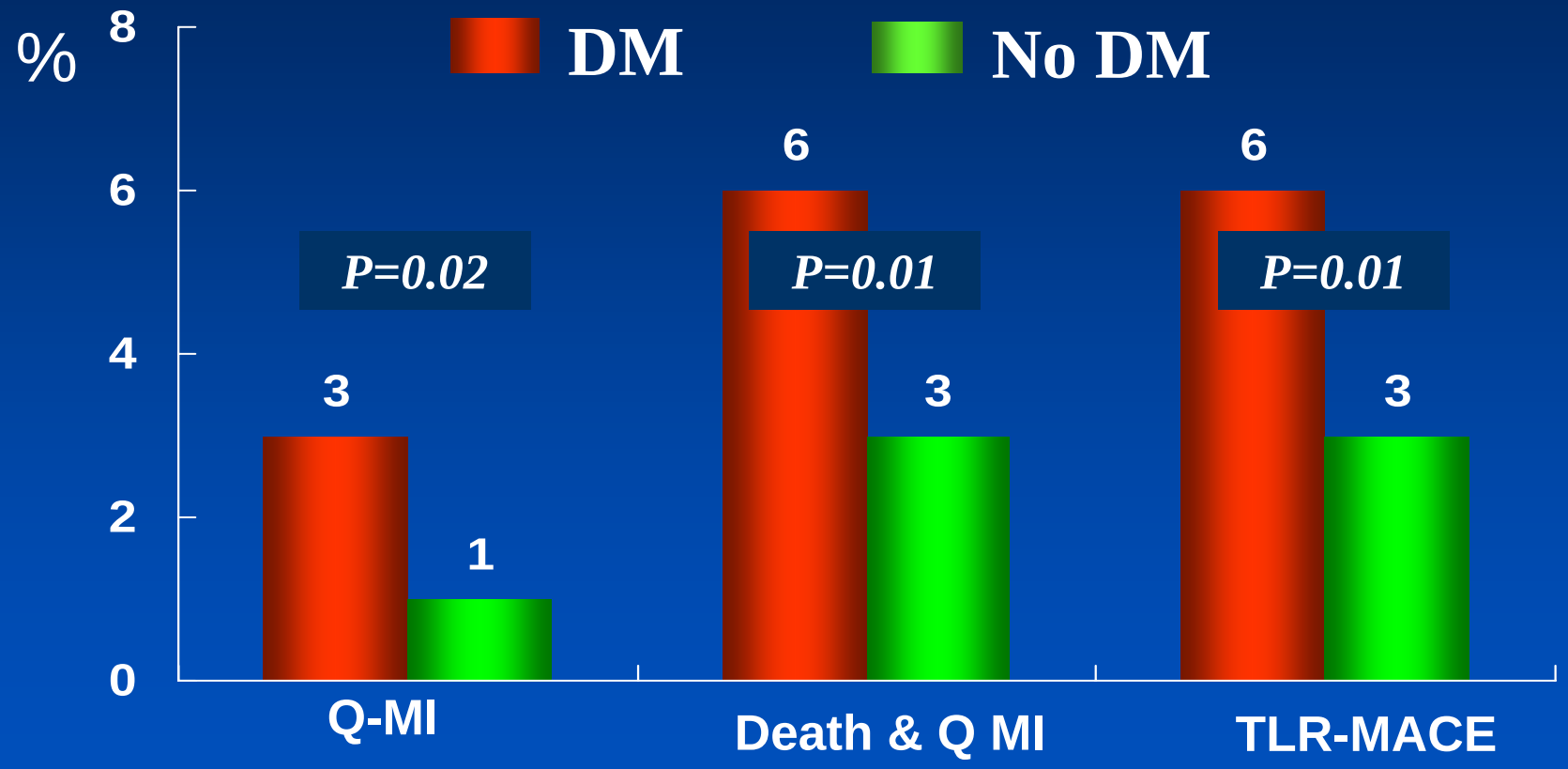
Matched comparison (192: 192)



