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,
University of Ulsan College of Medicine, Seoul, Korea

DECLARE – Disclosure Information

No relationships to disclose for any of the authors

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Background

- Cilostazol, a phosphodiesterase III inhibitor, has been known to reduce smooth muscle proliferation and intimal hyperplasia after endothelial injury and lower restenosis after balloon angioplasty and stent implantation.

- Triple antiplatelet therapy (aspirin, clopidogrel and cilostazol) significantly reduced platelet aggregation and stent thrombosis compared with standard dual antiplatelet therapy (aspirin and clopidogrel) after bare-metal stent implantation.

Multivariate Predictors of In-Segment Restenosis after SES

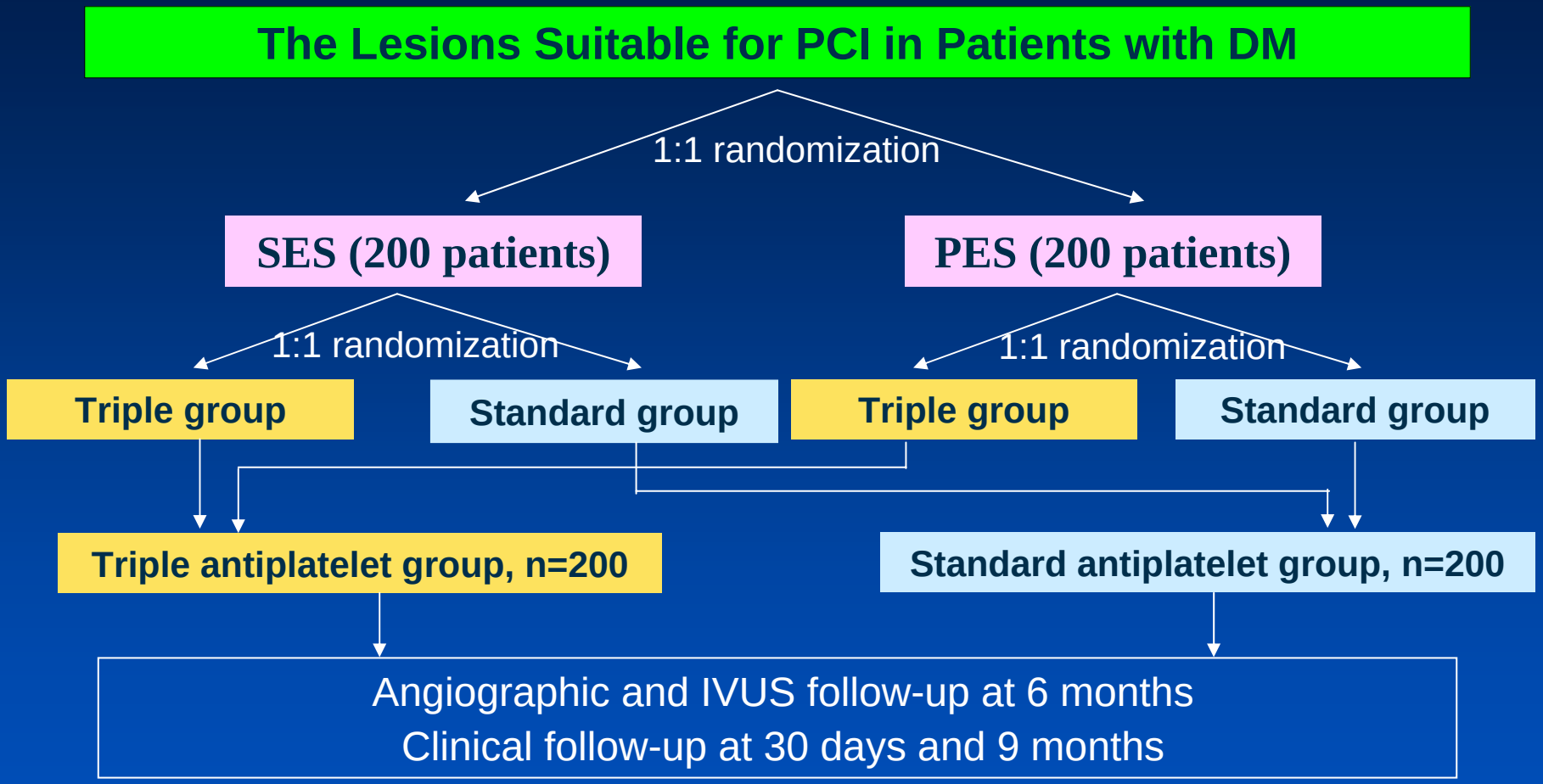
	OR	95% CI	p
ISR	4.16	1.63-11.01	<0.01
Ostial lesion	4.84	1.81-12.07	<0.01
DM	2.63	1.14-6.31	0.02
Stent length	1.42	1.21-1.68	<0.01
Ref diameter	0.46	0.24-0.87	0.03
LAD	0.30	0.10-0.69	<0.01

Lemos PA et al. Circulation 2004;109:1366-1370

Objective

- To compare the safety and the efficacy of triple antiplatelet therapy with standard dual antiplatelet therapy after drug-eluting stents implantation in patients with diabetes mellitus in a randomized controlled trial.

