

Triple Antiplatelet Therapy in DES era : Default Strategy in High Risk Population

Seung-Whan Lee, MD, PhD

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

Newer generation DES era...

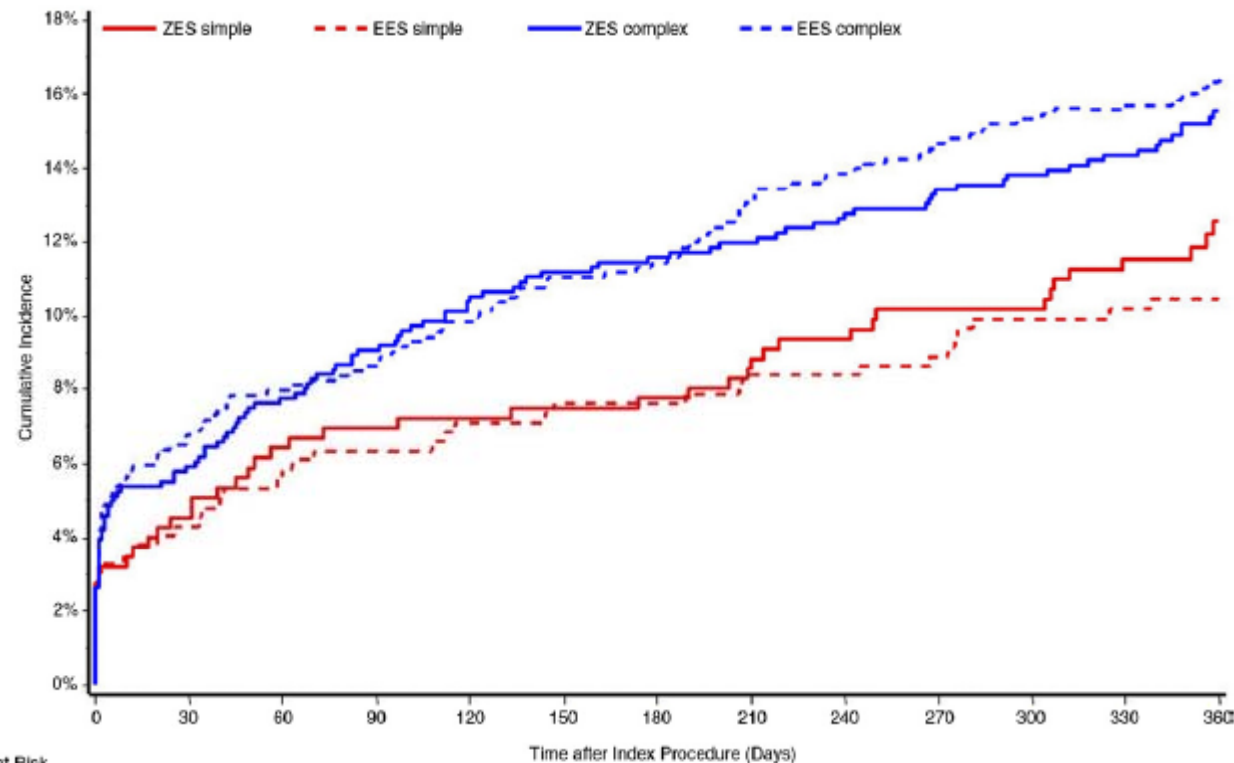
- Restenosis has not been major concern, but complex PCI patients has still substantial rate of restenosis and cardiac events.
- So, to prevent or limit these events has been still our major concern

Complex PCI-All comer trial

Variable	Zotarolimus-Eluting Stent (N=1140)	Everolimus-Eluting Stent (N=1152)	Difference (95% CI) [†]
Complexity of coronary artery disease			
No. of treated lesions per patient	1.46±0.73	1.48±0.77	-0.02 (-0.08 to 0.04)
SYNTAX score [‡]	14.8±9.3	14.6±9.2	0.2 (-0.6 to 1.0)
At least one small vessel (reference vessel diameter, ≤2.75 mm) — no./total no. (%)	652/962 (67.8)	656/973 (67.4)	0.4 (-3.8 to 4.5)
At least one lesion length >18 mm — no./total no. (%)	175/962 (18.2)	206/973 (21.2)	-3.0 (-6.5 to 0.6)
At least one bifurcation or trifurcation — no./total no. (%)	190/1126 (16.9)	202/1139 (17.7)	-0.9 (-4.0 to 2.3)
At least one total occlusion — no./total no. (%)	184/1127 (16.3)	197/1145 (17.2)	-0.9 (-4.0 to 2.2)
At least one in-stent restenosis — no./total no. (%)	91/1126 (8.1)	91/1139 (8.0)	0.1 (-2.1 to 2.3)
Off-label stent use — no. (%)§	764 (67.0)	756 (65.6)	1.4 (-2.5 to 5.3)

N Engl J Med 2010;363:136-46

PCI outcomes: composite endpoint



No. at Risk	0	30	60	90	120	150	180	210	240	270	300	330	360
EES Complex	756	734	699	689	683	675	666	661	646	640	633	628	622
ZES Complex	764	743	714	700	690	679	674	671	665	659	654	651	642
EES Simple	396	385	377	370	368	365	363	363	357	356	354	349	341
ZES Simple	376	366	356	349	347	346	345	343	338	336	333	333	324

N Engl J Med 2010;363:136-46

PCI outcomes: stent thrombosis

	Complex Patients				Simple Patients				p Value for Interaction*
	ZES (n = 764)	EES (n = 756)	Difference [95% CI]	p Value	ZES (n = 376)	EES (n = 396)	Difference [95% CI]	p Value	
Definite ST									
Acute	0.4%	0.1%	0.3% [−0.3% to 0.8%]	0.62	0.3%	0.0%	0.3% [−0.3% to 0.8%]	0.49	0.98
Subacute	0.5%	0.0%	0.5% [0.0% to 1.1%]	0.12	0.3%	0.0%	0.3% [−0.3% to 0.8%]	0.49	1.00
Early	0.9%	0.1%	0.8% [0.1% to 1.5%]	0.07	0.5%	0.0%	0.5% [−0.2% to 1.3%]	0.24	0.97
Late	0.4%	0.3%	0.1% [−0.5% to 0.7%]	1.00	0.5%	0.0%	0.5% [−0.2% to 1.3%]	0.24	0.97
Overall	1.2%	0.4%	0.8% [−0.1% to 1.7%]	0.14	1.1%	0.0%	1.1% [0.0% to 2.2%]	0.06	0.98
Definite or probable ST									
Acute	0.5%	0.3%	0.3% [−0.4% to 0.9%]	0.69	0.3%	0.0%	0.3% [−0.3% to 0.8%]	0.49	0.98
Subacute	0.9%	0.4%	0.5% [−0.3% to 1.4%]	0.34	0.3%	0.3%	0.0% [−0.7% to 0.7%]	1.00	0.61
Early	1.3%	0.7%	0.7% [−0.4% to 1.7%]	0.30	0.5%	0.3%	0.3% [−0.6% to 1.2%]	0.62	0.97
Late	0.5%	0.3%	0.3% [−0.4% to 0.9%]	0.69	0.8%	0.0%	0.8% [−0.1% to 1.7%]	0.12	0.97
Overall	1.7%	0.9%	0.8% [−0.4% to 1.9%]	0.26	1.4%	0.3%	1.1% [−0.2% to 2.4%]	0.12	0.38
Definite, probable, or possible ST									
Acute	0.5%	0.3%	0.3% [−0.4% to 0.9%]	0.69	0.3%	0.0%	0.3% [−0.3% to 0.8%]	0.49	0.98
Subacute	0.9%	0.4%	0.5% [−0.3% to 1.4%]	0.34	0.3%	0.3%	0.0% [−0.7% to 0.7%]	1.00	0.61
Early	1.3%	0.7%	0.7% [−0.4% to 1.7%]	0.30	0.5%	0.3%	0.3% [−0.6% to 1.2%]	0.62	0.98
Late	1.2%	1.3%	−0.2% [−1.3% to 1.0%]	0.82	1.6%	0.3%	1.4% [−0.0% to 2.8%]	0.06	0.09
Overall	2.4%	2.0%	0.4% [−1.1% to 1.9%]	0.73	2.2%	0.5%	1.7% [0.0% to 3.3%]	0.06	0.14