Radke PW et al. Am J Cardiol 2006;98:1218

Impact of DM on clinical outcomes after SES

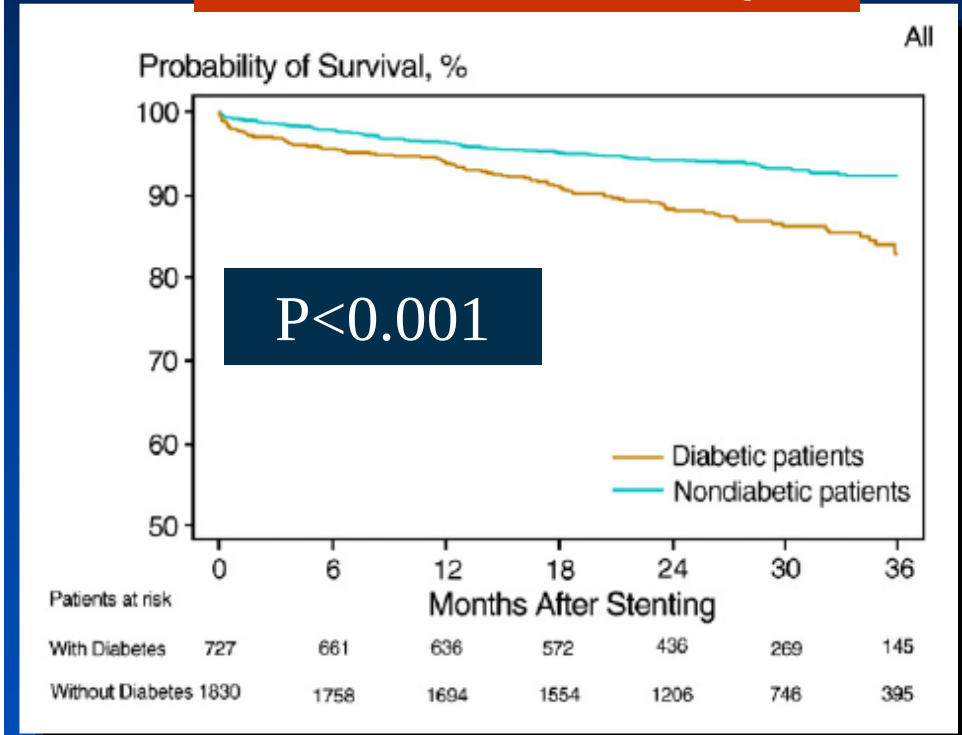
6-month follow-up



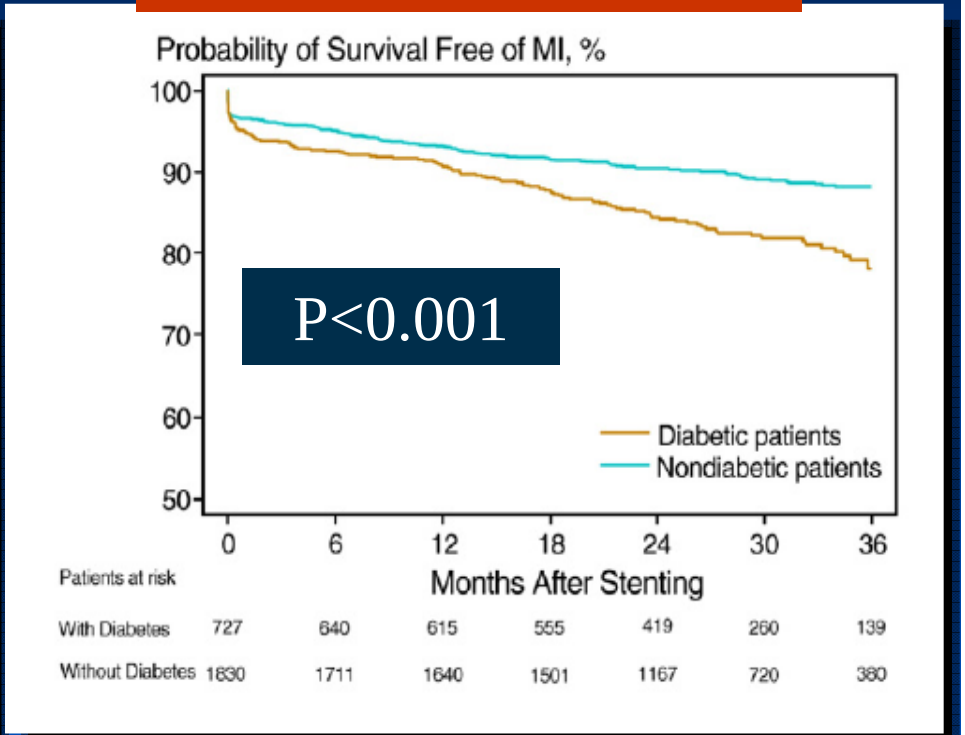
Kuchulakanti et al. Am J Cardiol 2005;96:1100

Long-term clinical outcome

All-cause mortality



Death or MI



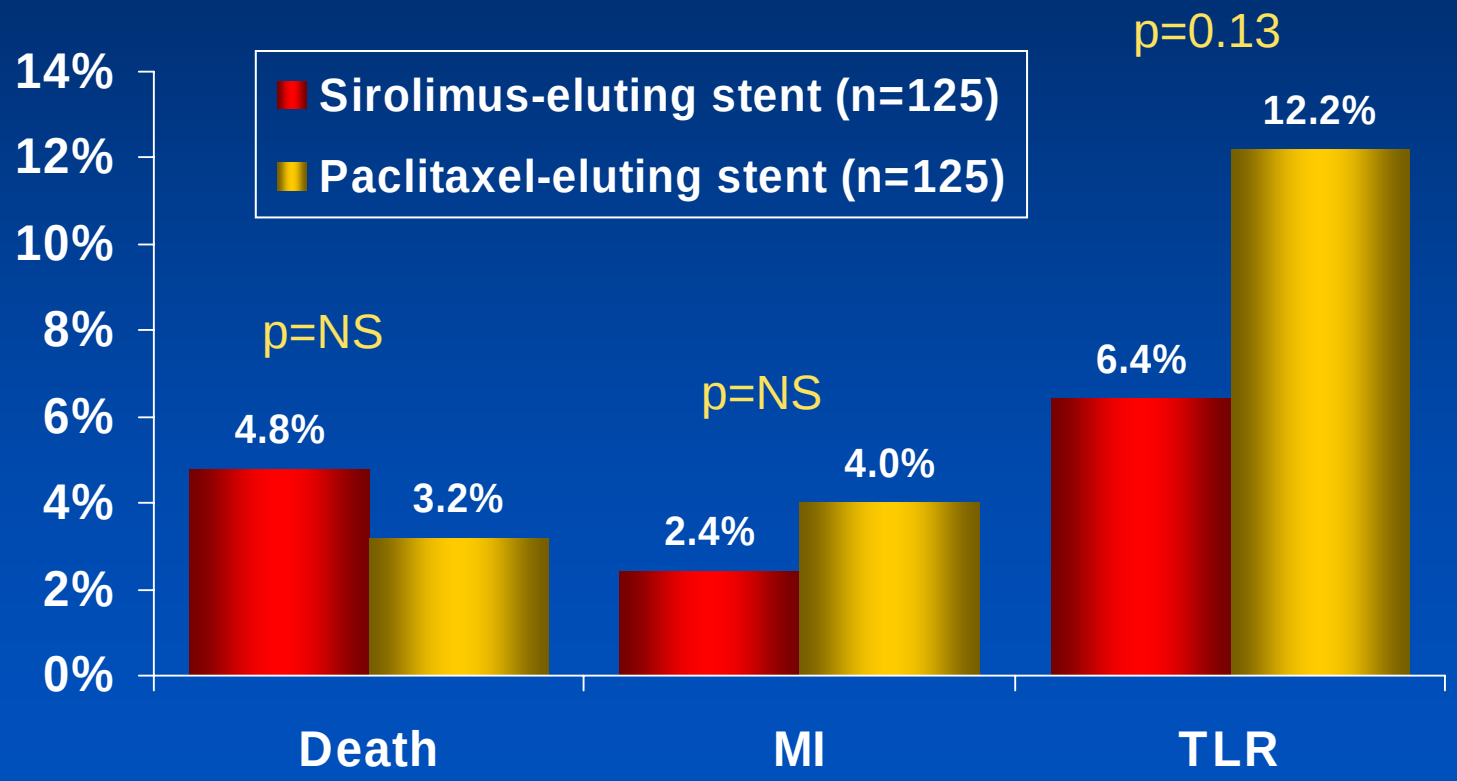
Diabetes is independent predictor of 3-year mortality

SES vs. PES

ISAR-DIABETES Trial

Nine-month outcomes

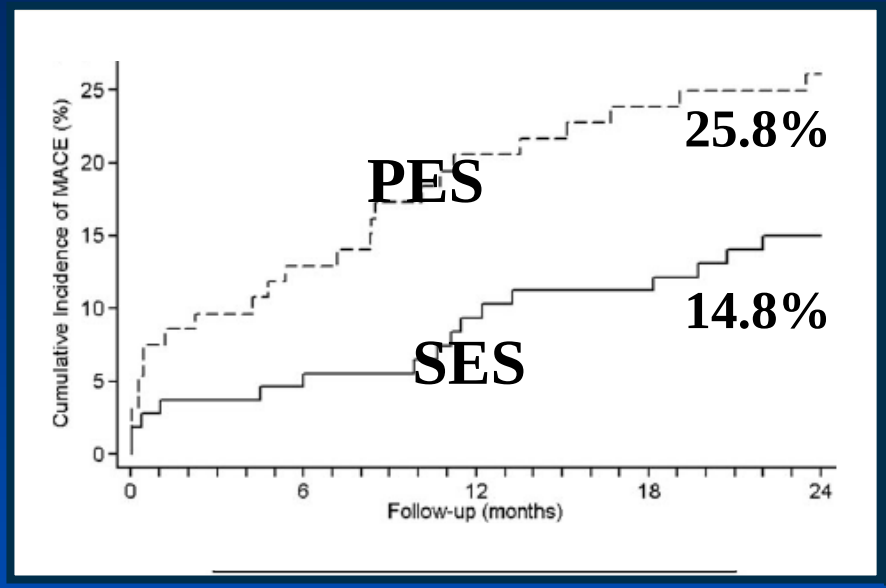
SES showed significant reduction of restenosis, which did not translate into improved clinical outcomes owing to small population