DECLARE-DIABETES Trial Design



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

Investigators in Korea

Asan Medical Center

Seung-Jung Park, MD, PhD
Seong-Wook Park, MD, PhD
Cheol Whan Lee, MD, PhD
Myeong-Ki Hong, MD, PhD
Young-Hak Kim, MD, PhD
Seung-Whan Lee, MD, PhD
Duk-Woo Park, MD, PhD
Sung-Cheol Yun, PhD

Chonbuk National University

Jae-Ki Ko, MD, PhD
Hyun-Sook Kim, MD, PhD

Chungnam National University

In-Whan Seong, MD, PhD
Si Wan Choi, MD, PhD
Jae-Hwan Lee, MD, PhD
Jae-Hyeong Park, MD, PhD

Soonchunhyang University

Soonchunhyang, Korea
Nae-Hee Lee, MD
Yoon Haeng Cho, MD

Pusan National University

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

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

Primary Endpoint

- Comparison of the standard and the triple antiplatelet treatments: In-stent late loss at 6 month angiographic follow-up study

Secondary Endpoint

- Efficacy end points
  - In-segment late loss and restenosis rate
  - MACE: composite of death, MI, and TLR at 30 days and 9 month
  - TVR
  - Stent thrombosis
  - Restenosis rate of SES, PES according to use of cilostazol

- Safety end points
  - Bleeding episode, major and minor
  - Incidence of drug discontinuation
  - CBC or LFT abnormality
  - Gastrointestinal

PCI Techniques and Antithrombotic Drug Regimen

- From at least 24 hours prior to the procedure and thereafter, all patients received aspirin (200 mg daily) and clopidogrel (a loading dose of 300 mg)
- Once the guide wire had crossed the target lesion, patients were randomly assigned in a 1:1 ratio to sirolimus-eluting stent (SES) or paclitaxel-eluting stent (PES) implantation
- After DES randomization, patients were randomly allocated in a 1: 1 ratio to the triple antiplatelet group or the dual antiplatelet therapy
- Patients in the triple group received a loading dose of 200 mg cilostazol immediately after the procedure and 100 mg twice a day for 6 months..
- After procedure; aspirin 100 mg/d indefinitely
- **Triple - cilostazol 200 mg/d + clopidogrel 75mg/d > at least 6 months**
- **Dual - clopidogrel 75mg/d > at least 6 months**

Patient Demographics

	Triple (n=200)	Standard (n=200)	*p*
Age (yrs)	61±9	61±9	0.704
Men	118 (59.0%)	114 (57.0%)	0.685
Treatment of DM			0.591
Dietary alone	20 (10.0%)	17 (8.5%)	
OHA	151 (75.5%)	147 (73.5%)	
Insulin	29 (14.5%)	36 (18.0%)	
Glycosylated Hb	7.8±1.9	7.6±1.6	0.237
Hypertension	119 (59.5%)	119 (59.5%)	0.889
Smoking	48 (24.0%)	63 (31.5%)	0.094
Hypercholesterolemia	61 (30.5%)	57 (28.5%)	0.661
LVEF (%)	59±10	58±10	0.357

Target lesion and Clinical Presentation

	Triple (n=200)	Standard (n=200)	*p*
Stented site			0.333
LAD	126 (63.0%)	114 (57.0%)	
LCX	27 (13.5%)	26 (13.0%)	
RCA	47 (23.5%)	60 (30.0%)	
Multi-vessel disease	131(65.5%)	125(62.5%)	0.532
Diagnosis			0.861
Stable angina	83 (41.5%)	85 (42.5%)	
Unstable angina	76 (38.0%)	71 (35.5%)	
Myocardial infarction	41 (20.5%)	44 (22.0%)	

Procedural Characteristics

	Triple (n=200)	Standard (n=200)	*p*
SES/PES	100/100	100/100	1.0
Maximal pressure (atm)	15.2±3.8	14.8±3.4	0.321
Use of IVUS	65 (32.5%)	66 (33.0%)	0.915
Use of GP IIb/IIIa inhibitor	8 (4.0%)	10 (5.0%)	0.630
Number of stents per lesion	1.30±0.59	1.27±0.51	0.587
Multi-vessel stenting	73 (36.5%)	60 (30.0%)	0.168
Total stent length	33.5±15.2	32.1±13.9	0.348