N Engl J Med 2010;363:136-46

Comparison of Everolimus- and Sirolimus-Eluting Stents in Patients With Long Coronary Artery Lesions

**A Randomized LONG-DES-III (Percutaneous Treatment of LONG
Native Coronary Lesions With Drug-Eluting Stent-III) Trial**

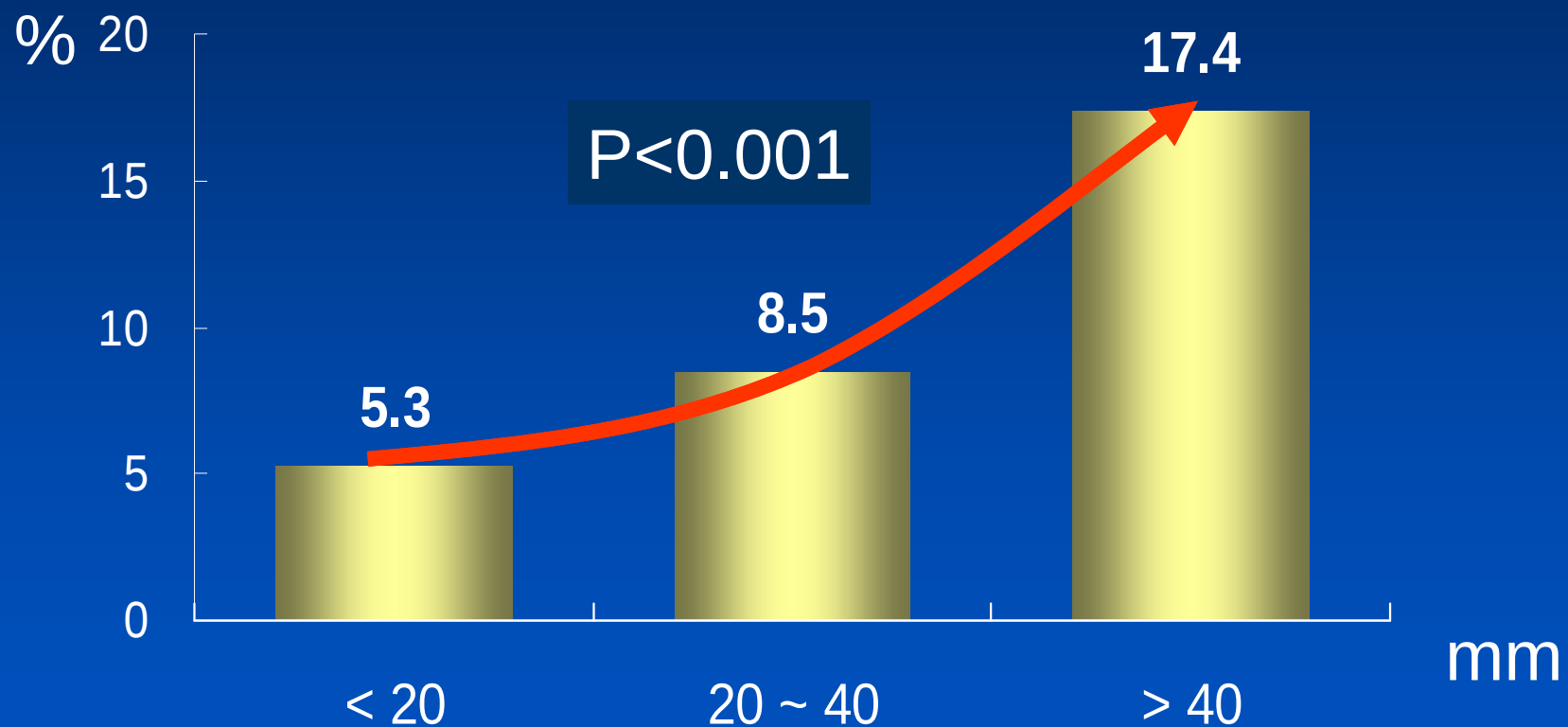
Stent length: 46.5 mm

Restenosis rate:

Xience: 7.3%

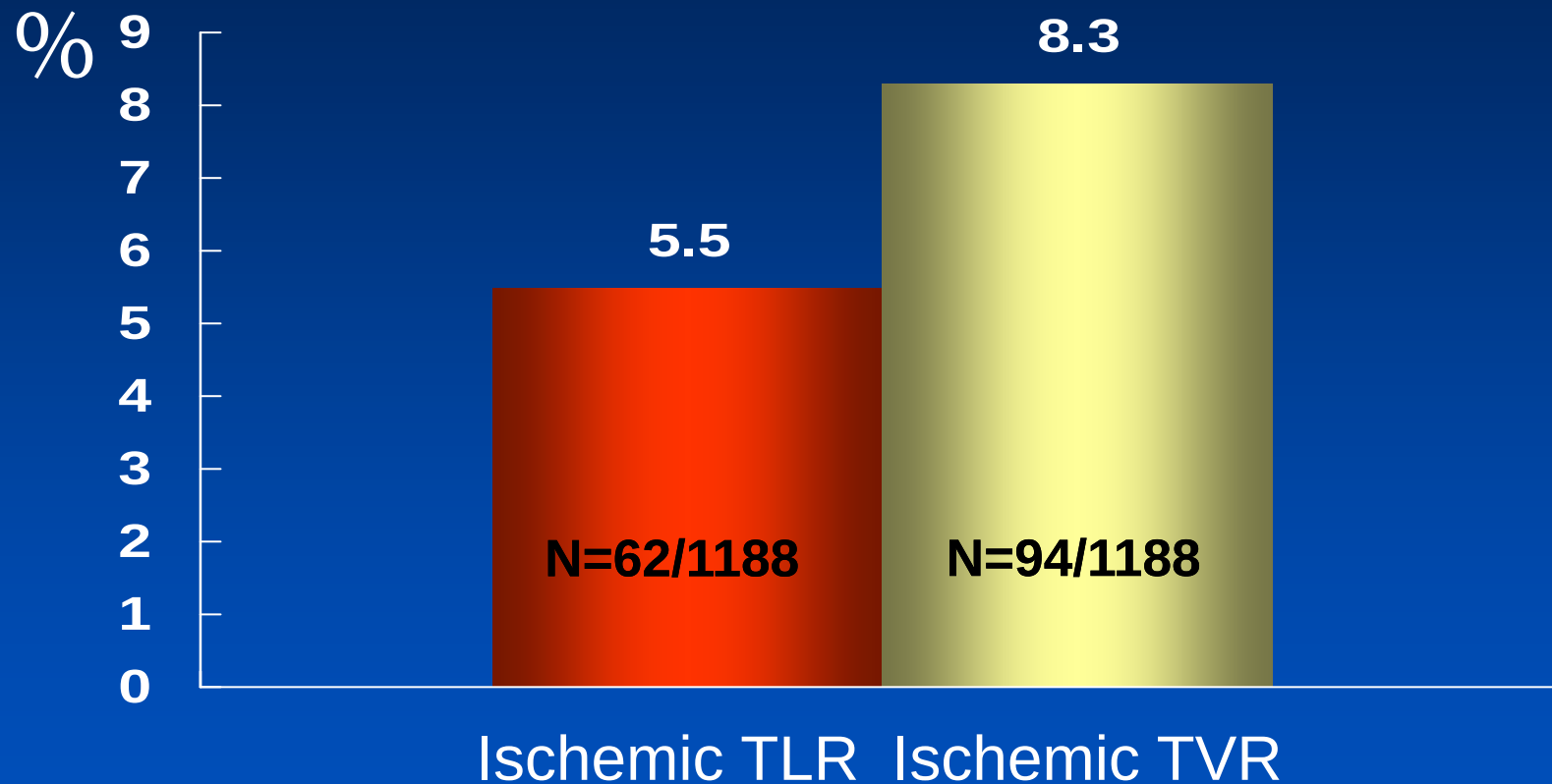
Park DW, et al. J Am Coll Cardiol Intv 2011;4:1096–103

