Impact of Triple Antiplatelet Therapy on Angiographic Restenosis after Drug-Eluting Stent : Results from Pooled Analysis of DECLARE trials

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Incidence, Predictors, Treatment, and Long-Term Prognosis of Patients With Restenosis After Drug-Eluting Stent Implantation for Unprotected Left Main Coronary Artery Disease

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Restenosis rate:17%

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Predictors of Restenosis

Table 3 Univariate and Multivariate Predictors of ISR

Variable	Univariate	p Value	Multivariate	p Value
Male	0.61 (0.38–0.99)	0.045	0.41 (0.24–0.69)	0.007
Diabetes mellitus	1.82 (1.14–2.90)	0.012		
Renal failure	3.74 (1.36–10.25)	0.011		
Extent of diseased vessel		0.022		
Left main only	1.00			
Plus single-vessel disease	2.11 (0.76–5.86)	0.15		
Plus double-vessel disease	3.82 (1.49–9.80)	0.005		
Plus triple-vessel disease	2.58 (0.97–6.87)	0.06		
Restenotic lesion	4.20 (2.26–7.84)	<0.001	4.59 (2.40–8.77)	<0.001
Bifurcation involvement	2.40 (1.34–4.31)	0.003	2.56 (1.27–5.19)	0.009
Complex stenting with ≥2 stents in bifurcation lesion*	3.03 (1.64–5.55)	<0.001	2.50 (1.28–4.76)	0.007
Total number of stents	2.60 (1.97–3.43)	<0.001	4.76 (2.94–7.67)	<0.001
Total length of stents	1.01 (1.00–1.02)	0.003		
Maximal balloon pressure	0.89 (0.83–0.95)	0.001		
Maximal balloon size	0.51 (0.27–0.98)	0.043		

Values are hazard ratio (95% confidence interval). *Compared with simple cross-over stenting of distal bifurcation lesions.
ISR = in-stent restenosis.

Randomized, non-inferiority trial of three limus agent-eluting stents with different polymer coatings: the Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents (ISAR-TEST-4) Trial‡

Robert A. Byrne*, Adnan Kastrati[1], Sebastian Kufner[1], Steffen Massberg[1], K. Anette Birkmeier[1], Karl-Ludwig Laugwitz[2], Stefanie Schulz[1], Jürgen Pache[1], Massimiliano Fusaro[1], Melchior Seyfarth[1], Albert Schömig[1,2], and Julinda Mehilli[1] for the Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents (ISAR-TEST-4) Investigators

Restenosis rate:

Cypher: 13.4%

Xience: 10.1%

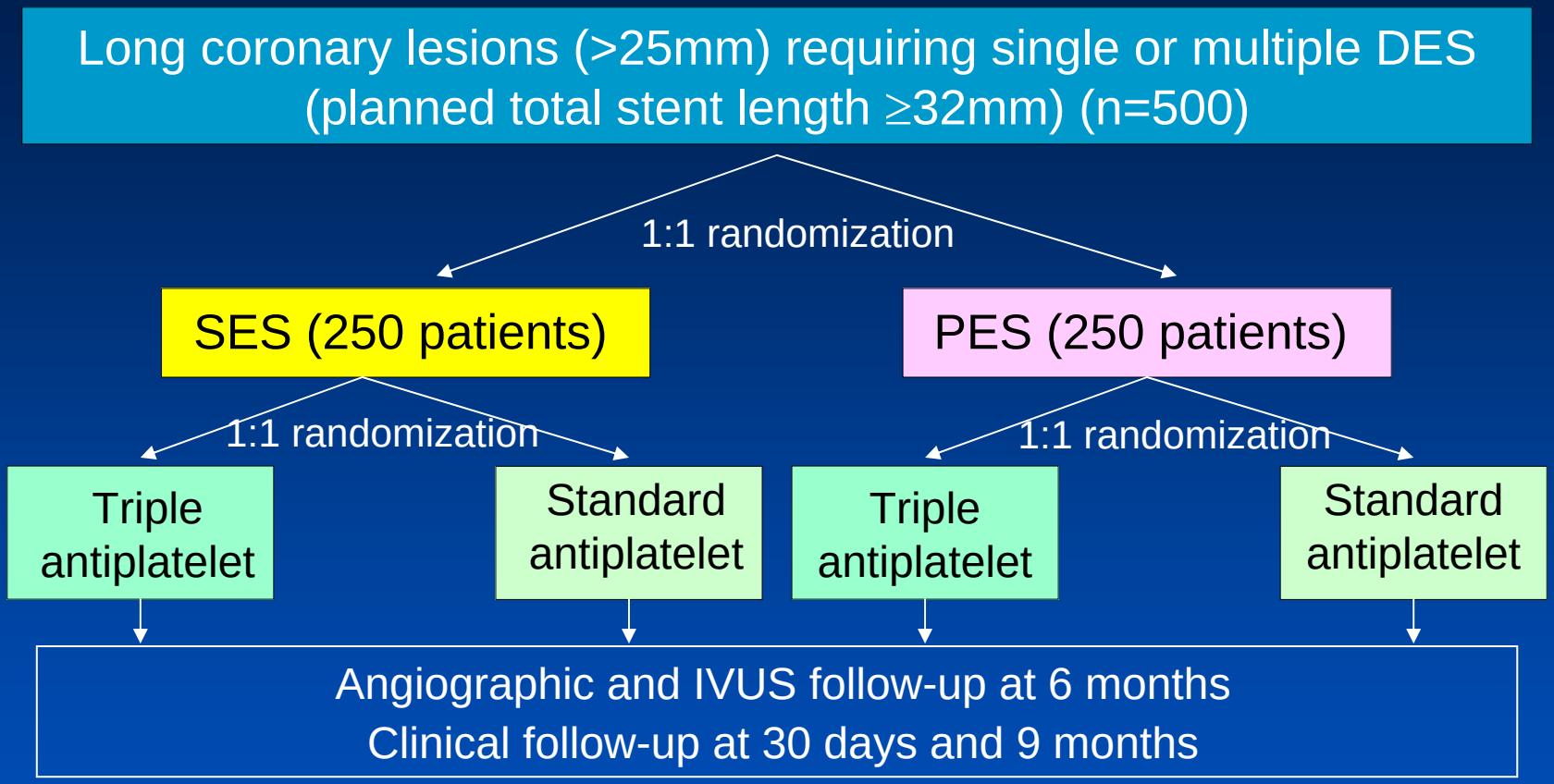
Comparison of Everolimus-Eluting and Sirolimus-Eluting Stents in Patients with Long Coronary Artery Disease: A Randomized LONG-DES III Trial

Stent length: 46.5 mm

Restenosis rate:

Xience: 7.3%

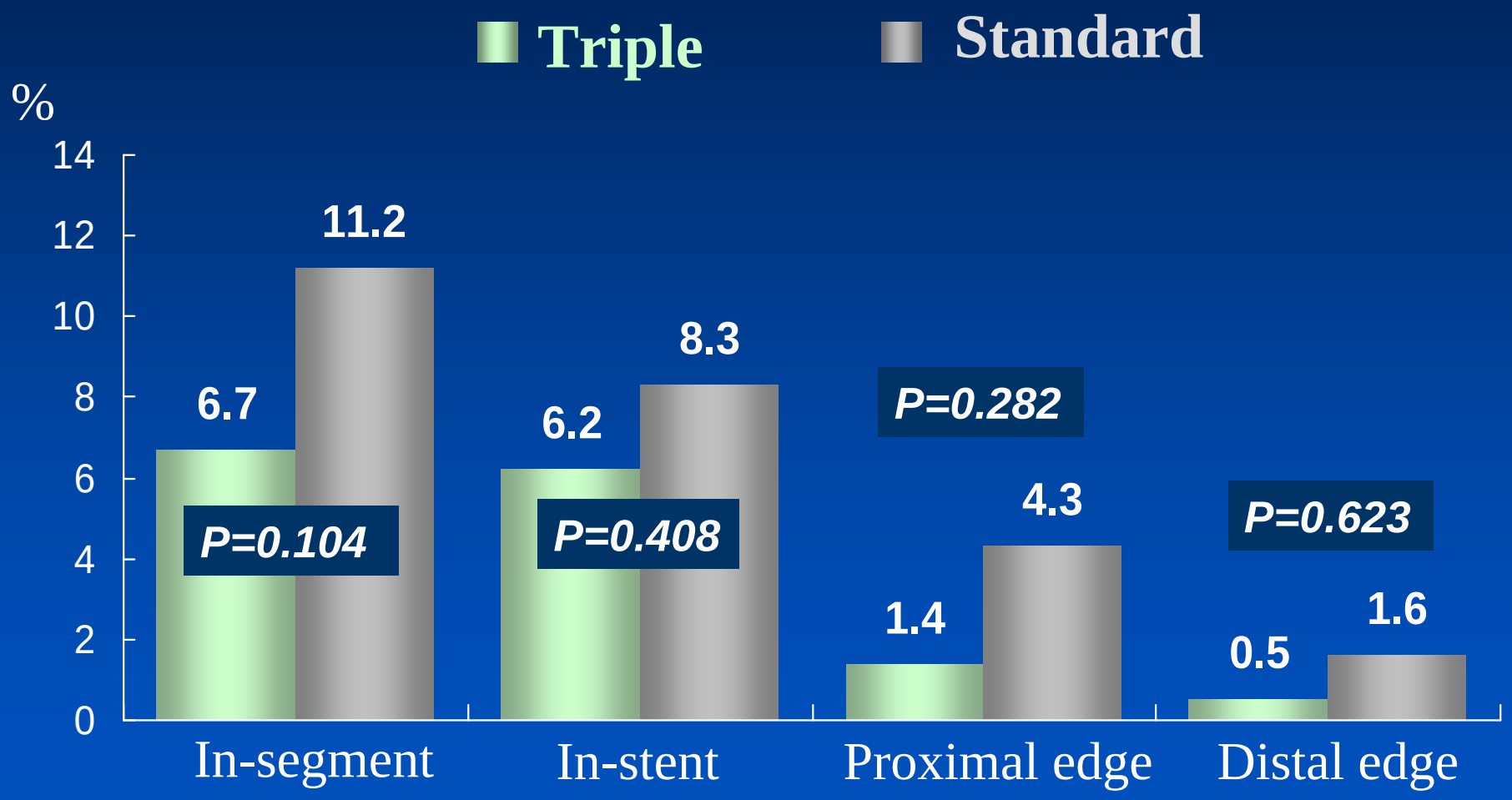
DECLARE-LONG Trial design



* 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. Am J Cardiol. 2007;100:1103-8

Angiographic Restenosis



Lee SW, Park SW et al. Am J Cardiol. 2007;100:1103-8

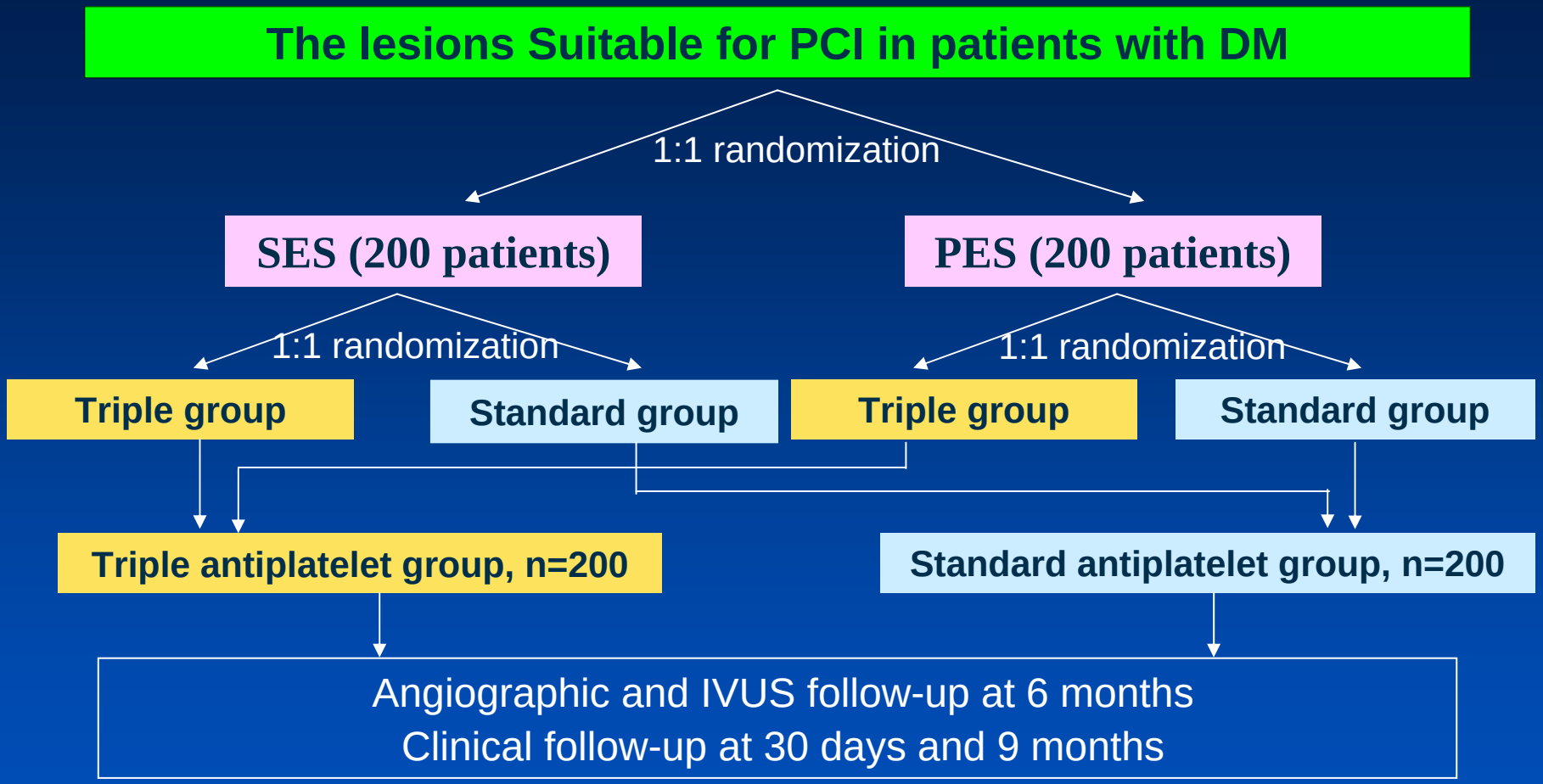
MACE at 9-Months

DECLARE-LONG

	Triple	Standard	P
Patients	250	250	
Death	0	2 (0.8%)	0.499
Cardiac	0	1 (0.4%)	
Non-cardiac	0	1 (0.4%)	
MI	1 (0.4%)	1 (0.4%)	0.652
Stent thrombosis	1 (0.4%)	1 (0.4%)	1.0
Acute	0	0	
Subacute	1*	0	
Late	0	1**	
TLR	7 (2.8%)	17 (6.8%)	0.036
Death/MI/TVR	9 (3.6%)	20 (8.0%)	0.036
Death/MI/TLR	8 (2.8%)	19 (7.6%)	0.016

* This patient had subacute stent thrombosis and underwent TLR.
** This patient was presented with STEMI and cardiogenic shock 3 months after the index procedure. Before emergent revascularization, this patient was dead.