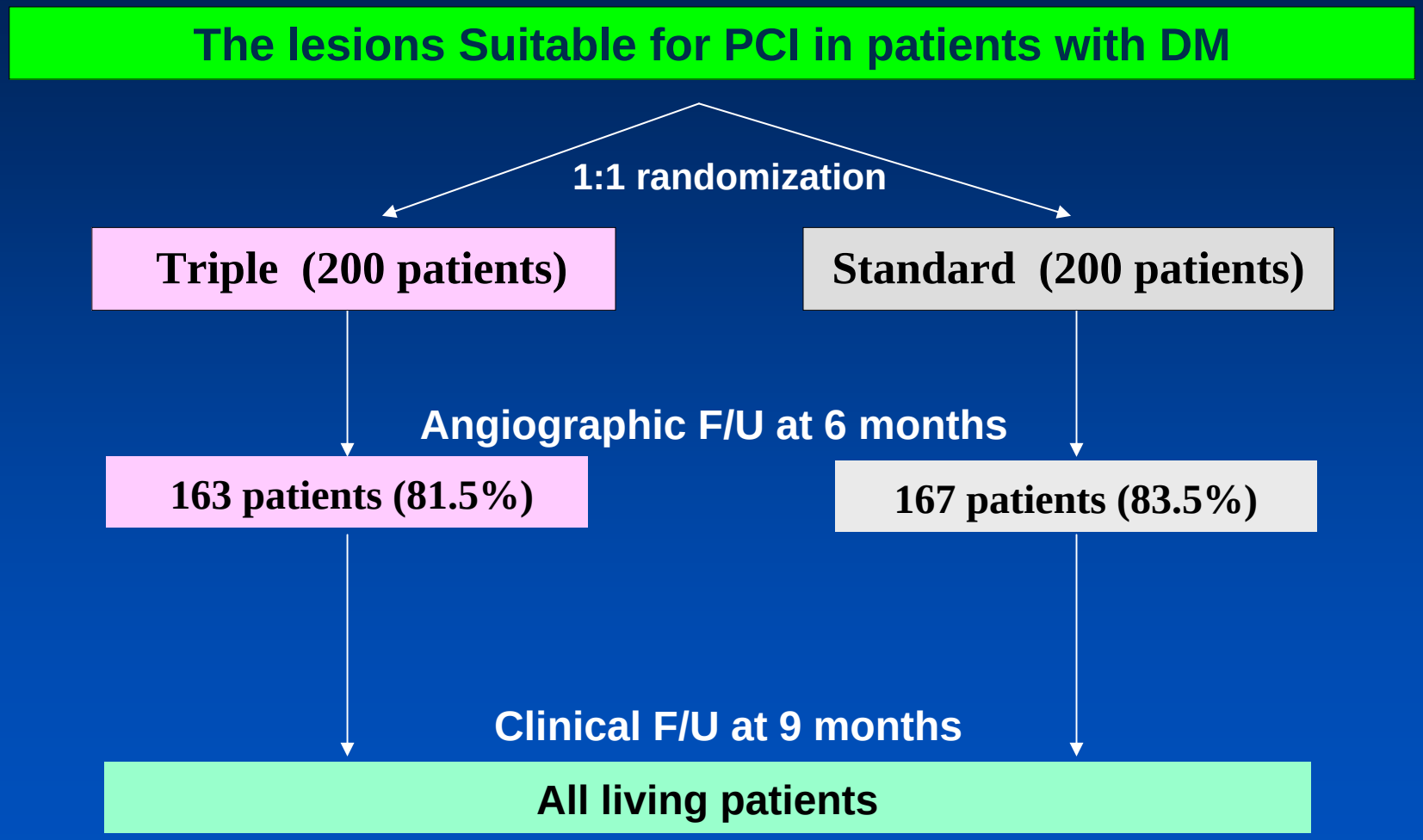
Angiographic Measurements
Pre-Procedure

	Triple (n=200)	Standard (n=200)	*p*
Reference vessel (mm)	2.81±0.40	2.78±0.46	0.505
Lesion length (mm)	26.7 ±13.3	26.3 ±13.8	0.806
MLD (mm)	0.79±0.47	0.73±0.49	0.170
Diameter stenosis (%)	68.4±13.5	69.0±14.2	0.708

Angiographic Measurements *Post-Procedure*

	Triple (n=200)	Standard (n=200)	*p*
Reference vessel (mm)	2.81±0.40	2.78±0.46	0.505
MLD (mm)			
In-stent	2.55±0.42	2.57±0.44	0.548
In-segment	2.24±0.44	2.24±0.49	0.930
Acute gain (mm)			
In-stent	1.75±0.56	1.84±0.61	0.109
In-segment	1.44±0.55	1.51±0.63	0.218
Diameter stenosis (%)			
In-stent	11.1±11.2	8.3±11.8	0.034
In-segment	20.6±11.2	18.8±11.2	0.135