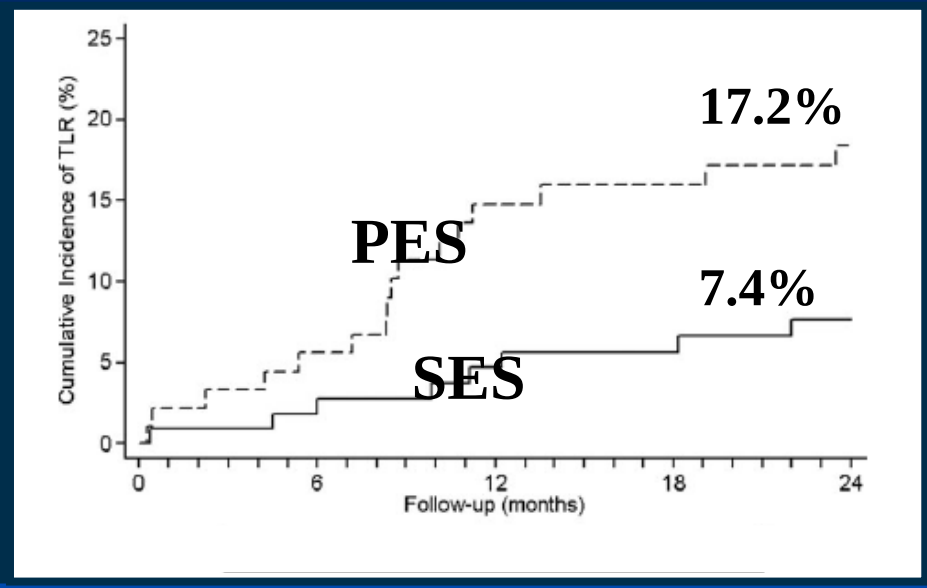


Kastrati et al., NEJM 2005;353:663-70

SIRTAX Trial

Two-year outcomes in diabetic subgroup





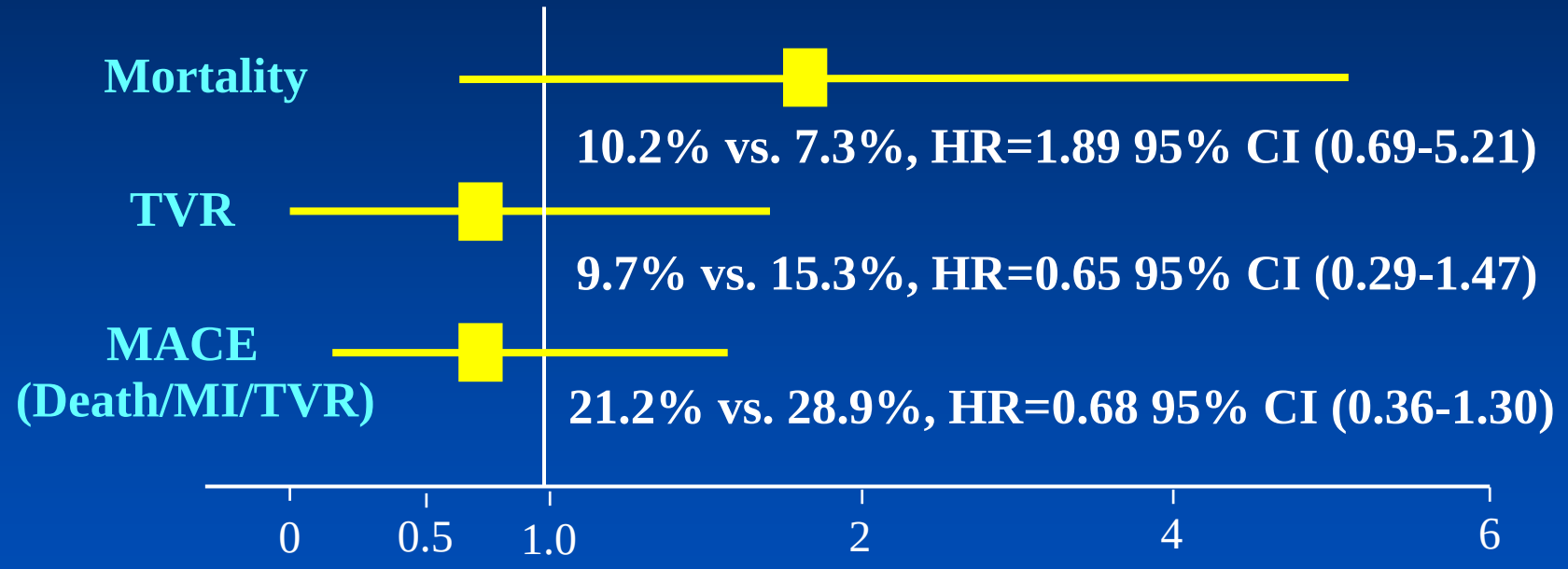
HR=0.52; 95% CI 0.28–0.99; P=0.05

HR=0.39; 95% CI 0.17–0.90; P=0.03

Billinger M et al., Eur H Journal 2008;29:718-25

Adjusted Hazard Ratios for 2-year Outcomes Comparing PES and SES

Adjustment with propensity score



Favors PES (n=250) **Favors SES (n=206)**

Daemen J et al., Eur H Journal 2008;28:26-32

A Randomized Comparison of Sirolimus-versus Paclitaxel-eluting stent implantation in Patients with Diabetes Mellitus