DECLARE-DIABETES Trial Design



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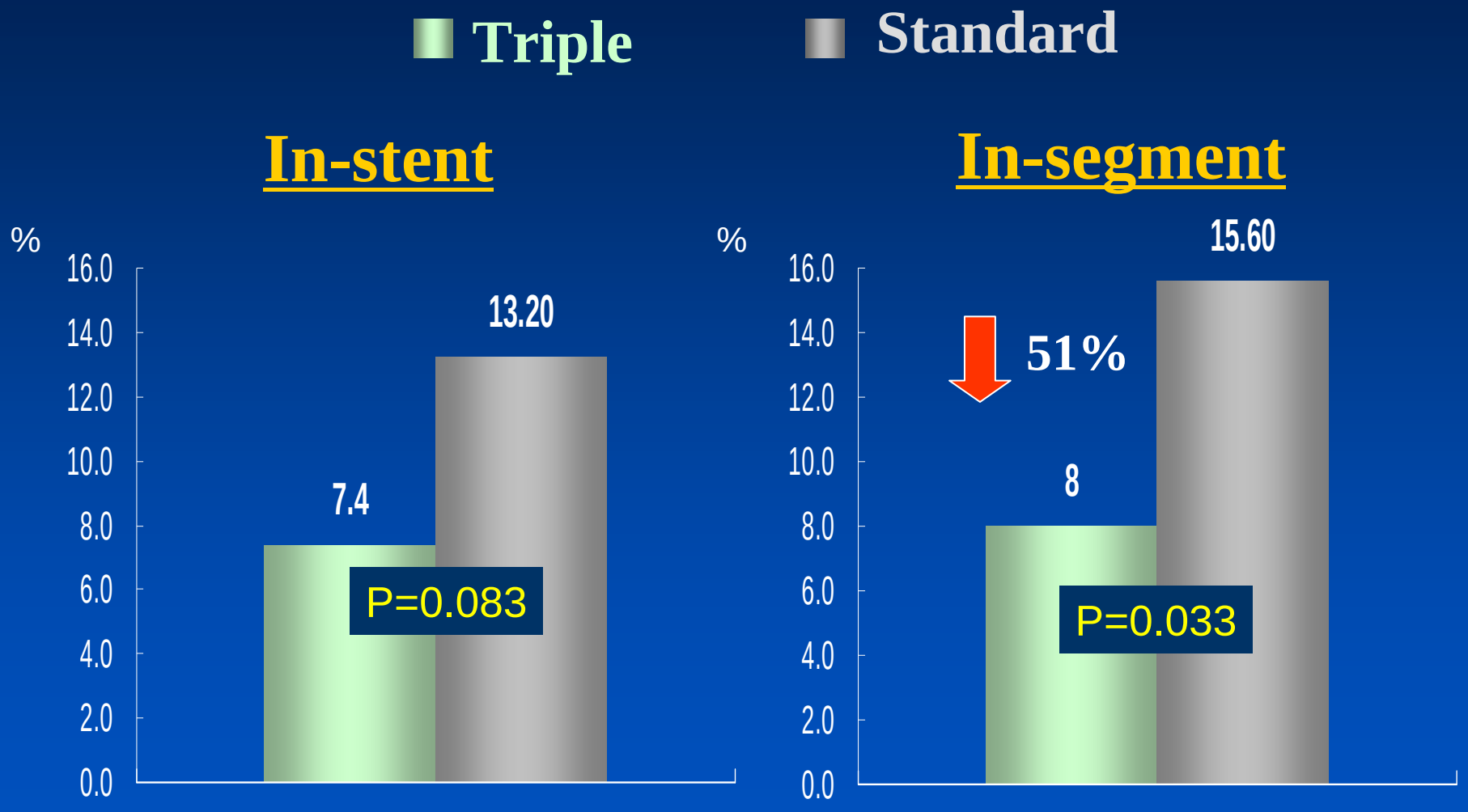
Lee SW, Park SW et al. J Am Coll Cardiol March, 2008;51:1181-7

Restenosis rate



Lee SW, Park SW et al. J Am Coll Cardiol March, 2008;51:1181-7

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 was dead due to non-target vessel AMI 6 months after index procedure.

Study Design (DECLARE-LONG II)

(Multicenter, randomized double blind clinical trial)

Long coronary lesions (≥25mm) requiring single or multiple Endeavor stent (planned total stent length ≥30mm)

Successful stenting

1:1 randomization

Aspirin + clopidogrel + cilostazol* (n=250)	Aspirin + clopidogrel + placebo* (n=249)

Angiographic and IVUS follow-up at 8 months
Clinical follow-up at 12 months

* aspirin plus clopidogrel plus **study drug** for 8 months

Primary endpoint:
In-stent late loss at 8 months by QCA

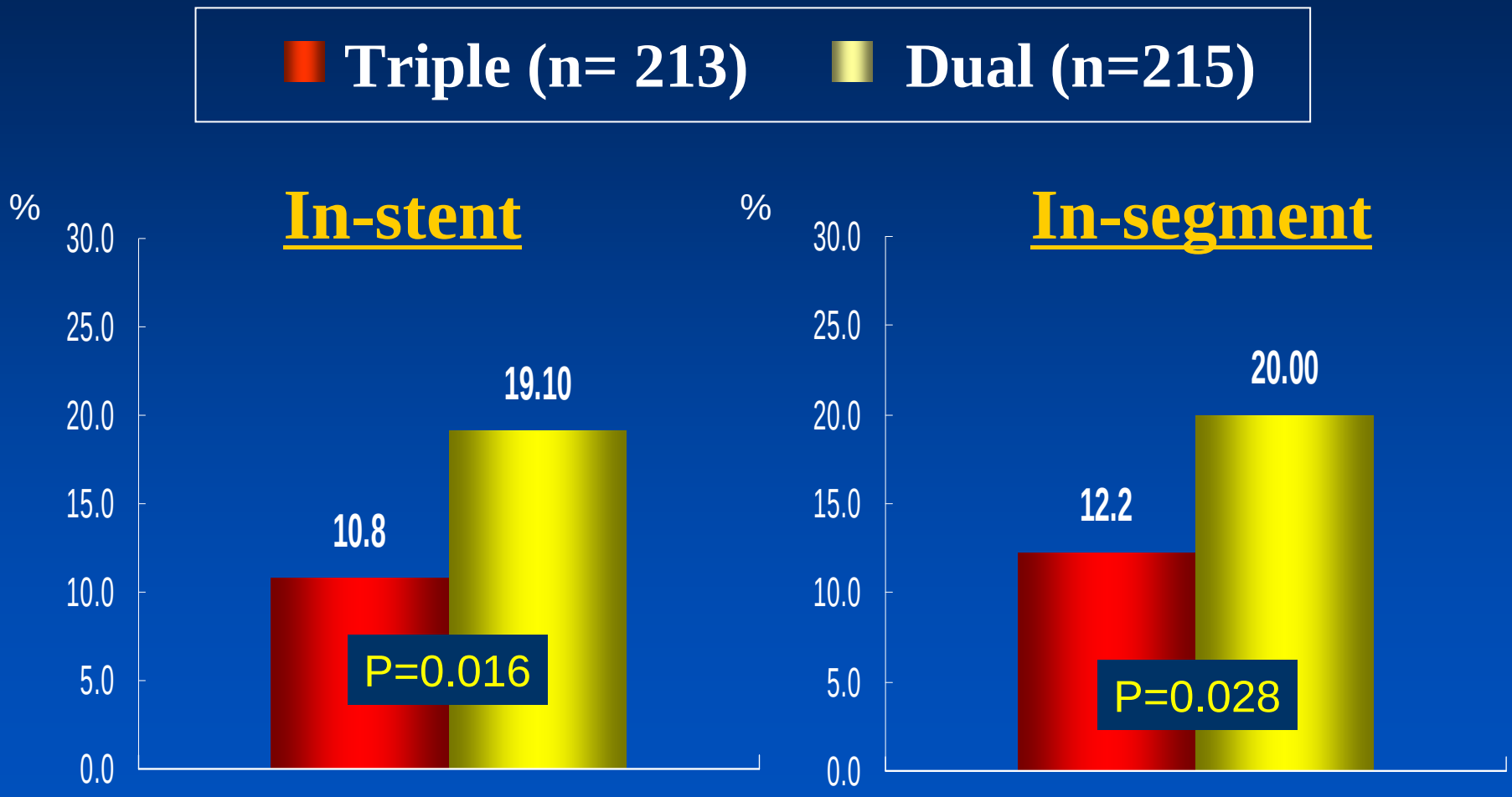
Drug compliance and adverse drug events monitoring: compliance questionnaire