Stented Segment is still Independent Predictor of Restenosis



Lee CW et al. Am J Cardiol 2006;97:506-511

Xience stents in Diabetes



Stone GW, et al. Circulation 2011;124:869-72

CLINICAL RESEARCH

Interventional Cardiology

Randomized Trial of Optimal Treatment Strategies for In-Stent Restenosis After Drug-Eluting Stent Implantation

Hae-Geun Song, MD,* Duk-Woo Park, MD,* Young-Hak Kim, MD,* Jung-Min Ahn, MD,* Won-Jang Kim, MD,* Jong-Young Lee, MD,* Soo-Jin Kang, MD,* Seung-Whan Lee, MD,* Cheol Whan Lee, MD,* Seong-Wook Park, MD,* Seungbong Han, PhD,† In-Whan Seong, MD,‡ Nae-Hee Lee, MD,§ Bong-Ki Lee, MD,|| Keun Lee, MD,¶ Seung-Wook Lee, MD,# Deuk-Young Nah, MD,** Seung-Jung Park, MD*

Seoul, Daejeon, Bucheon, Chuncheon, Kwangju, and Gyeongju, Korea

Restenosis rate: Xience for diffuse ISR: 14.3%

J Am Coll Cardiol. 2012;59:1093-1100



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

Jong-Young Lee, MD,* Duk-Woo Park, MD, PhD,* Young-Hak Kim, MD, PhD,*
Sung-Cheol Yun, PhD,† Won-Jang Kim, MD, PhD,* Soo-Jin Kang, MD, PhD,*
Seung-Whan Lee, MD, PhD,* Cheol-Whan Lee, MD, PhD,* Seong-Wook Park, MD, PhD,*
Seung-Jung Park, MD, PhD*

Restenosis rate:17%

J Am Coll Cardiol. 2011;57:1349-58



Predictors of Restenosis

Table 3 Univariate and Multivariate Predictors of ISR

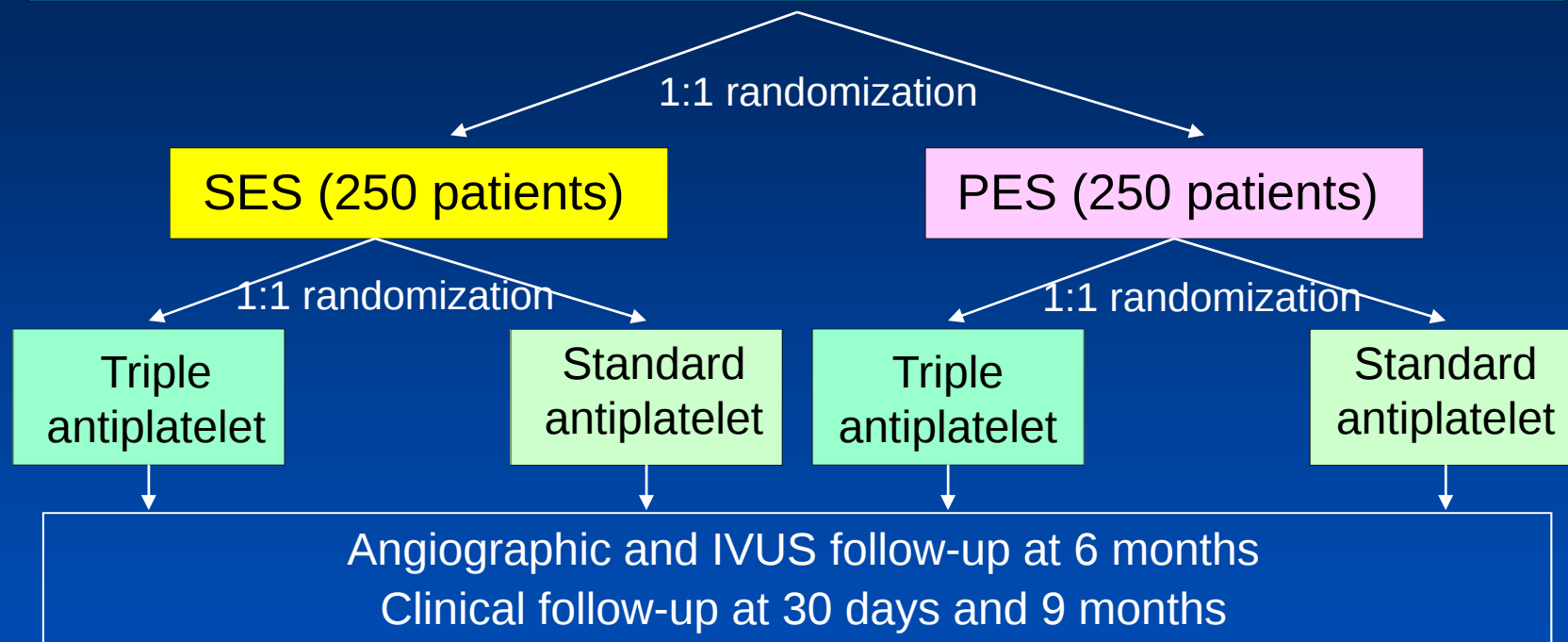
Variable	Univariate	p Value	Multivariate	p Value
Male	0.61 (0.38–0.99)	0.045	0.41 (0.24–0.69)	0.007
Diabetes mellitus	1.82 (1.14–2.90)	0.012		
Renal failure	3.74 (1.36–10.25)	0.011		
Extent of diseased vessel		0.022		
Left main only	1.00			
Plus single-vessel disease	2.11 (0.76–5.86)	0.15		
Plus double-vessel 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.