:*D*rug-*E*luting *S*tenting for Patients with *Diabetes* mellitus

The DES-DIABETES Trial

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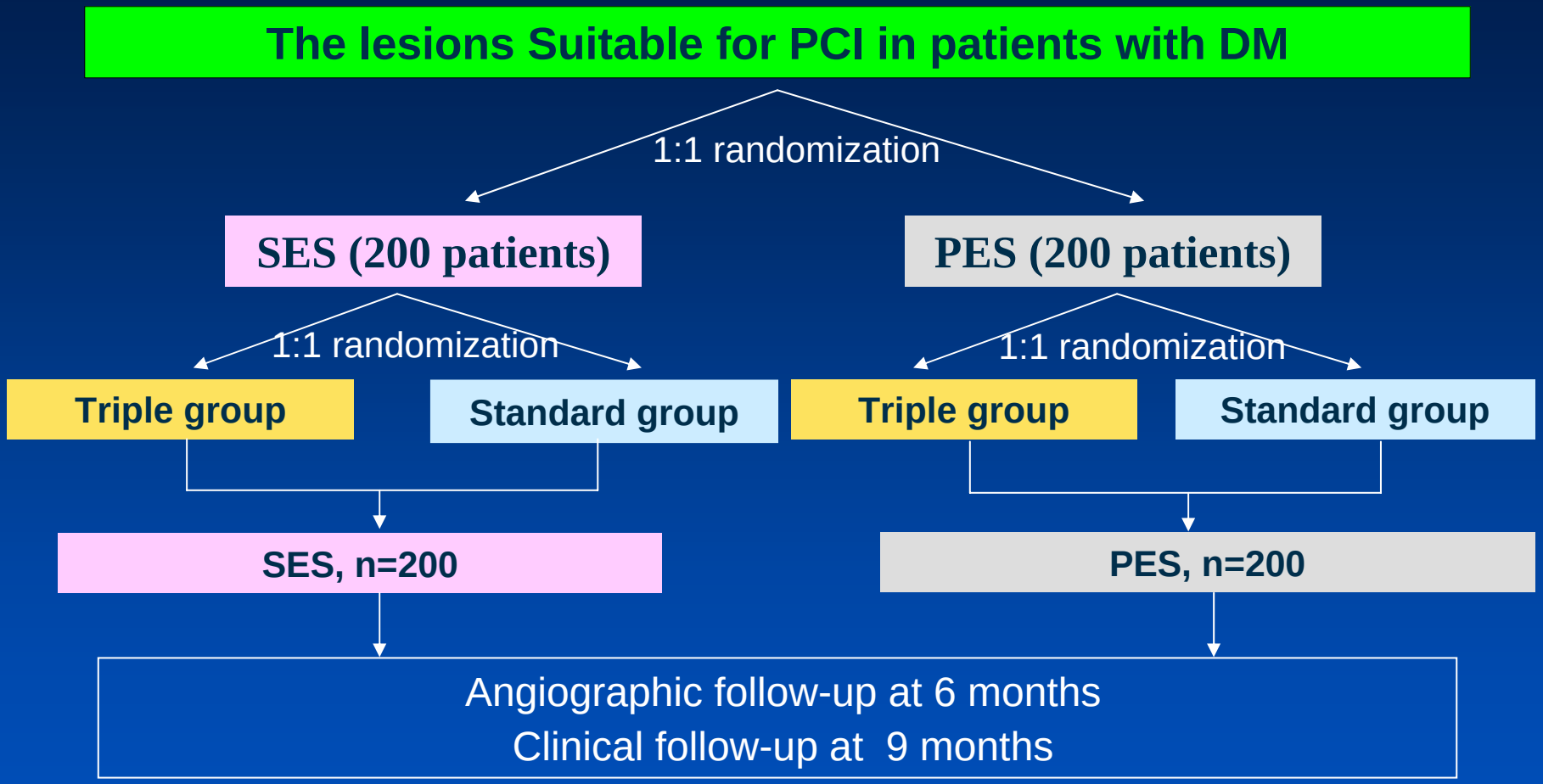
Lee SW, Park SW, et al. J Am Coll Cardiol 2008;52:727–33

Objective

To compare the effectiveness of sirolimus-eluting stent (SES) and paclitaxel-eluting stent (PES) in patients with DM.

Lee SW, Park SW, et al. J Am Coll Cardiol 2008;52:727–33

DES-DIABETES Trial Design



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

Lee SW, Park SW, et al. J Am Coll Cardiol 2008;52:727–33

DES-DIABETES Trial Design

Journal of the American College of Cardiology
© 2008 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 51, No. 12, 2008
ISSN 0735-1097/08/$34.00
doi:10.1016/j.jacc.2007.11.049

CLINICAL RESEARCH Interventional Cardiology

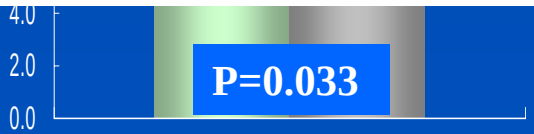
Drug-Eluting Stenting Followed by Cilostazol Treatment Reduces Late Restenosis in Patients With Diabetes Mellitus

The DECLARE-DIABETES Trial (A Randomized Comparison of Triple Antiplatelet Therapy With Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation in Diabetic Patients)

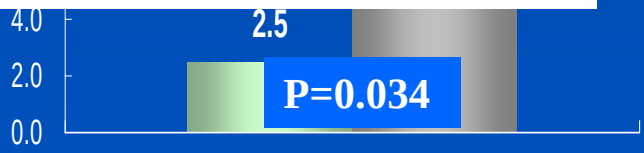
Seung-Whan Lee, MD, PhD,* Seong-Wook Park, MD, PhD, FACC,* Young-Hak Kim, MD, PhD,* Sung-Cheol Yun, PhD,* Duk-Woo Park, MD, PhD,* Cheol Whan Lee, MD, PhD,* Myeong-Ki Hong, MD, PhD,* Hyun-Sook Kim, MD, PhD,† Jae-Ki Ko, MD, PhD,† Jae-Hyeong Park, MD, PhD,‡ Jae-Hwan Lee, MD,‡ Si Wan Choi, MD,‡ In-Whan Seong, MD, PhD,‡ Yoon Haeng Cho, MD, PhD,§ Nae-Hee Lee, MD, PhD,§ June Hong Kim, MD, PhD,‖ Kook-Jin Chun, MD,‖ Seung-Jung Park, MD, PhD, FACC*

Seoul, Jeonju, Daejeon, Bucheon, and Busan, Korea

Trip … roup



Restenosis rate



9-month TLR

Investigators in Korea

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Kook-Jin Chun, MD, PhD
June Hong Kim, MD, PhD

Inclusion Criteria

Clinical

- Patients with angina and documented ischemia
  or patients with documented silent ischemia
- Age >18 years, < 75 ages
- Written informed consent

Angiographic

- *De novo* coronary lesion suitable for stent implantation
- Target lesion stenosis > 50% by visual estimate
- Reference vessel size ≥ 2.5 mm by visual estimation

Lee SW, Park SW, et al. J Am Coll Cardiol 2008;52:727–33

Exclusion Criteria

- Contraindication to aspirin, clopidogrel or cilostazol
- Left main disease
- Graft vessel stenosis
- LVEF<30%
- Hematological disease (WBC <3,000/mm3, platelet<100,000/mm3)
- Hepatic dysfunction (> 2 times normal)
- Renal dysfunction (Cr ≥2.0mg/dL)
- Life expectancy < 1 year
- Inability to follow the protocol
- Bifurcation lesion requiring a planned stenting in the side branch
- Primary angioplasty for (AMI) within 24 hours