CBC, LFT, hsCRP, HBA1c at baseline, 30 days, 90 days, 180 days, 270 days, 360 days (±1 month),

Verify now (aspirin/P2Y12): postprocedure 48 hours, 1 month

IVUS analysis

Restenosis rate



MACE at 12-Months

DECLARE-LONG II

	Triple (N=250)	Standard (N=249)	*p*
Death	6 (2.4%)	3 (1.2%)	0.504
MI	4 (1.6%)	4 (1.6%)	0.995
Ischemic driven TLR	13 (5.2%)	25 (10.0%)	0.042
Stent thrombosis	4 (1.6%)	1 (0.4%)	0.179
Acute	1 (0.4%)	0	
Subacute	2 (0.8%)	1 (0.4%)	
Late	1 (0.4%)	0	
Ischemic driven TVR	13 (5.2%)	26 (10.4%)	0.029
Death/MI/ischemic driven TVR	18 (7.2%)	31 (12.4%)	0.049
Death/MI/ischemic driven TLR	18 (7.2%)	30 (12.0%)	0.066

Background

- Although DES has reduced angiogrpahic restenosis and improved long-term outcomes compared with BMS implantation in patients with DM or complex lesions subsets, the diabetics or the patients with long lesions have a higher adverse cardiac outcomes after DES implantation

- We previously performed randomized, multicenter, prospective study showing triple antiplatelet therapy for 6 or 8 months in patients with DM (DECLARE-DIABETES trial) or long lesions (DECLARE-LONG I and II trials) was superior to dual antiplatelet therapy in reducing angiographic restenosis.

Background

- However, the primary endpoint of each DECLARE trial (DECLARE-DIABETES, DECLARE-LONG I and II) was late loss using small sample size.

- So, we want to evaluate the impact of triple antiplatelet therapy on angiographic restenosis after DES implantation and to find the predictor of angiographic restenosis

Study population

400 patients of DECLARE-DIABETES trial,
500 patients of DECLARE-LONG I trial
499 patients of DECLARE-LONG II trial

Triple antiplatelet therapy (n=700)
Aspirin 100mg/d + Clopidogrel 75mg/d
+ Cilostasol* 100mg bid for 6 or 8 months

Standard (dual) antiplatelet therapy (n=699)
Aspirin 100mg/d + Clopidogrel 75mg/d
for at least 6 or 12 months

***Cilostazol was added immediately after successful stenting (a loading dose of 200 mg cilostazol)**

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

Study Endpoint

- Six- or Eight months restenosis
- Late loss and restenosis in each DES
  (Cypher, Taxus, Endeavor stent)
- Predictors of angiographic restenosis

Patient Demographics

	Triple (n=700)	Standard (n=699)	*p*
Age (yrs)	61±9	61±9	0.303
Men	455 (65.0%)	451 (64.5%)	0.539
Diabetes	377 (53.9%)	365 (52.2%)	0.783
Hypertension	402 (57.4%)	418 (59.8%)	0.368
Smoking	218 (31.1%)	231 (33.0%)	0.446
Hypercholesterolemia (≥ 200mg/dL)	242 (34.6%)	240 (34.4%)	0.941
LVEF (%)	60±9	59±9	0.022

Target lesion and Clinical Presentation

	Triple (n=700)	Standard (n=699)	*p*
Stented site			**0.723**
LAD	429 (61.3%)	422 (60.4%)	
LCX	90 (12.9%)	84 (12.0%)	
RCA	181 (25.9%)	193 (27.6%)	
Diagnosis			**0.836**
Stable angina	311 (44.4%)	320 (45.8%)	
Unstable angina	273 (39.0%)	262 (37.5%)	
AMI	116 (16.6%)	117 (16.7%)	

Procedural Characteristics

	Triple (n=700)	Standard (n=699)	*p*
SES/PES/ZES	225/225/250	225/225/249	0.999
Maximal pressure (atm)	15.8±3.7	15.4±3.4	0.084
Use of IVUS	365 (52.1%)	359 (51.4%)	0.769
Number of stents per lesion	1.4±0.6	1.4±0.6	0.592
Total stent length/target lesion	37.7±14.0	37.5±13.6	0.830

Angiographic Measurements
Pre-Procedure

	Triple (n=700)	Standard (n=699)	*p*
Reference vessel (mm)	2.91±0.43	2.89±0.45	0.526
Lesion length (mm)	31.9 ±13.4	32.2 ±13.4	0.691
MLD (mm)	0.82±0.49	0.79±0.48	0.346
Diameter stenosis (%)	70.5±15.6	70.6±15.5	0.921

Angiographic Measurements
Post-Procedure

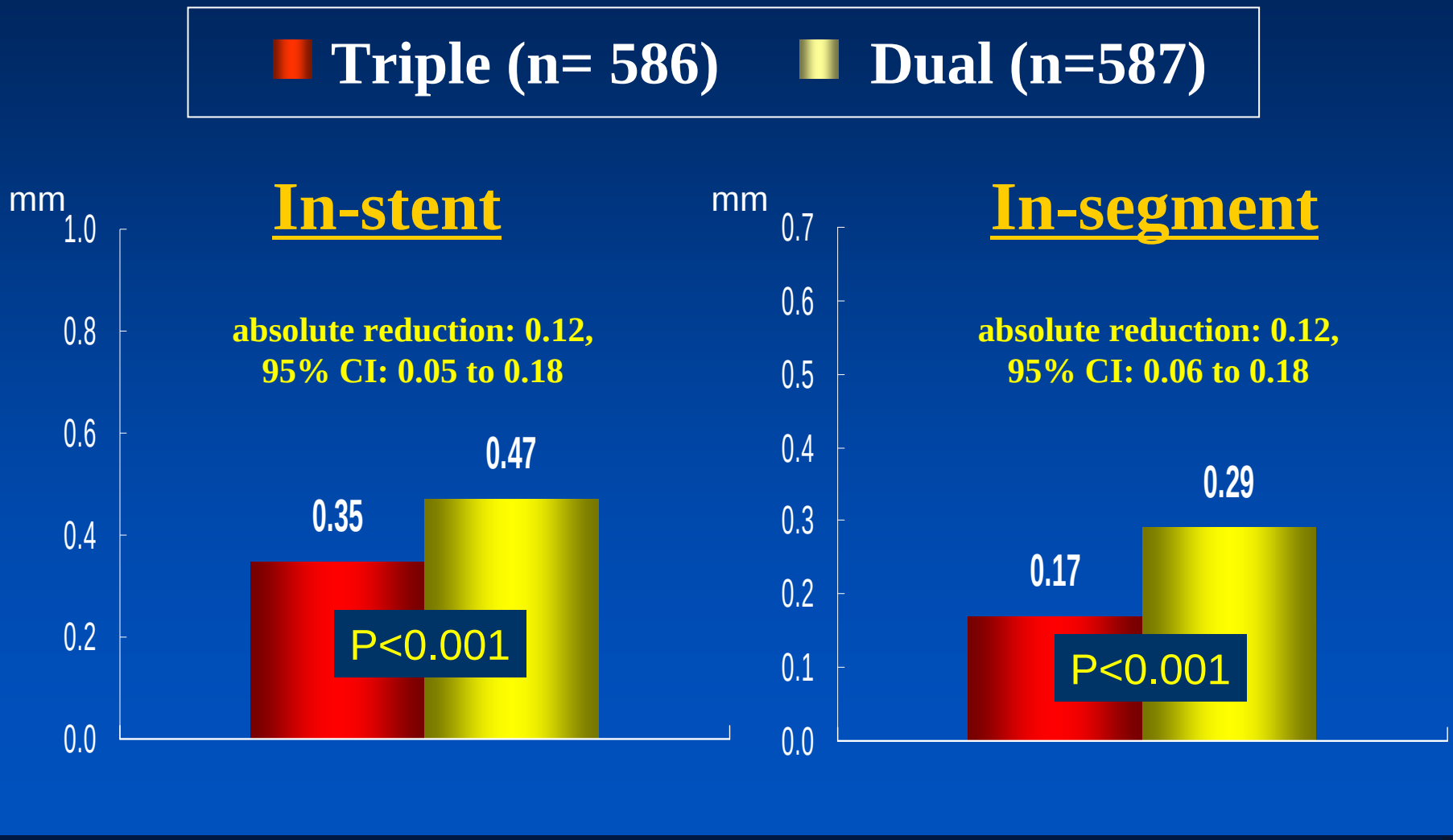
	Triple (n=700)	Standard (n=699)	*p*
Reference vessel (mm)	2.91±0.43	2.89±0.45	0.526
MLD (mm)			
In-stent	2.58±0.41	2.58±0.43	0.938
In-segment	2.25±0.47	2.25±0.49	0.820
Acute gain (mm)			
In-stent	1.76±0.57	1.79±0.60	0.384
In-segment	1.44±0.61	1.46±0.65	0.554
Diameter stenosis (%)			
In-stent	8.1±13.1	7.5±12.0	0.429
In-segment	17.4±11.2	17.0±10.6	0.531