DECLARE-LONG Trial design

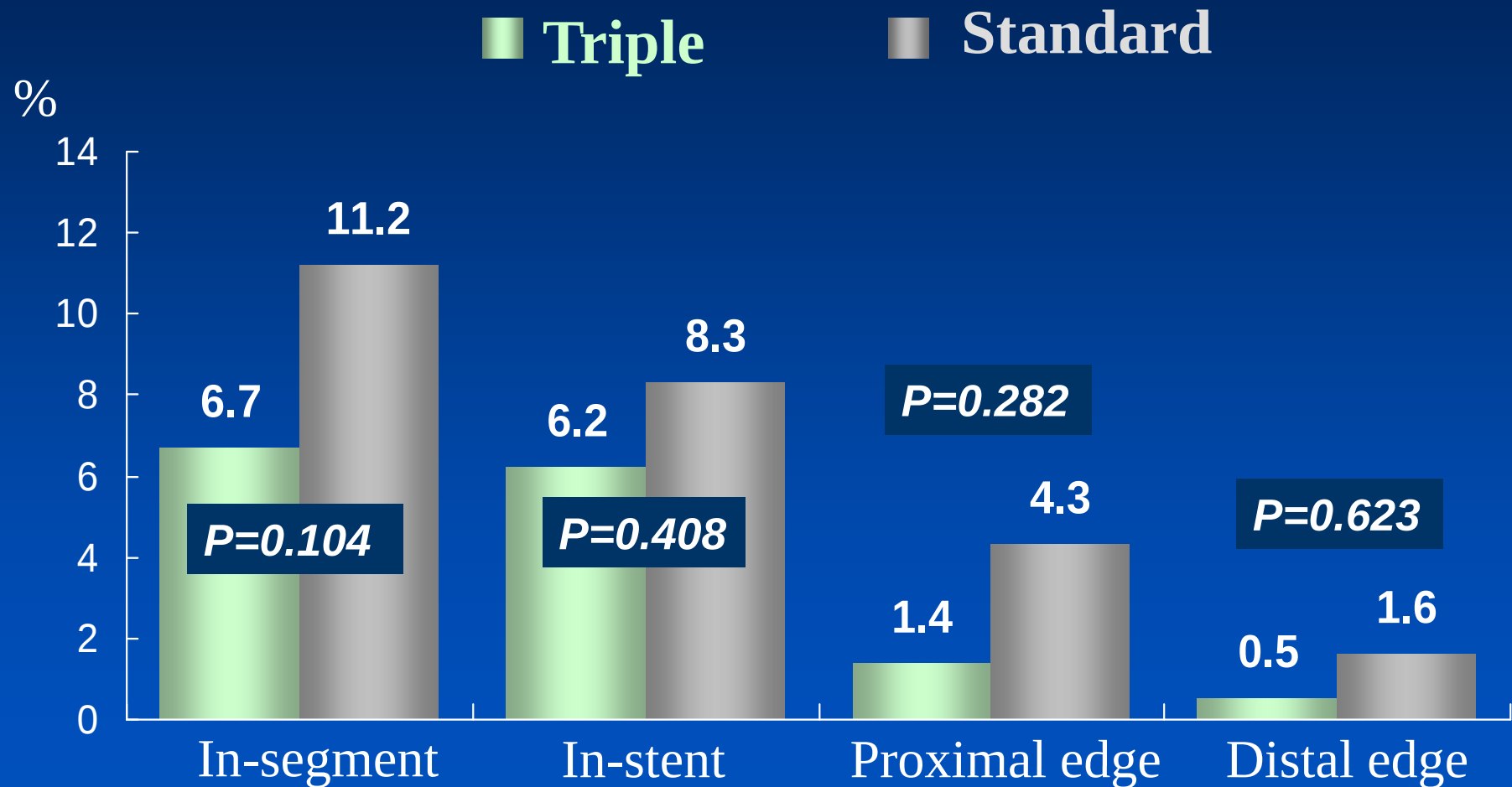
Long coronary lesions (>25mm) requiring single or multiple DES
(planned total stent length ≥ 32 mm) (n=500)



- * 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

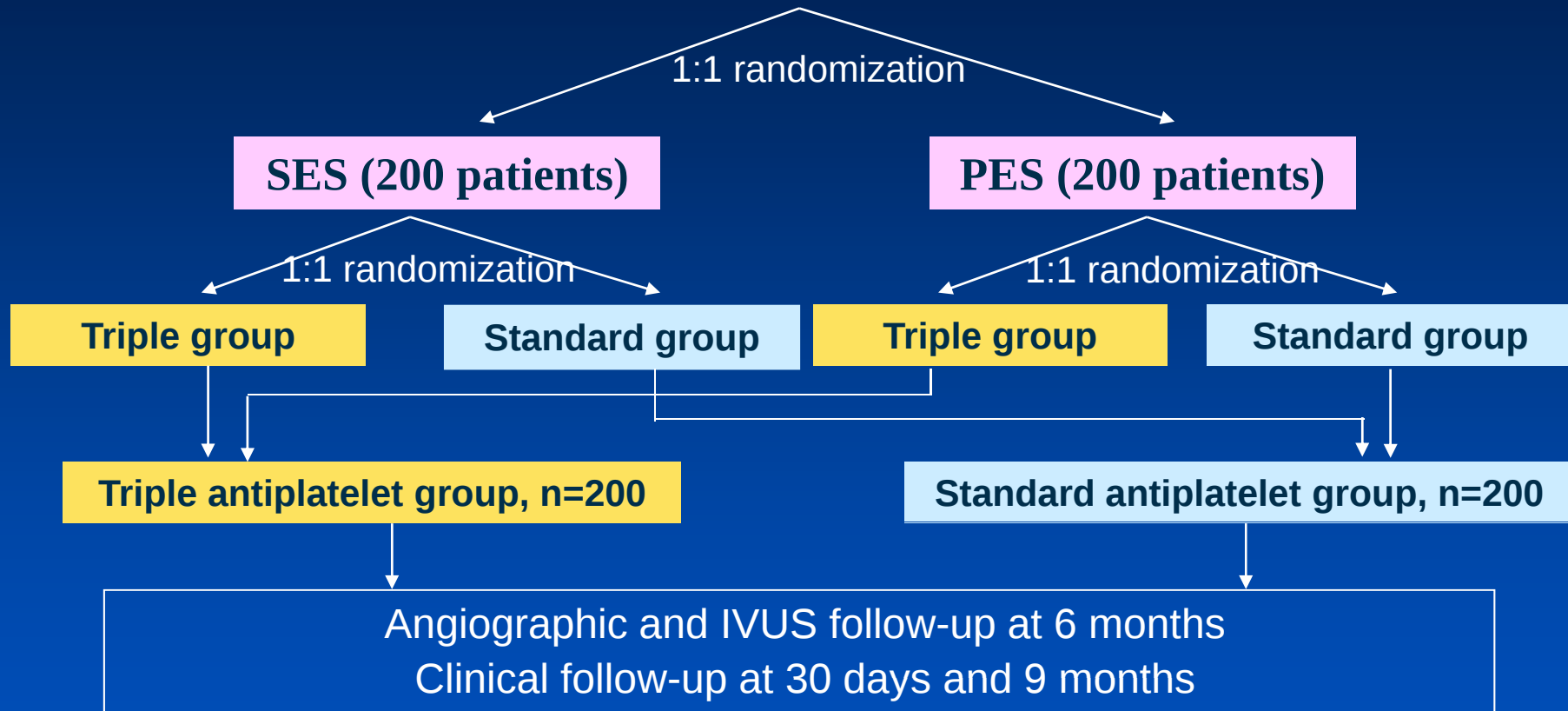
* This patient had subacute stent thrombosis and underwent TLR.

** 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

The lesions Suitable for PCI in patients with DM



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

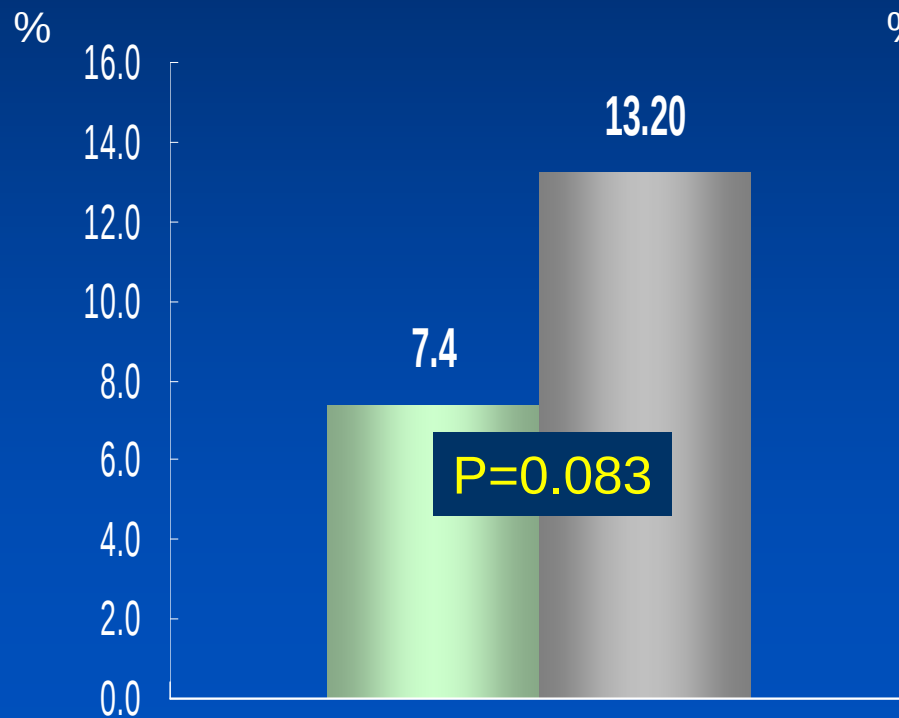
Lee SW, Park SW et al. J Am Coll Cardiol March, 2008;51:1181-7