Lee SW, Park SW, et al. J Am Coll Cardiol 2008;52:727–33

Primary Endpoint

Comparison of SES and PES implantation:

In-segment restenosis at 6 month

angiographic follow-up study

Lee SW, Park SW, et al. J Am Coll Cardiol 2008;52:727–33

Secondary Endpoint

- In-stent & In-segment late loss
- In-stent restenosis rate
- Target vessel revascularization
- Target lesion revascularization
- MACE: composite of death, MI, & TLR at 9 month
- TVR-MACE
- Stent thrombosis

Lee SW, Park SW, et al. J Am Coll Cardiol 2008;52:727–33

Sample Size Calculation

- **Assumptions for the primary endpoint**
  - **SES in-segment restenosis: 7%**
  - **PES in-segment restenosis: 19%**
  - **Significant level α (two-sided): 0.05**
  - **Power: 90%**
  - **Assumption; 20% follow-up loss of angiographic re-study**
  - **Sample size: total 400 patients (200 patients per group)**

Lee SW, Park SW, et al. J Am Coll Cardiol 2008;52:727–33

Patient Demographics

	SES (n=200)	PES (n=200)	*p*
Age (yrs)	61±9	61±9	0.622
Men	122 (61.0%)	110 (55.0%)	0.224
Treatment of DM			0.972
Dietary alone	18 (9.0%)	19 (9.5%)	
OHA	150 (75.0%)	148 (74.0%)	
Insulin	32 (16.0%)	33 (16.5%)	
Glycosylated Hb	7.7±1.8	7.8±1.6	0.682
Hypertension	114 (57.0%)	124 (62.0%)	0.308
Smoking	54 (27.0%)	57 (28.5%)	0.738
Hypercholesterolemia	55 (27.0%)	63 (31.5%)	0.380
LVEF (%)	59±10	58±10	0.370

Target lesion and Clinical Presentation

	SES (n=200)	PES (n=200)	*p*
Stented site			**0.707**
LAD	122 (61.0%)	118 (59.0%)	
LCX	28 (14.0%)	25 (12.5%)	
RCA	50 (25.0%)	57 (28.5%)	
Multi-vessel disease	119 (59.5%)	137 (68.5%)	**0.170**
Diagnosis			**0.098**
Stable angina	86 (43.0%)	82 (41.0%)	
Unstable angina	80 (40.0%)	67 (33.5%)	
Myo. infarction	34 (17.0%)	51 (25.5%)	

Procedural Characteristics

	SES (n=200)	PES (n=200)	*p*
Maximal pressure (atm)	15.4±3.6	14.6±3.6	0.028
Use of IVUS	67 (33.5%)	64 (32.0%)	0.749
Use of GP IIb/IIIa inhibitor	11 (5.5%)	7 (3.5%)	0.470
Number of stents per lesion	1.28±0.49	1.28±0.56	0.936
Multi-vessel stenting	64 (32.0%)	69 (34.5%)	0.596
Total stent length	32.5±15.2	33.2±15.2	0.665

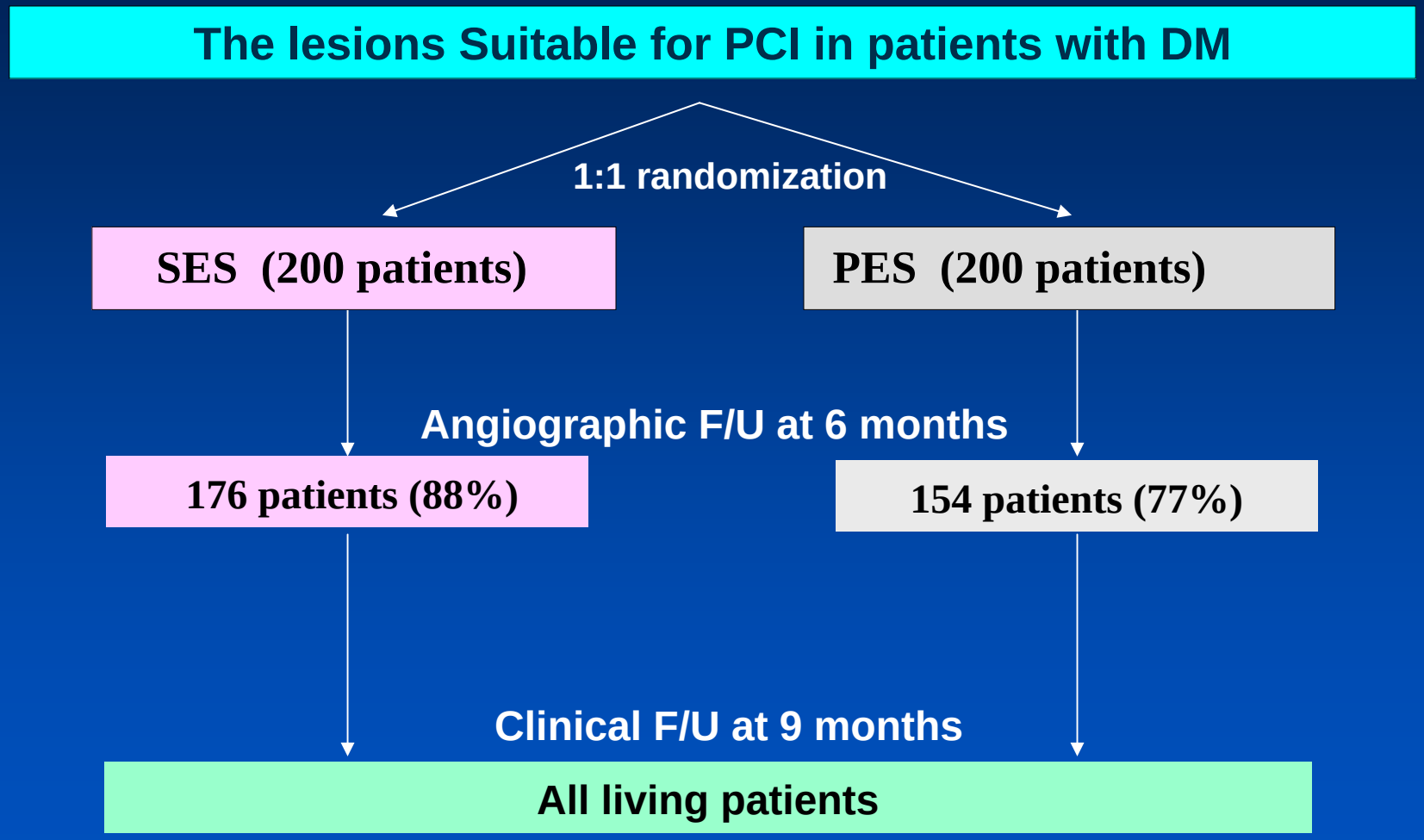
Angiographic Measurements
Pre-Procedure

	SES (n=200)	PES (n=200)	*p*
Reference vessel (mm)	2.80±0.43	2.80±0.43	0.962
Lesion length (mm)	25.8 ±12.9	27.2 ±14.2	0.338
MLD (mm)	0.79±0.50	0.73±0.46	0.236
Diameter stenosis (%)	68.1±14.7	69.4±12.7	0.423