Data Analysis



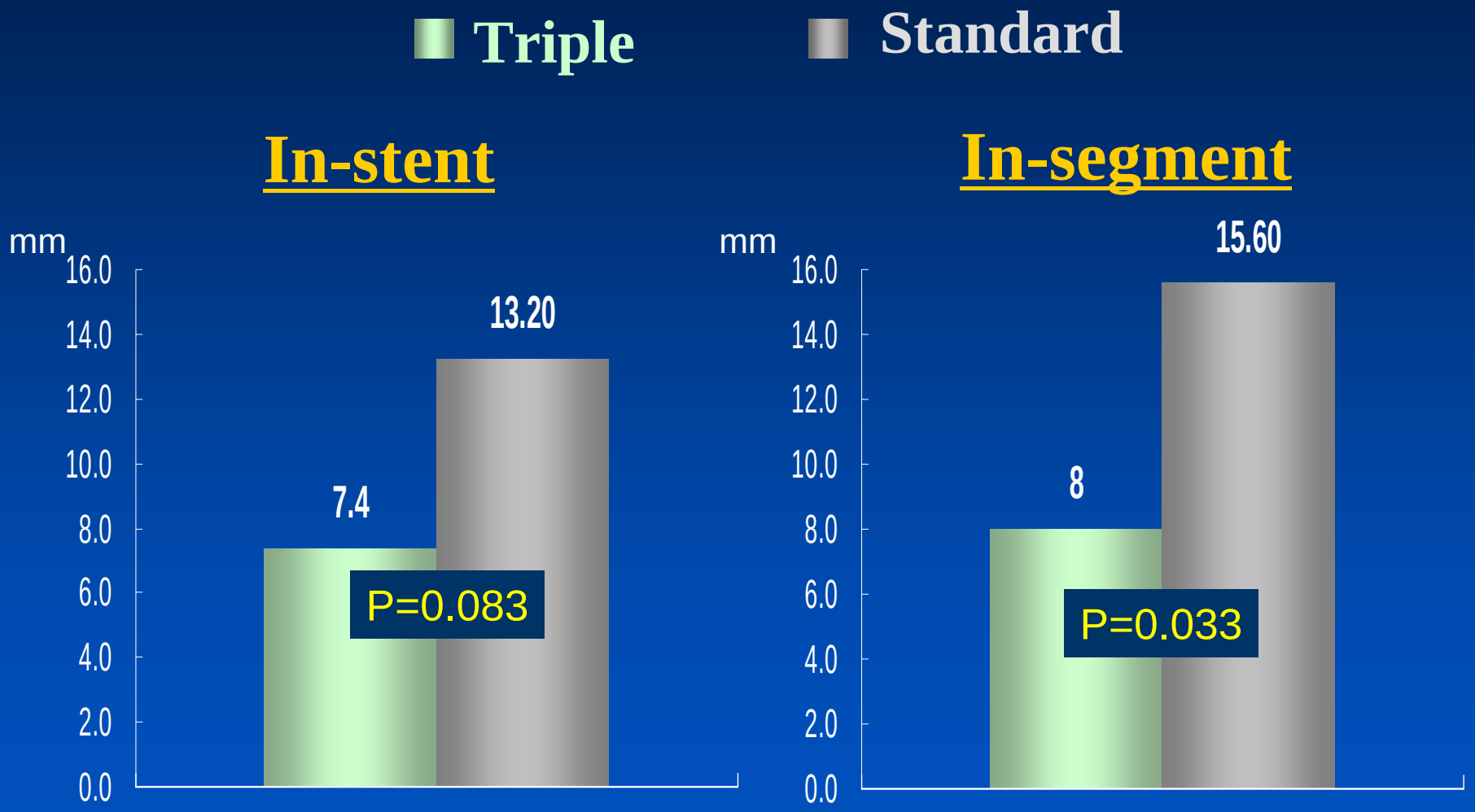
Angiographic Measurements
6-Months Follow-up

	Triple (n=163)	Standard (n=167)	*p*
Ref vessel (mm)	2.85±0.47	2.81±0.45	0.419
MLD (mm)			
In-stent	2.32±0.59	2.20±0.63	0.096
In-segment	2.15±0.55	2.03±0.58	0.046
Diameter stenosis (%)			
In-stent	18.5±18.7	20.9±20.5	0.244
In-segment	24.6±15.6	27.7±16.7	0.081