Restenosis rate

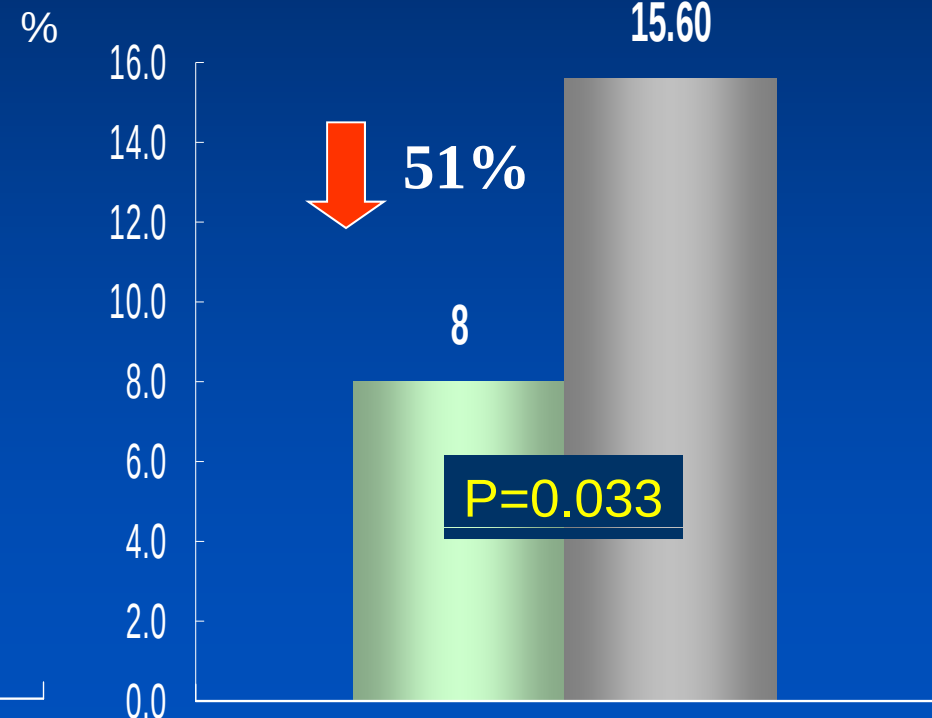
■ Triple

■ Standard

In-stent



In-segment



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

MACE at 9-Months ^{DECLARE-DIABETES}

	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 ($\geq 25\text{mm}$) requiring single or multiple Endeavor stent (planned total stent length $\geq 30\text{mm}$)

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

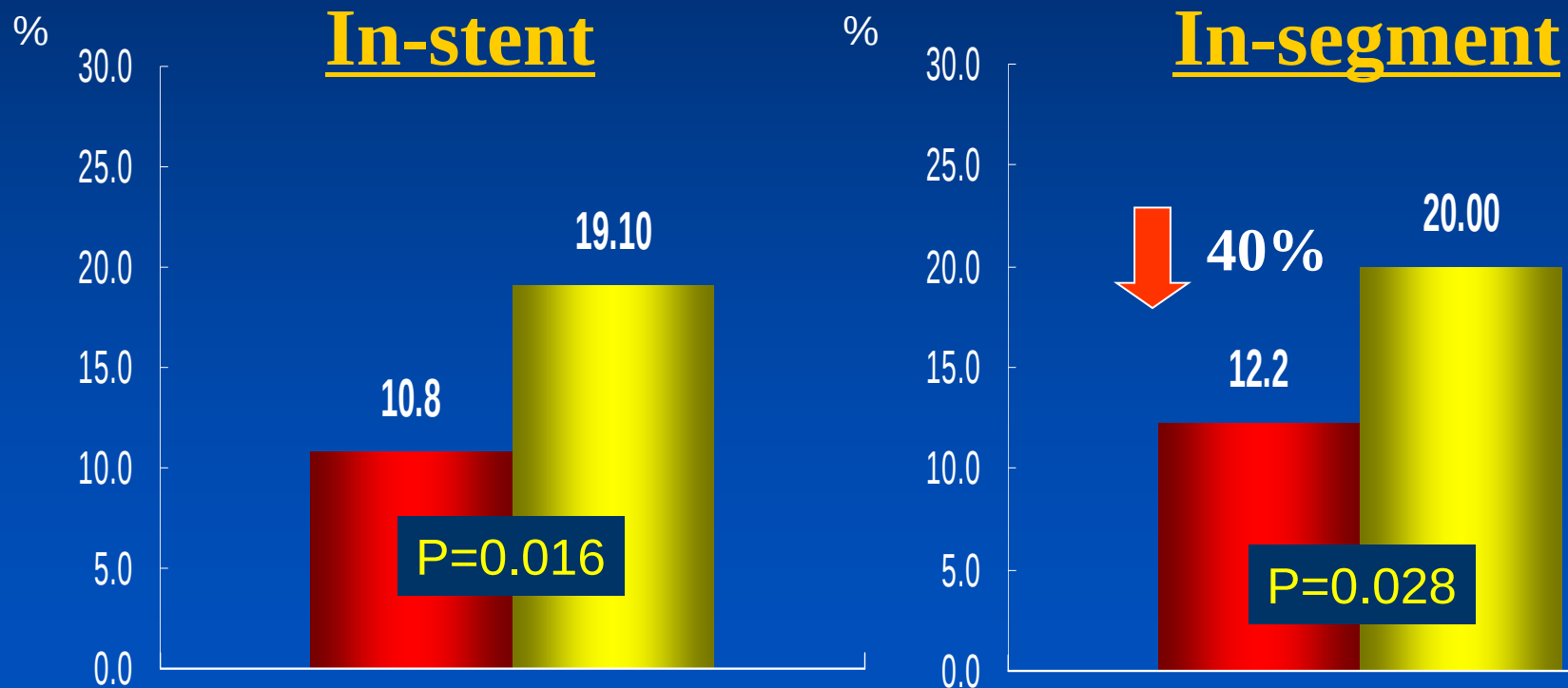
CBC, LFT, hsCRP, HBA1c at baseline, 30 days, 90 days, 180 days, 270 days, 360 days (± 1 month),

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

IVUS analysis

Restenosis rate

■ Triple (n= 213) ■ Dual (n=215)



Lee SW, et al. J Am Coll Cardiol, 2011;57:1264-70

MACE at 12-Months

DECLARE-LONG II

	Triple (N=250)	Standard (N=249)	<i>p</i>
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