Follow-up angiography

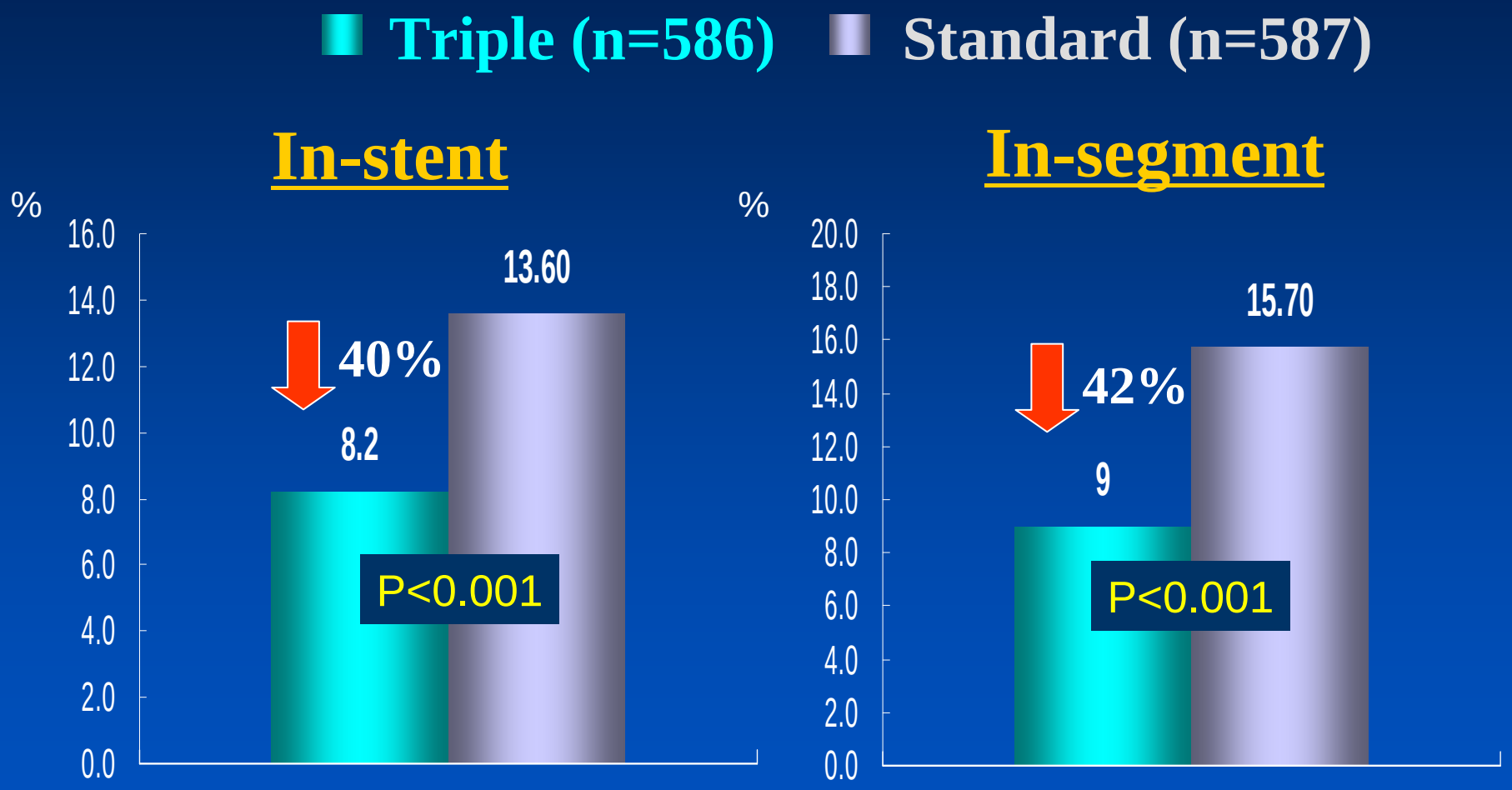
Follow-up CAG: 83.8% (1173/1399)

	Triple (n=586)	Standard (n=587)	*p*
Ref vessel (mm)	2.96±0.42	2.91±0.43	0.046
MLD (mm)			
In-stent	2.22±0.61	2.11±0.65	0.003
In-segment	2.07±0.55	1.95±0.59	<0.001
Diameter stenosis (%)			
In-stent	21.9±20.4	25.1±21.6	0.010
In-segment	26.3±17.7	29.7±18.6	0.001

Late loss


Triple (n= 586)
Dual (n=587)
In-stent
mm
1.0
0.8
0.6
0.4
0.2
0.0
absolute reduction: 0.12,
95% CI: 0.05 to 0.18
0.35
0.47
P<0.001
In-segment
mm
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
absolute reduction: 0.12,
95% CI: 0.06 to 0.18
0.17
0.29
P<0.001

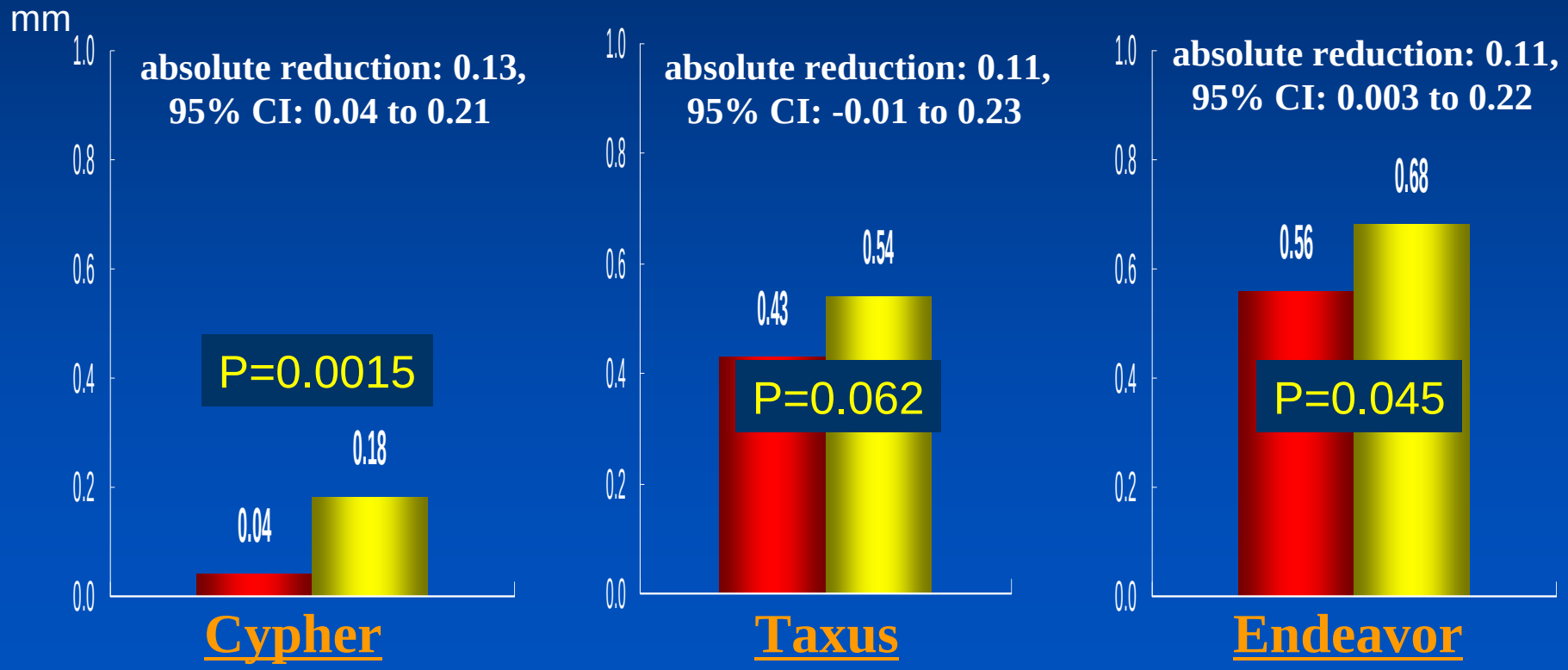
Overall restenosis rate



DES In-Stent Late loss

Triple (n= 586) Dual (n=587)