Angiographic Measurements
6-Months Follow-up

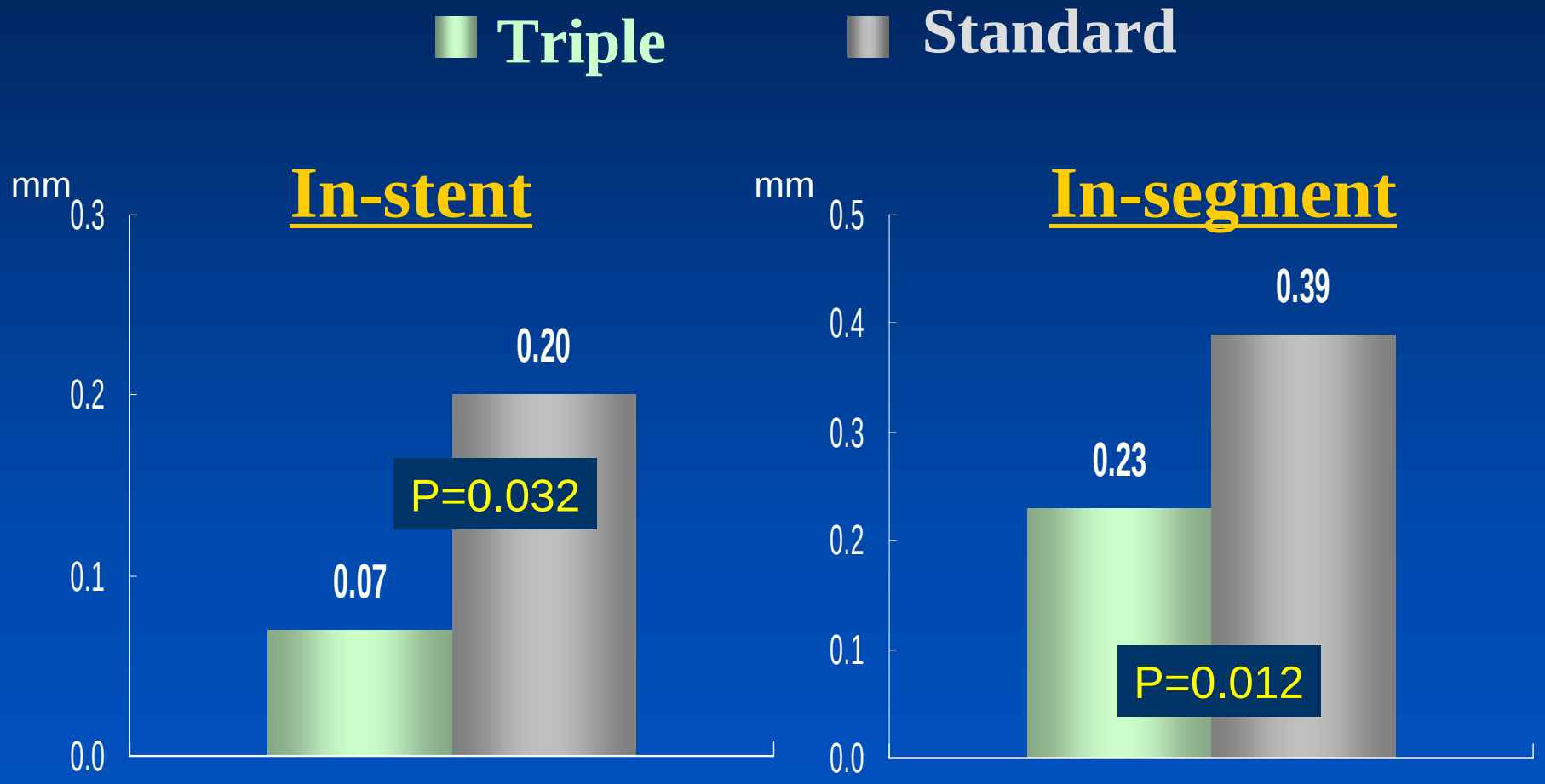
	Triple (n=163)	Standard (n=167)	*p*
Late loss (mm)			
In-stent	**0.25±0.53**	**0.38±0.54**	**0.025**
In-segment	0.42±0.50	0.53±0.49	0.031
Loss index			
In-stent	0.12±0.39	0.25±0.71	0.047
In-segment	0.27±0.37	0.35±0.33	0.037