Angiographic Measurements *Post-Procedure*

	SES (n=200)	PES (n=200)	*p*
MLD (mm)			
In-stent	2.55±0.46	2.57±0.41	0.559
In-segment	2.23±0.46	2.27±0.47	0.392
Acute gain (mm)			
In-stent	1.76±0.60	1.84±0.57	0.171
In-segment	1.43±0.60	1.53±0.59	0.119
Diameter stenosis (%)			
In-stent	10.5±11.5	8.9±11.6	0.230
In-segment	20.2±12.1	19.2±10.3	0.379

Data Analysis



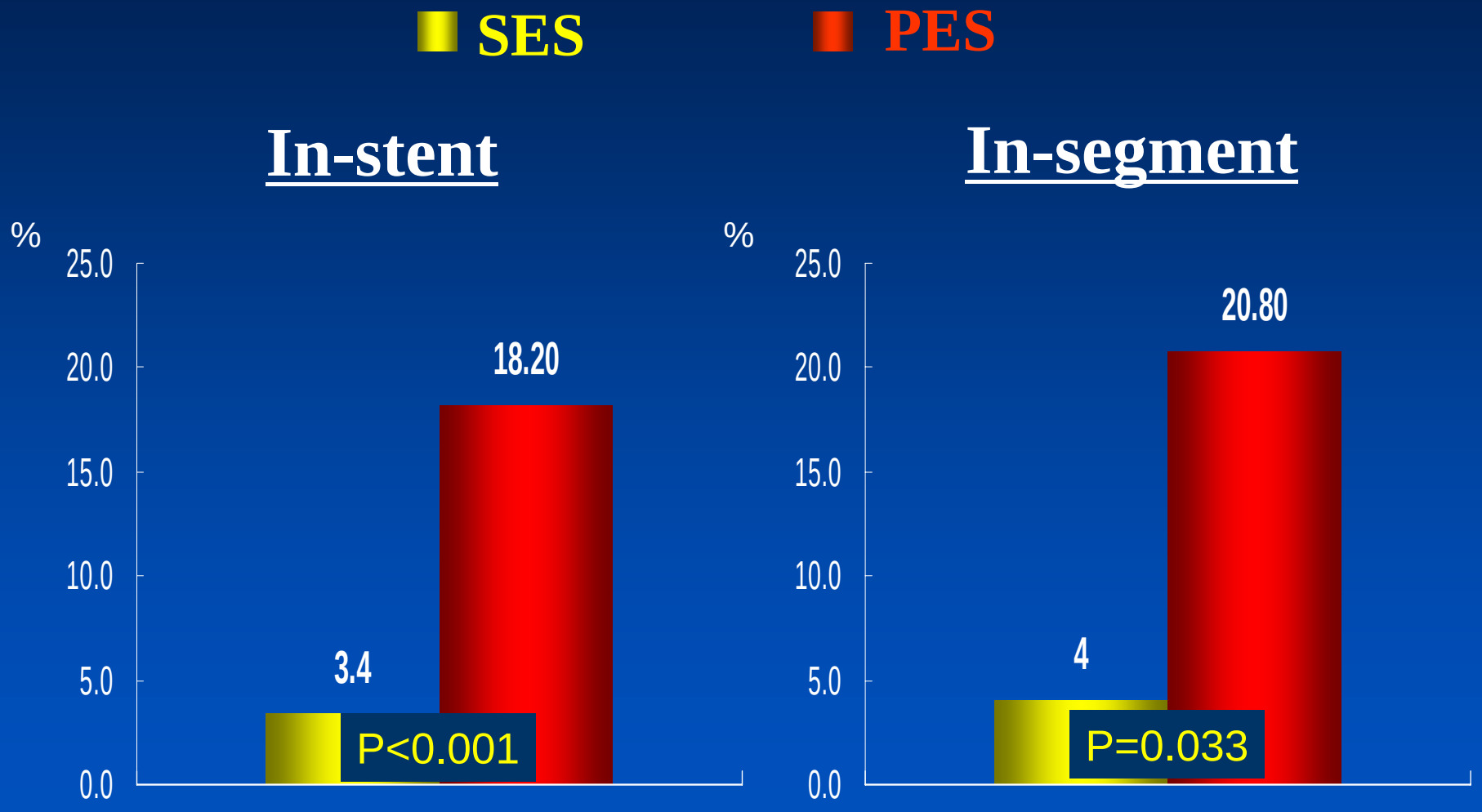
Angiographic Measurements
6-Months Follow-up

	SES (n=176)	PES (n=154)	*p*
MLD (mm)			
In-stent	2.44±0.51	2.01±0.67	<0.001
In-segment	2.24±0.50	1.93±0.60	<0.001
Diameter stenosis (%)			
In-stent	14.1±15.2	26.3±22.0	<0.001
In-segment	21.3±12.5	31.6±18.2	<0.001

Angiographic Measurements
6-Months Follow-up

	SES (n=176)	PES (n=154)	*p*
Late loss (mm)			
In-stent	0.13±0.43	0.53±0.57	<0.001
In-segment	0.31±0.40	0.67±0.53	<0.001
Loss index			
In-stent	0.06±0.27	0.29±0.35	<0.001
In-segment	0.23±0.37	0.51±0.58	<0.001

Restenosis rate



MACE at 9-Months

	SES	PES	P
Patients	200	200	
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
Stent thrombosis	1 (0.5%)	0	0.999
Acute	1 (0.5%)	1	
Subacute	0	0	
Late	0	0	
TLR	4 (2.0%)	15 (7.5%)	0.017
Death/MI/TVR	7 (3.5%)	17 (8.5%)	0.035
MACE (Death/MI/TLR)	4 (2.0%)	16 (8.0%)	0.010

Predictors of angiographic restenosis and 9-month clinical outcomes on multivariate analysis

	OR	95% CI	p
Angiographic restenosis			
SES	0.15	0.06-0.40	0.0001
Cilostazol	0.32	0.11-0.89	0.029
Lesion length	1.03	1.01-1.06	0.013
Post-MLD	0.17	0.05-0.28	0.005
TLR			
SES	0.24	0.07-0.81	0.021
Cilostazol	0.26	0.07-0.95	0.042
MACE			
SES	0.21	0.06-0.71	0.012