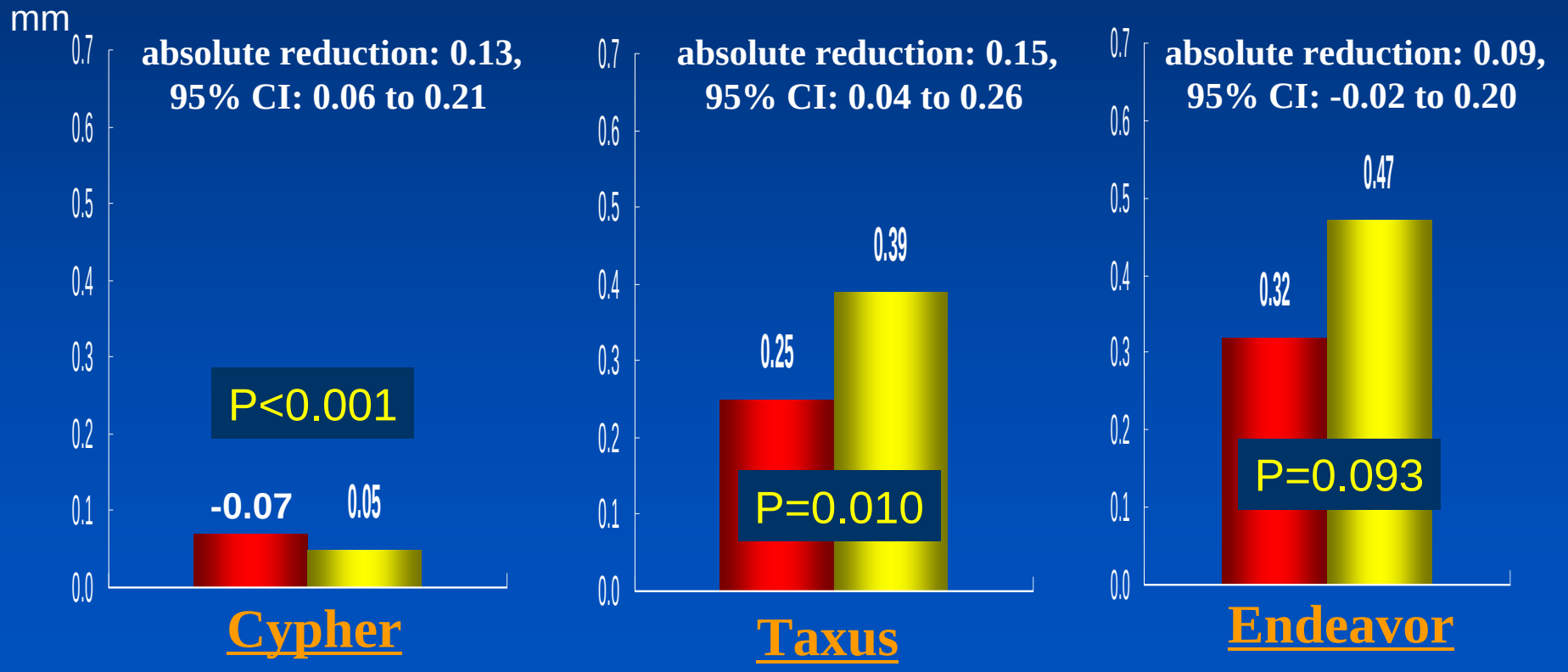
P value for interaction=0.97



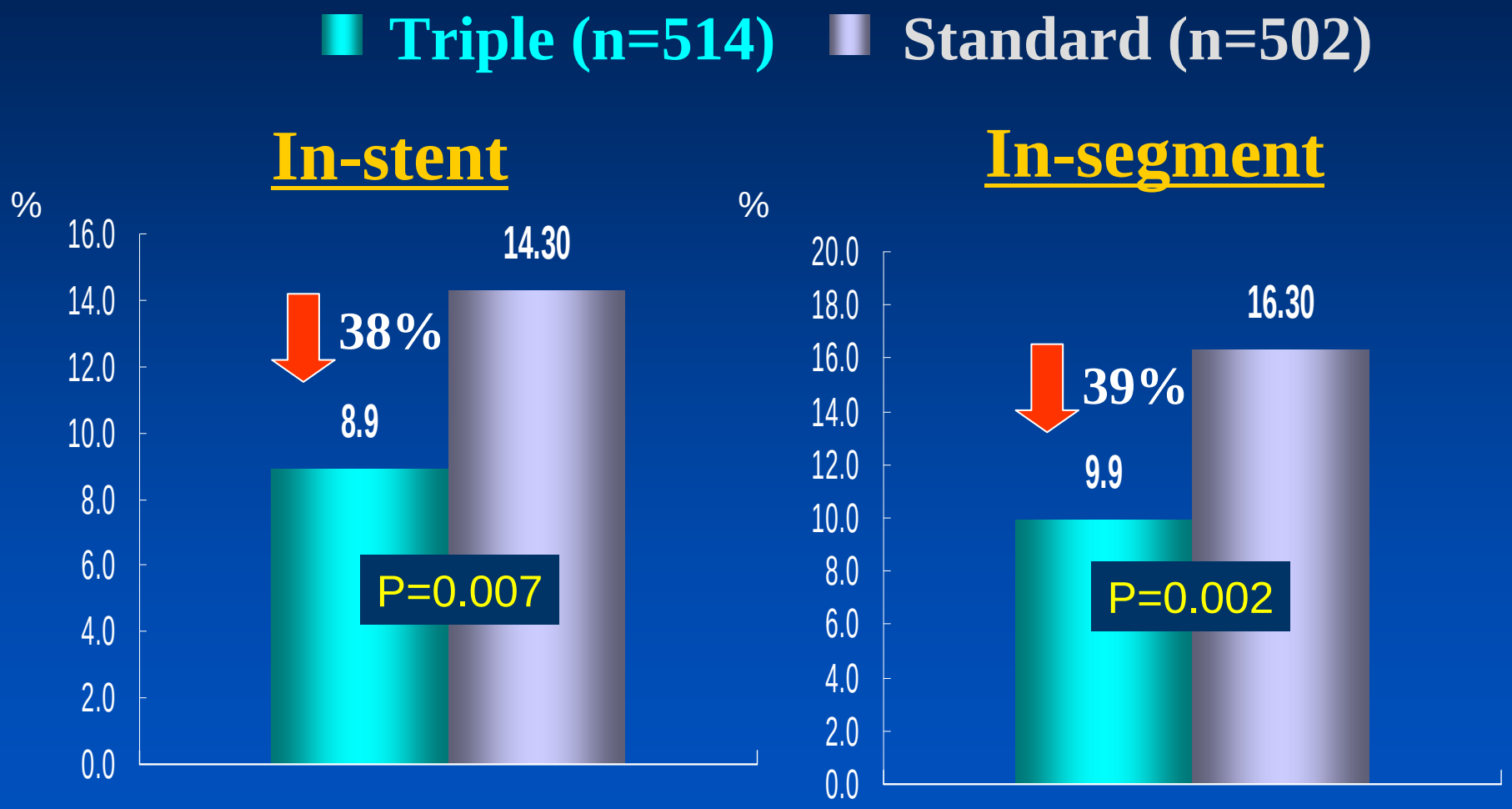
DES In-Segment Late loss

Triple (n= 586) Dual (n=587)