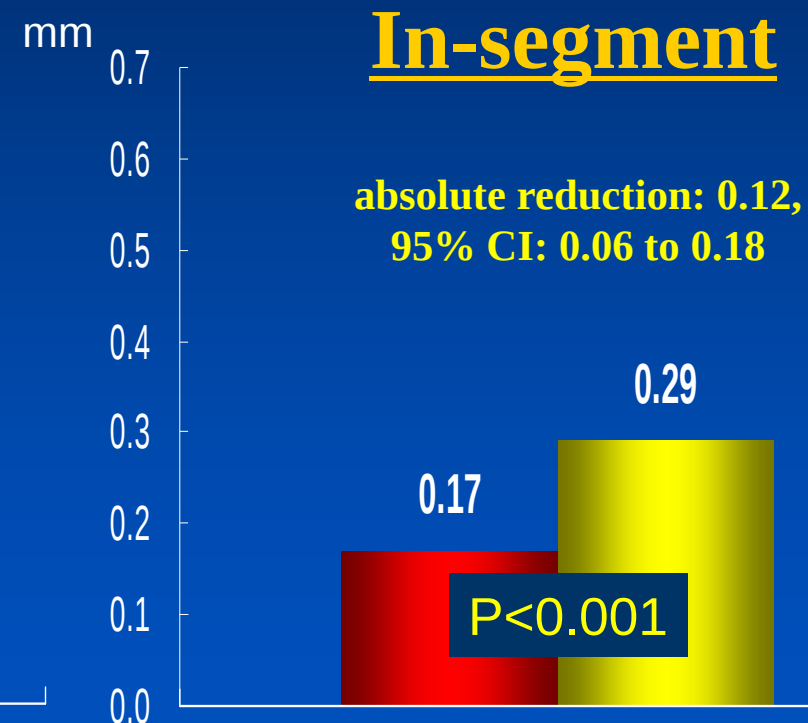
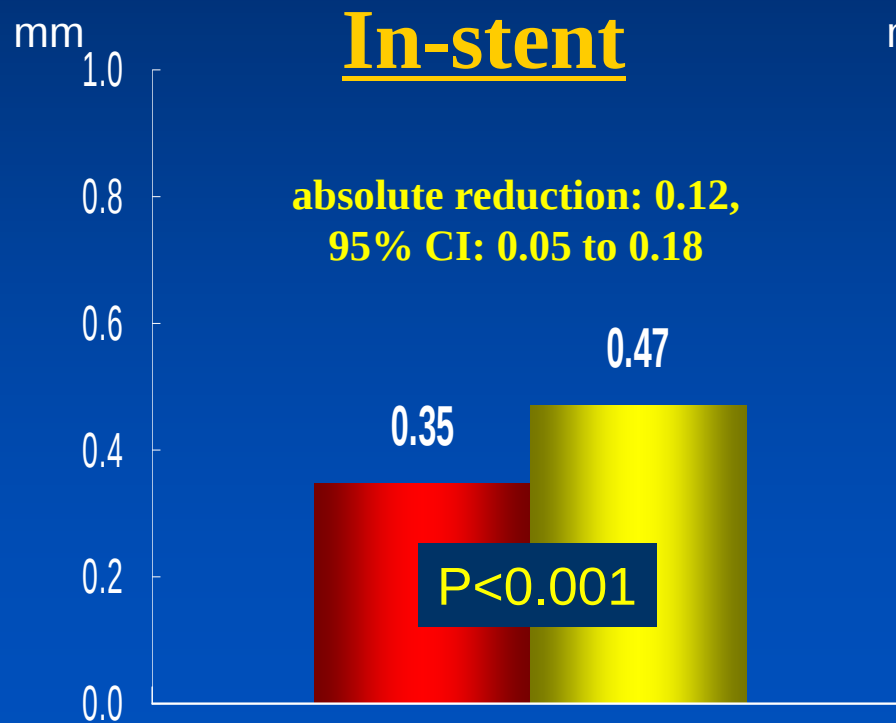
Lee SW, et al. J Am Coll Cardiol, 2011;57:1264-70



Pooled analysis of DECLAREs

Late loss

■ Triple (n= 586) ■ Dual (n=587)

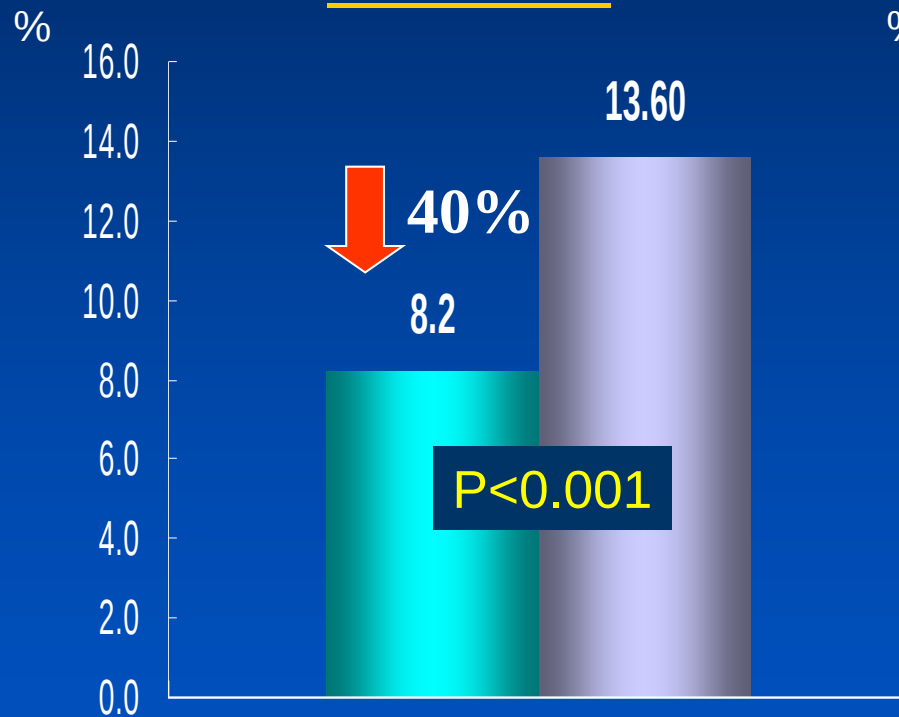


Overall restenosis rate

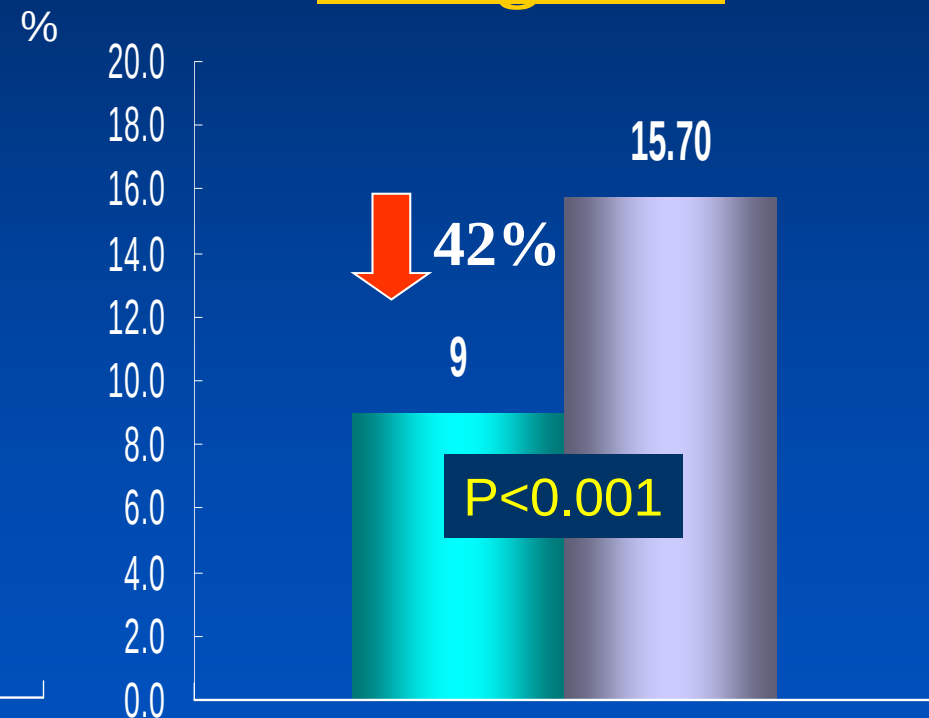
■ Triple (n=586)

■ Standard (n=587)