Lee SW, Park SW, et al. J Am Coll Cardiol 2008;52:727–33

A Randomized Comparison of Sirolimus-versus Paclitaxel-eluting stent implantation in Patients with Diabetes Mellitus

Two-year clinical outcomes of
The DES-DIABETES Trial

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Asan Medical Center,
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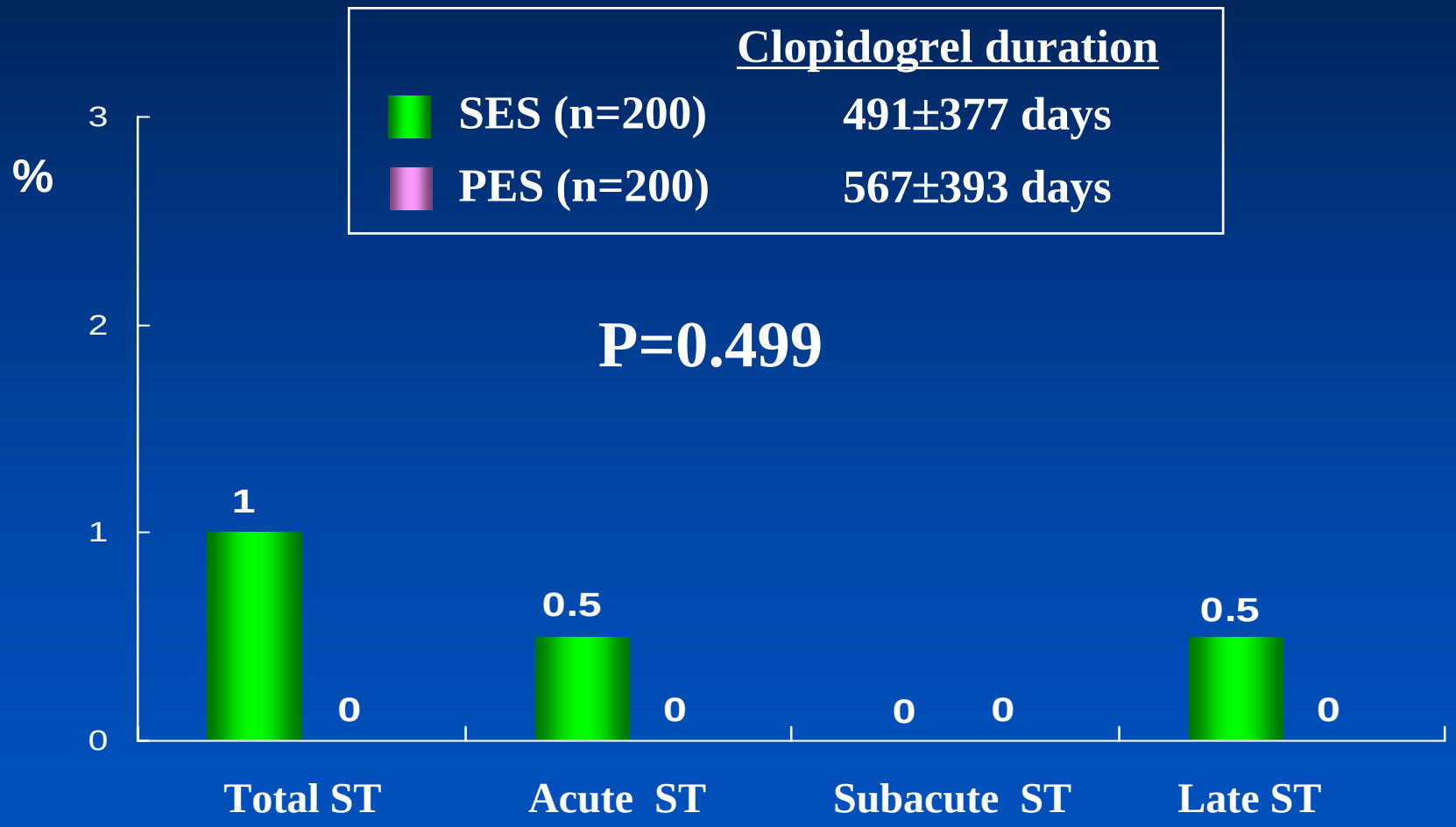
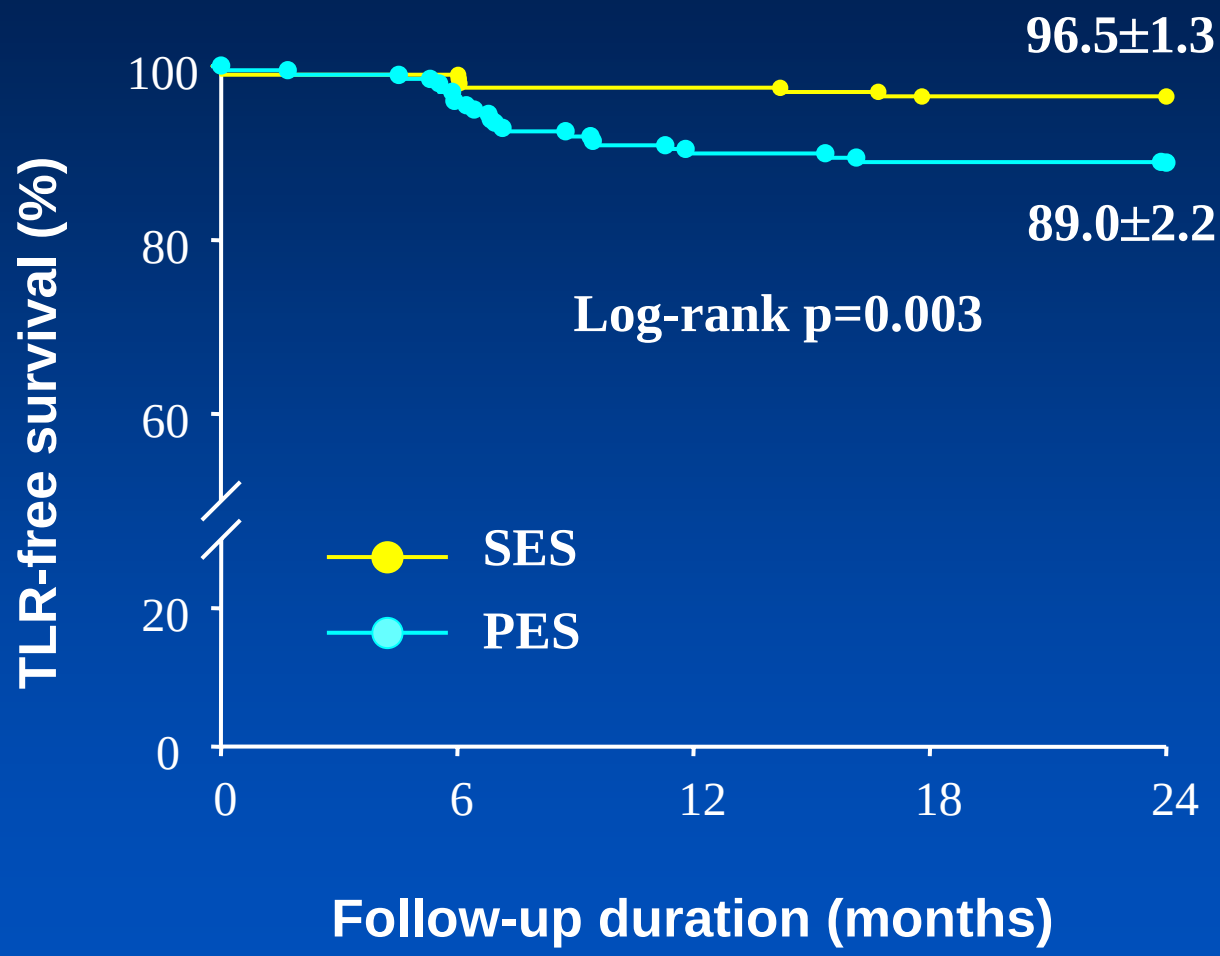
Lee SW, Park SW, et al. J Am Coll Cardiol 2009;53:812–3