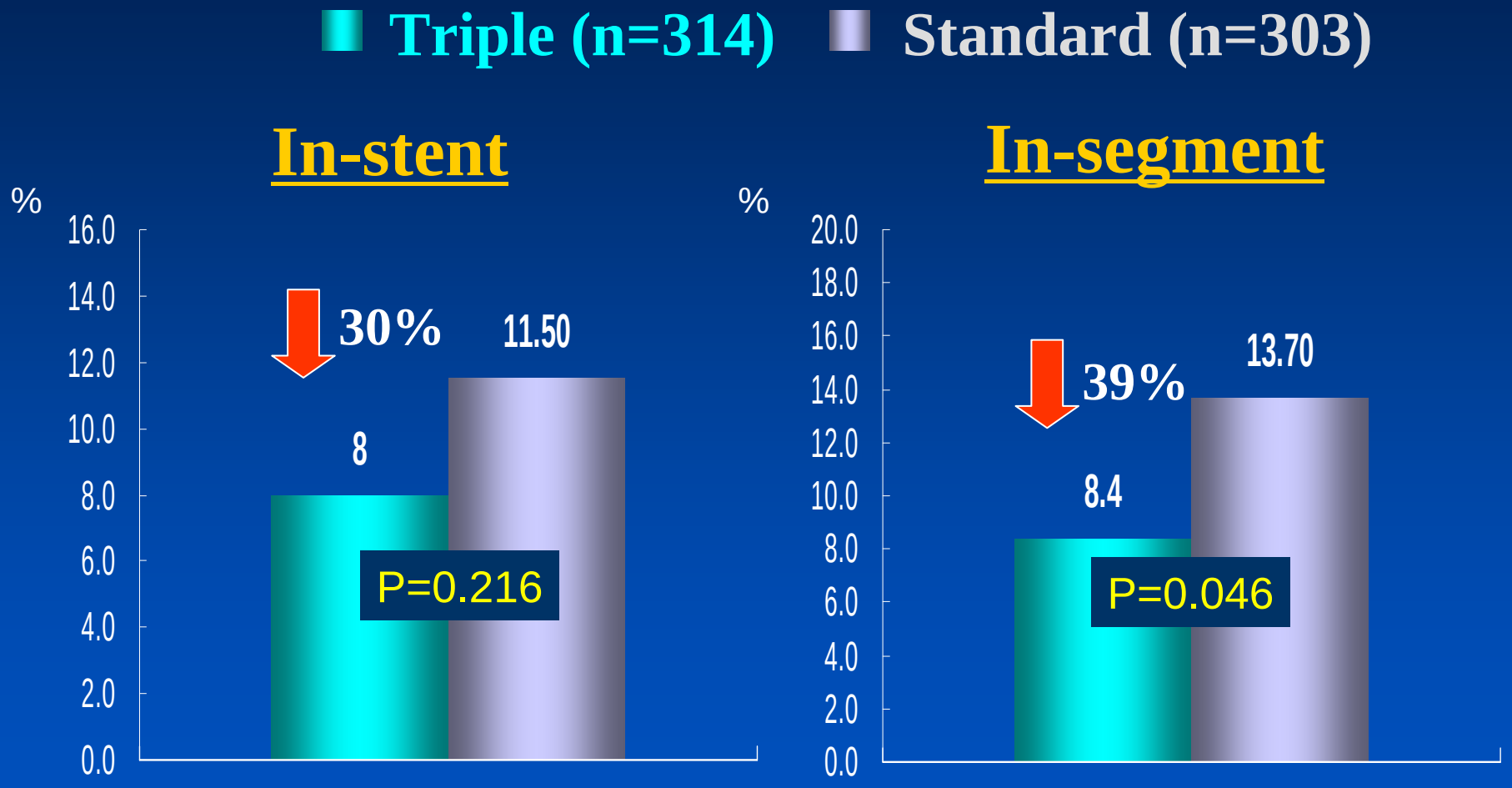
P value for interaction=0.75



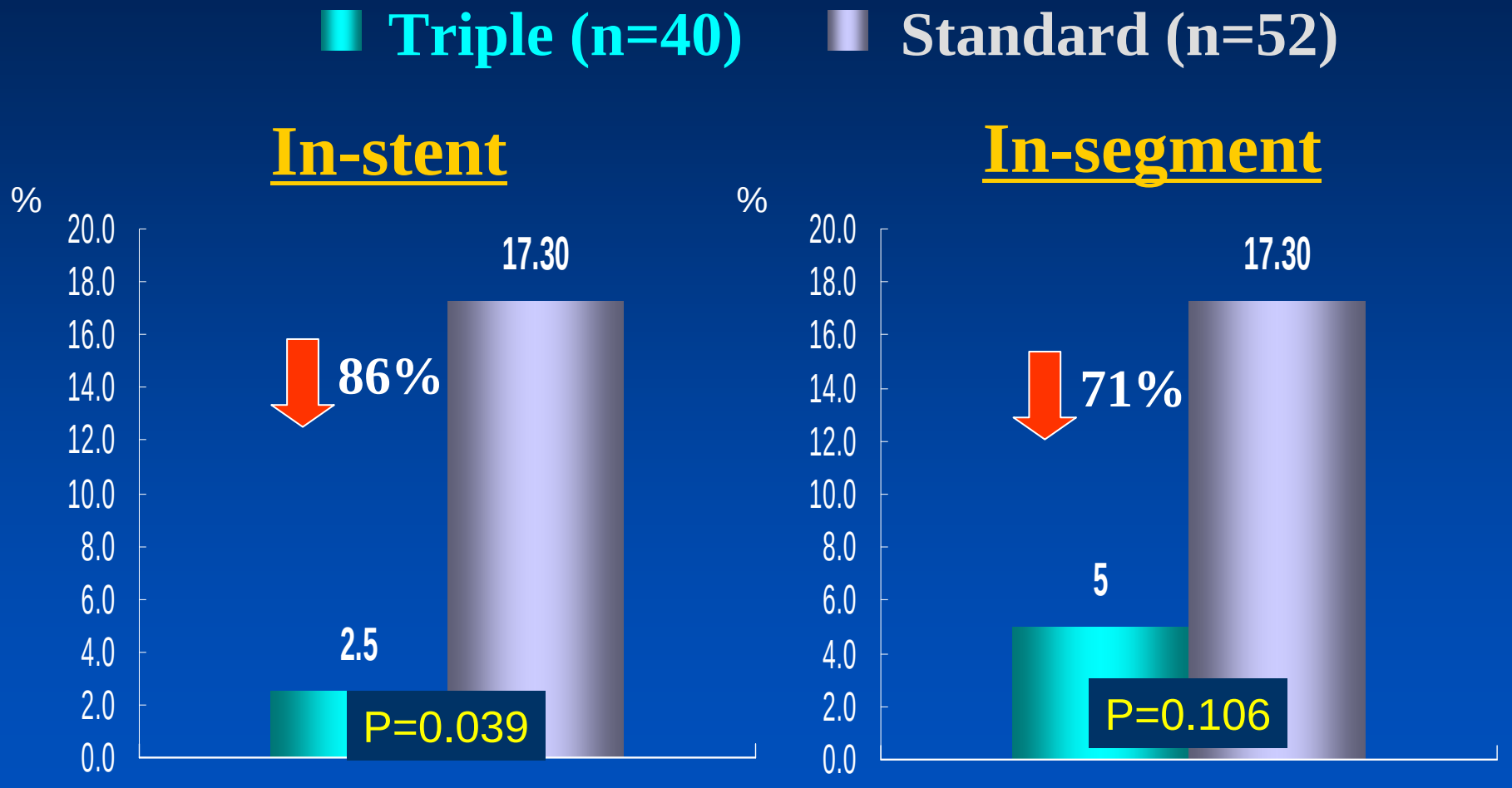
Long lesion restenosis rate



DM restenosis rate



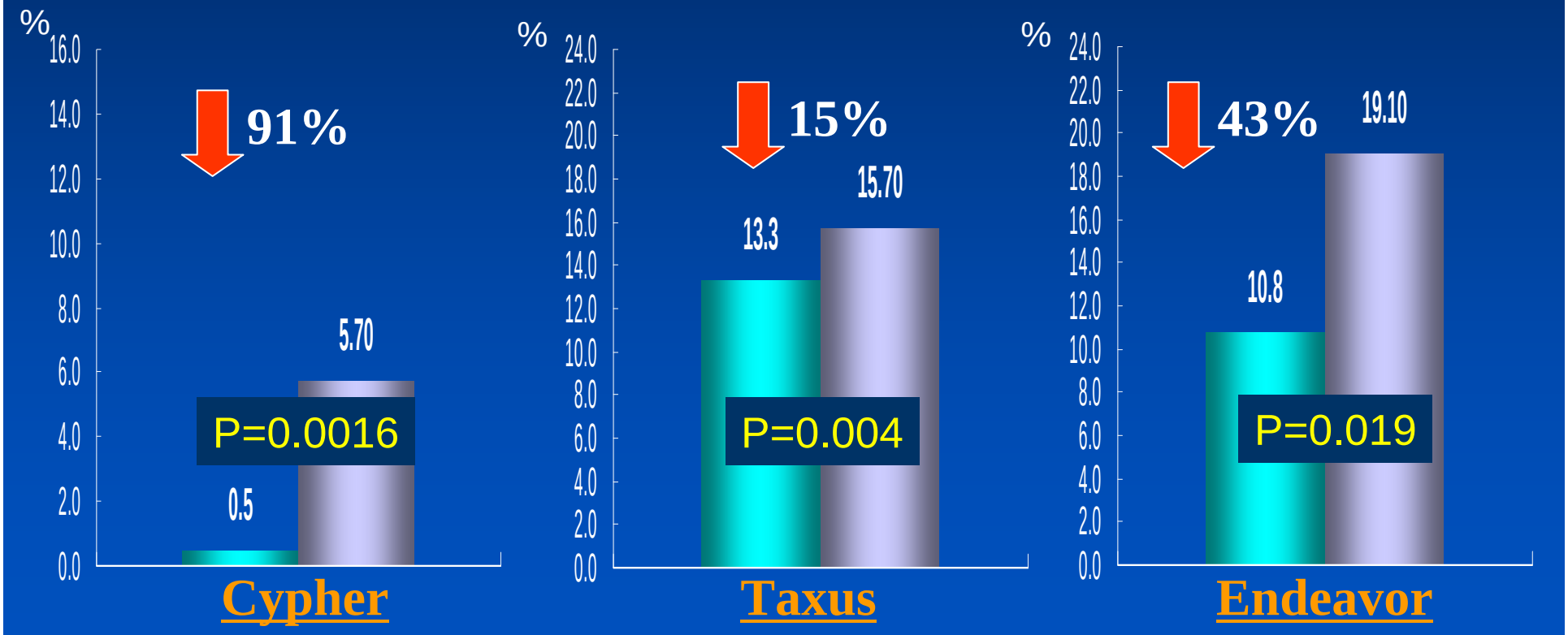
Insulin-DM restenosis rate



DES In-Stent Restenosis rate

Triple (n=586) Standard (n=587)

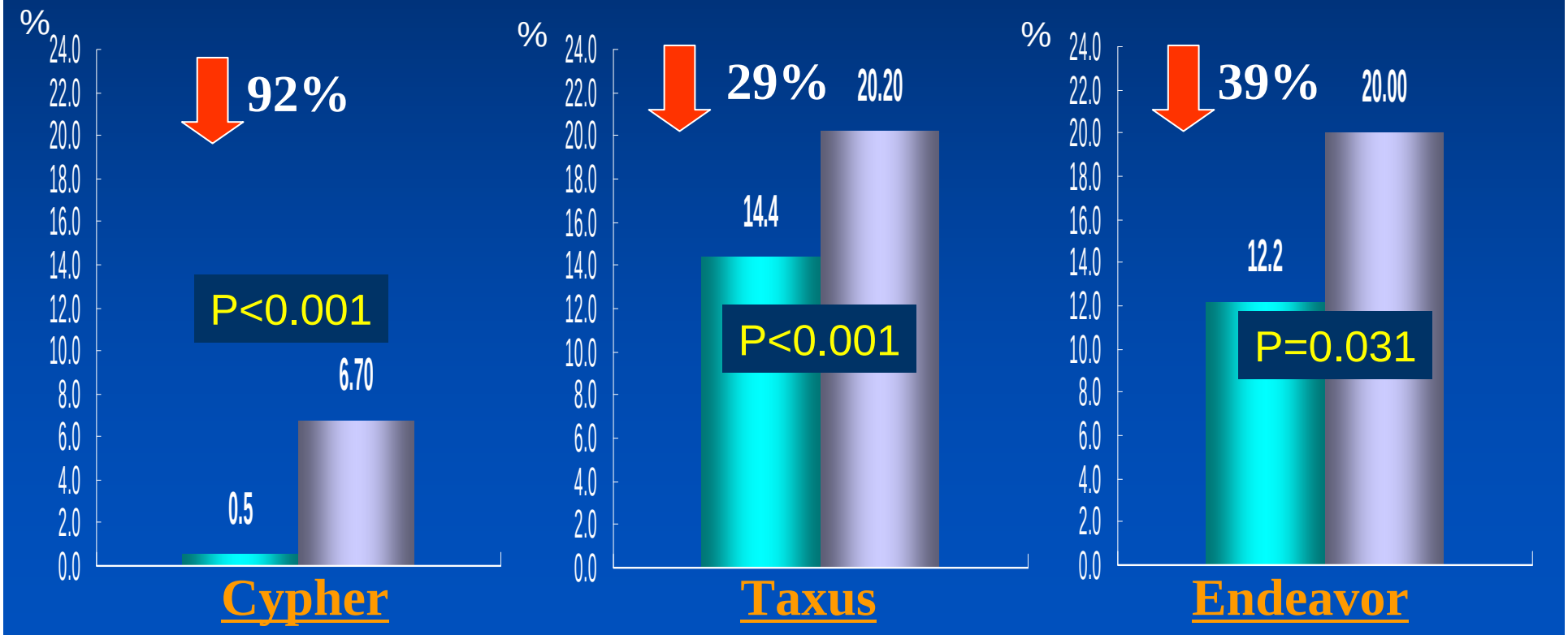
P value for interaction=0.027



DES In-Segment Restenosis rate

Triple (n=586) Standard (n=587)

P value for interaction=0.023



Independent Predictors of angiographic restenosis on multivariate analysis

	OR	95% CI	p
Overall population			
SES	0.12	0.09-0.14	<0.001
Triple antiplatelet therapy	0.49	0.35-0.67	<0.001
DM	1.99	1.37-2.89	<0.001
Stent length	1.03	1.02-1.04	<0.001
Post-procedural in-stent MLD	0.38	0.17-0.87	0.021

Conclusions

- Triple antiplatelet therapy for 6 or 8 months significantly reduced angiographic restenosis in patients with diabetes or long lesions.
- Triple antiplatelet therapy reduced late loss by 0.12 mm and restenosis by 40%.
- Impact of triple antiplatelet therapy on angiographic restenosis was most prominent in Cypher stent, compared with Taxus and Endeavor, which translated to very low restenosis rate (0.5%) in SES with low late loss.

Conclusions

- Insulin requiring DM patients also may have beneficial effect in triple group versus dual group.
- Several risk factors (SES, stent length, DM, post-MLD) served as independent predictors of angiographic restenosis.
- So, coronary stenting using newer generation DES with low late loss with achievement of larger post-MLD may reduce restenosis in high risk population of restenosis.