In-stent



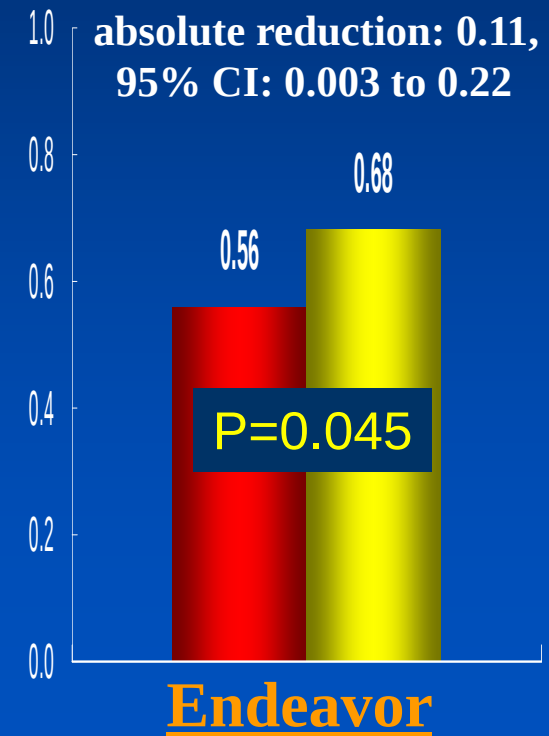
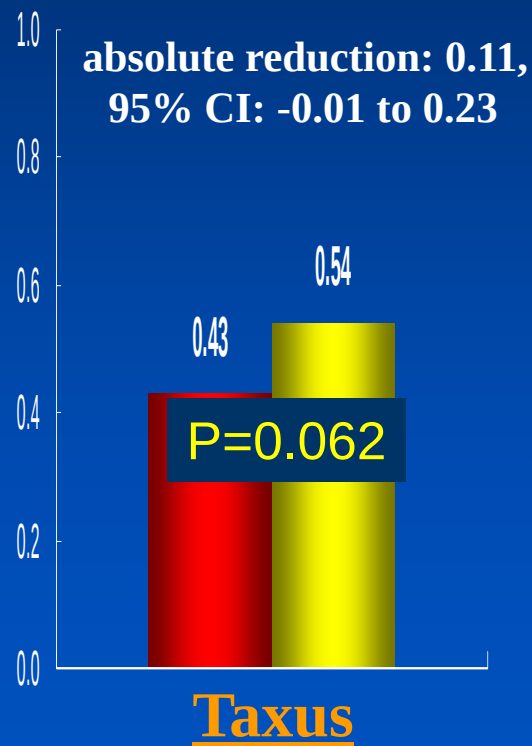
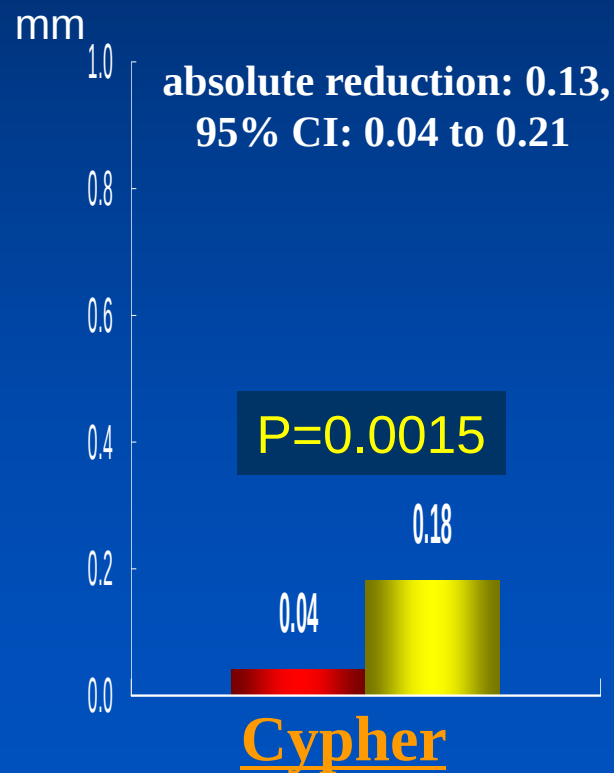
In-segment



DES In-Stent Late loss

■ Triple (n= 586) ■ Dual (n=587)

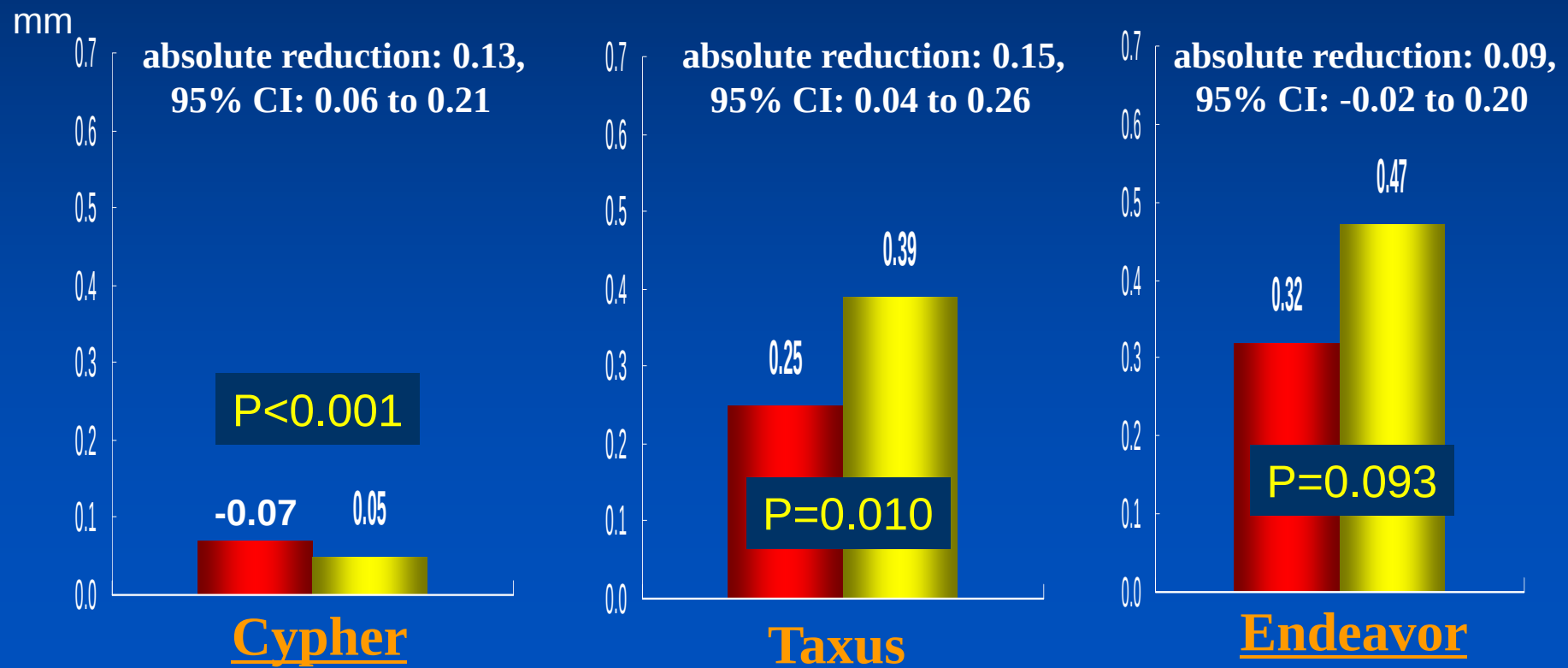
P value for interaction=0.97



DES In-Segment Late loss

■ Triple (n= 586) ■ Dual (n=587)