Restenosis rate



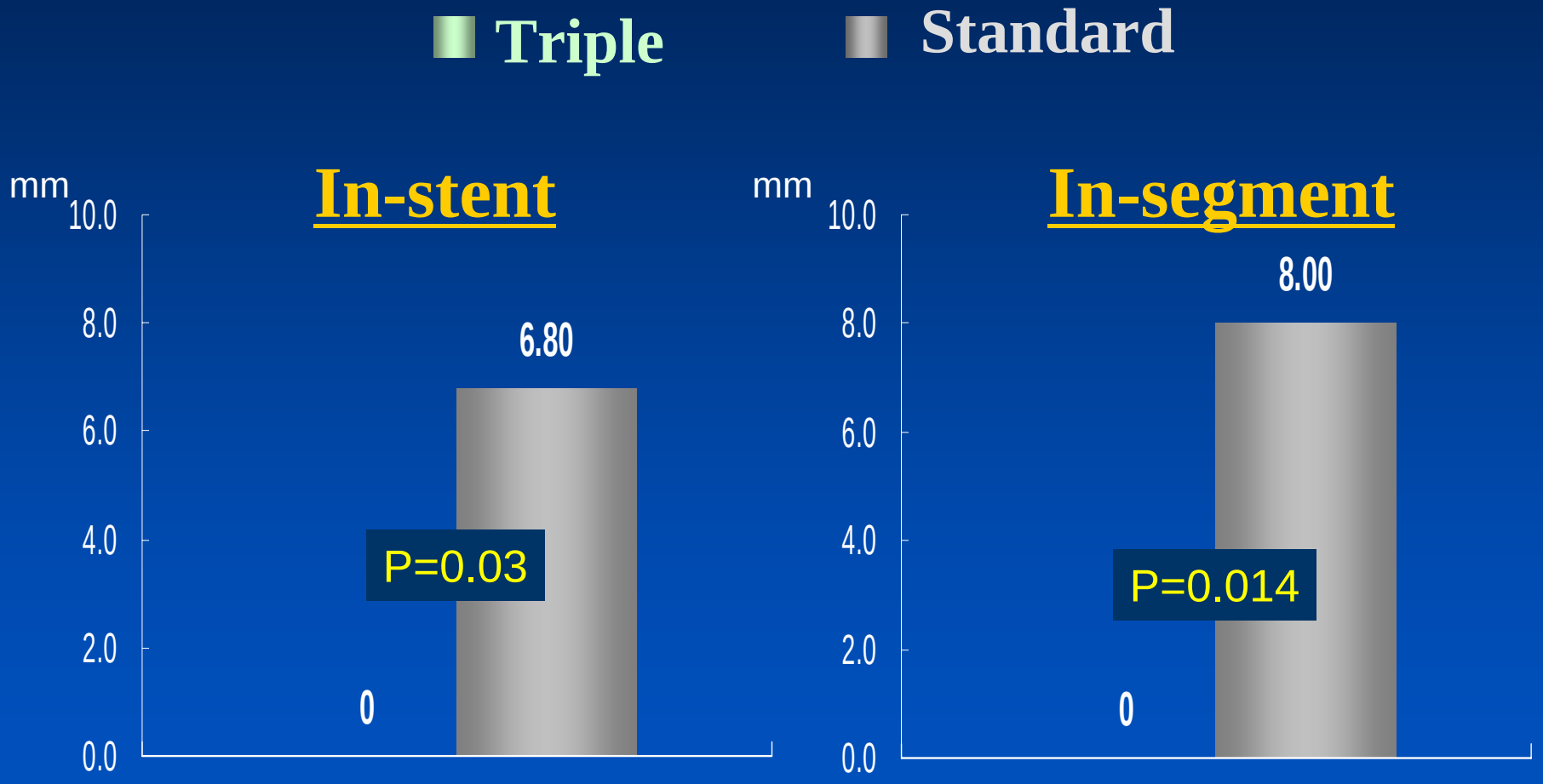
Late loss

In Patients treated with SES



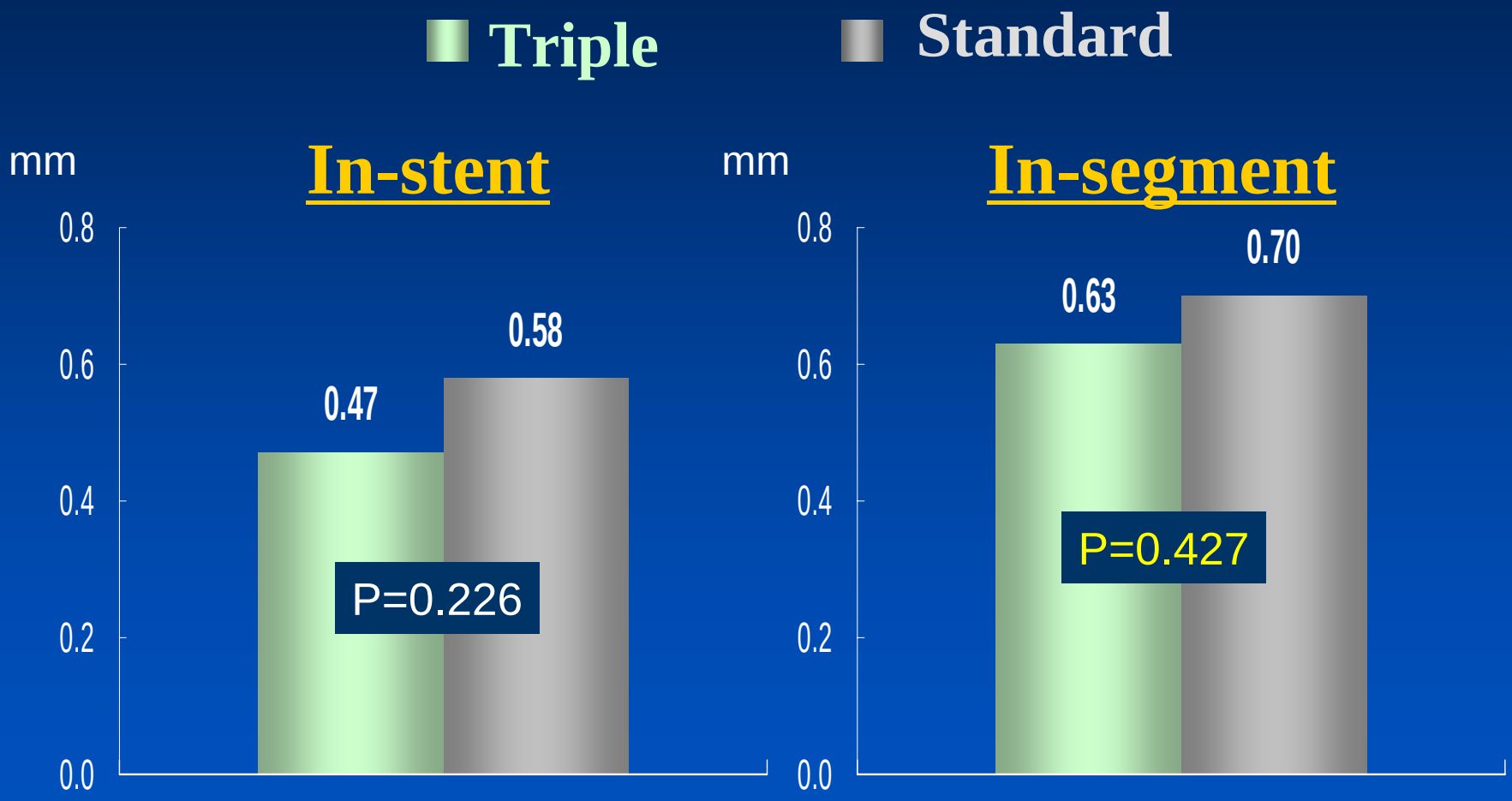
Restenosis rate

In Patients treated with SES



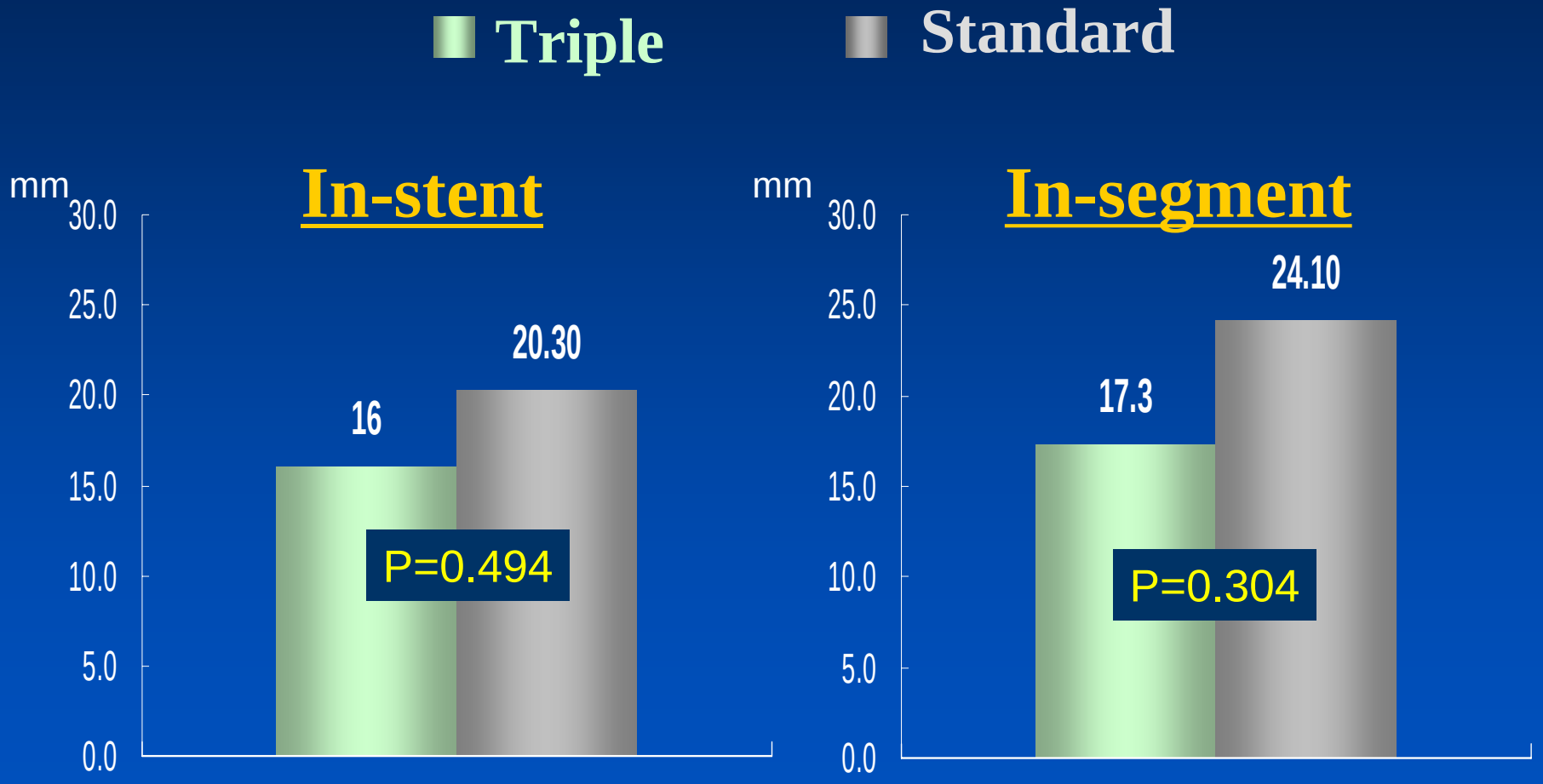
Late loss

In Patients treated with PES



Restenosis rate

In Patients treated with PES



Patterns of Restenosis

	Triple	Standard	P
Focal	8(61.5%)	16(61.5%)	0.999
IA	0	0	
IB	2	4	
IC	4	8	
ID	2	4	
Diffuse	5(38.5%)	10(38.5%)	0.999
II	3	8	
III	1	2	
IV	1	0	
Length of ISR, mm	11.1 ±6.1	15.7 ±12.0	0.219

DECLARE-DIABETES

MACE at 9-Months

	Triple	Standard	P
Patients	200	200	
Death	1(0.5%)*	0	0.999
Cardiac	1	0	
Non-cardiac	0	0	
MI	1 (0.5%)*	1 (0.5%)	0.999
Stent thrombosis	0	1 (0.5%)	0.999
Acute	0	1	
Subacute	0	0	
Late	0	0	
TLR	5 (2.5%)	14 (7.0%)	0.034