Two-year stent thrombosis



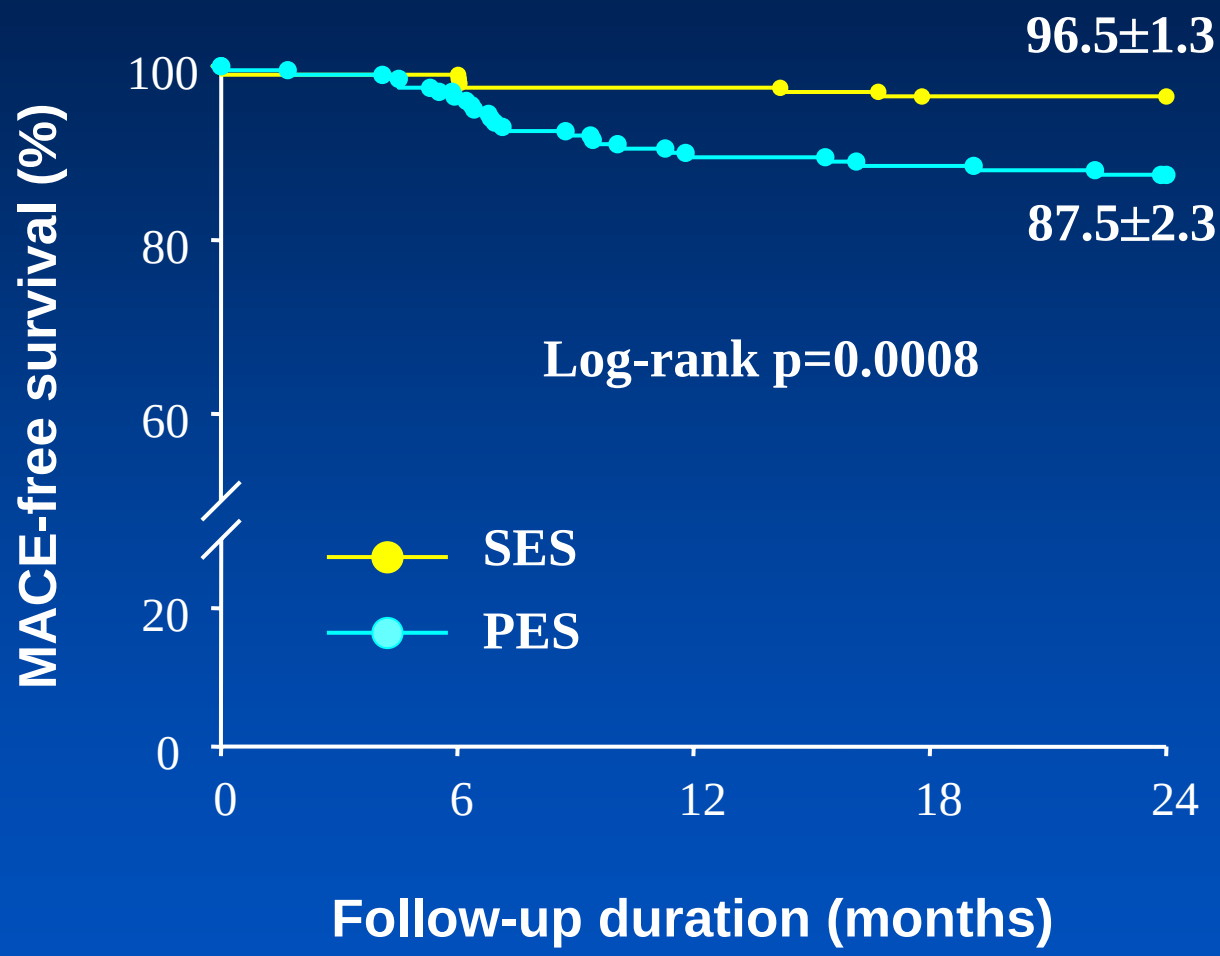
Lee SW, Park SW, et al. J Am Coll Cardiol 2009;53:812–3

Two-year TLR-free survival



Lee SW, Park SW, et al. J Am Coll Cardiol 2009;53:812–3

Two-year MACE-free survival



MACE: Death/MI/TLR

Lee SW, Park SW, et al. J Am Coll Cardiol 2009;53:812–3

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%)	0	
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 SW, Park SW, et al. J Am Coll Cardiol 2009;53:812–3

Independent Predictors of 2-year TLR and MACE on multivariate analysis

	HR	95% CI	p
TLR			
Cilostazol	0.42	0.19-0.98	0.033
SES	0.28	0.12-0.65	0.003
Post-procedural MLD	0.36	0.17-0.75	0.006
MACE			
SES	0.24	0.11-0.57	0.001
Post-procedural MLD	0.35	0.18-0.71	0.003

Lee SW, Park SW, et al. J Am Coll Cardiol 2009;53:812–3

Summary

- 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 with high post-procedural MLD may reduce angiographic restenosis, and improve 2-year clinical outcomes.
- Long-term use of clopidogrel in diabetic patients undergoing DES implantation may have a low risk of stent thrombosis.

Lee SW, Park SW, et al. J Am Coll Cardiol 2009;53:812–3

Conclusions

- **Based on the present data, patients with diabetes and an indication for PCI, a SES over PES should be the preferred type of DES.**

- **Long-term MACE rate is high in patients with diabetes even in DES era. Therefore, aggressive medical treatment, long-term clopidogrel treatment, and triple antiplatelet therapy (DECLARE-DIABETES) could improve the long-term clinical outcomes.**