Death/MI/TVR	8 (4.0%)	16 (8.0%)	0.092
MACE (Death/MI/TLR)	6 (3.0%)	14 (7.0%)	0.066

* This patient died due to non-target vessel AMI 6 months after index procedure.

Adverse Drug Effects

	Triple	Standard	P
Patients	200	200	
Bleeding	3 (1.5%)*	3 (1.5%)*	0.999
Rash	15 (7.5%)	5 (2.5%)	0.036
GI trouble	9 (4.5%)	5 (2.5%)	0.416
Thrombocytopenia	0	1 (0.5%)	0.999
Neutropenia	0	0	0.999
LFT abnormality	2 (1.0%)	1 (0.5%)	0.999
Drug discontinuation	29 (14.5%)	5 (4.5%)	<0.001

* All had ecchymosis without any episode of major bleeding requiring transfusion during follow-up.

Predictors of angiographic restenosis and 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
Cilostazol	0.14	0.02-0.94	0.043

Conclusions: Efficacy

- Triple antiplatelet combination therapy was associated with lower late luminal loss compared to the standard antiplatelet therapy after DES implantation in diabetic patients, suggesting the additive inhibitory effect of cilostazol on the neointimal hyperplasia.
- By the improved angiographic outcome with triple combination, the incidences of in-segment restenosis and subsequent TLR were significantly decreased in diabetic patients, as compared to the standard therapy.

Conclusions: Safety

- Drug discontinuation occurred more frequently in the triple antiplatelet patients compared to the standard antiplatelet patients.
- However, triple antiplatelet therapy has been safely applied without increase of serious bleeding episode.
- These findings may justify the additional use of cilostazol on the top of dual antiplatelet therapy in diabetic patients undergoing DES implantation.