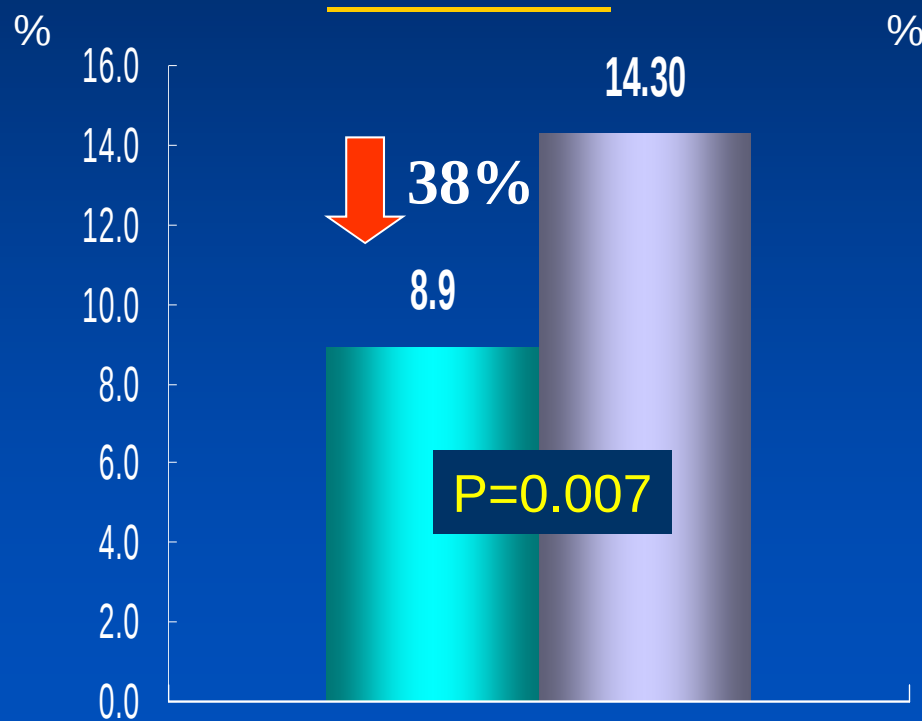
P value for interaction=0.75



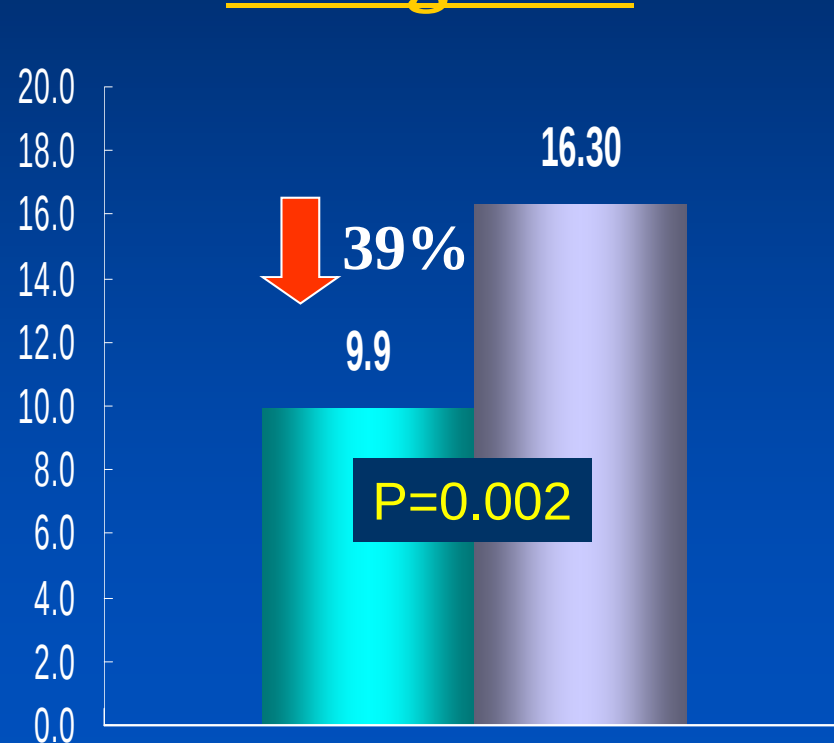
Long lesion restenosis rate

■ Triple (n=514) ■ Standard (n=502)

In-stent



In-segment

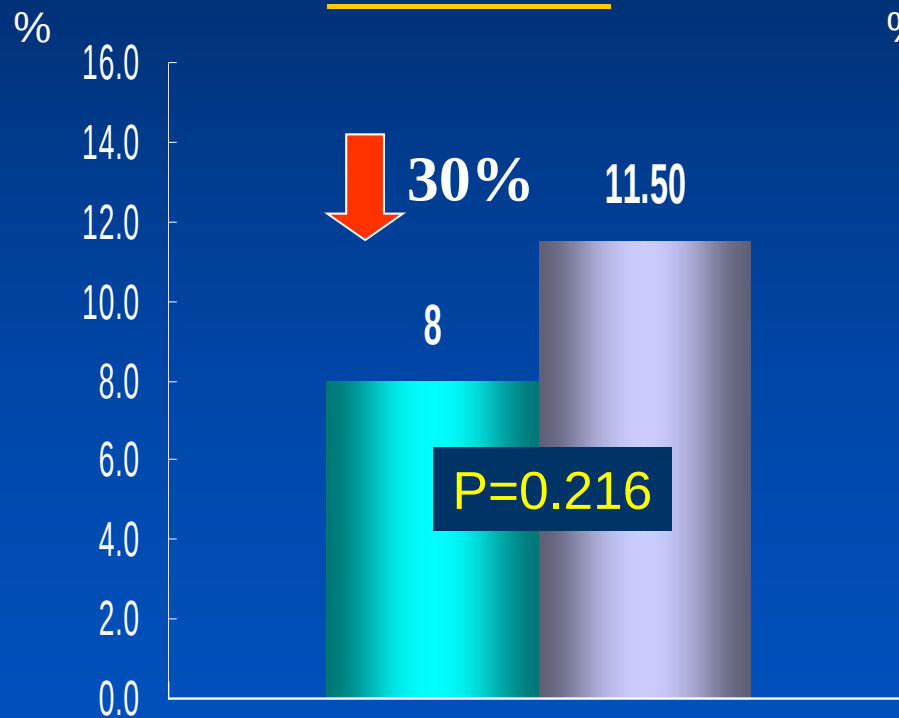


DM restenosis rate

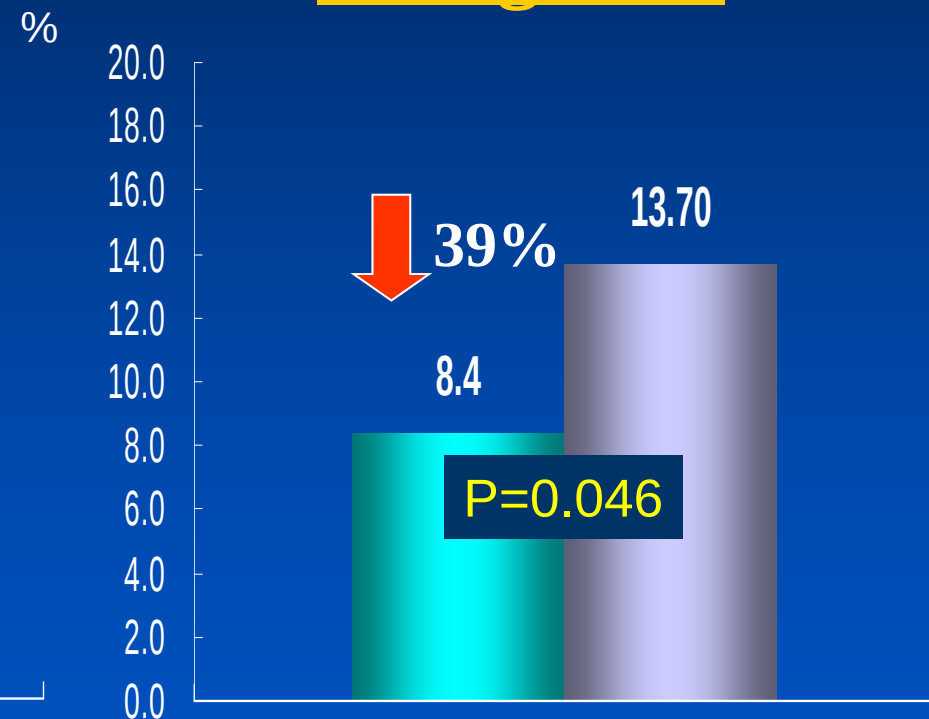
■ Triple (n=314)

■ Standard (n=303)

In-stent



In-segment

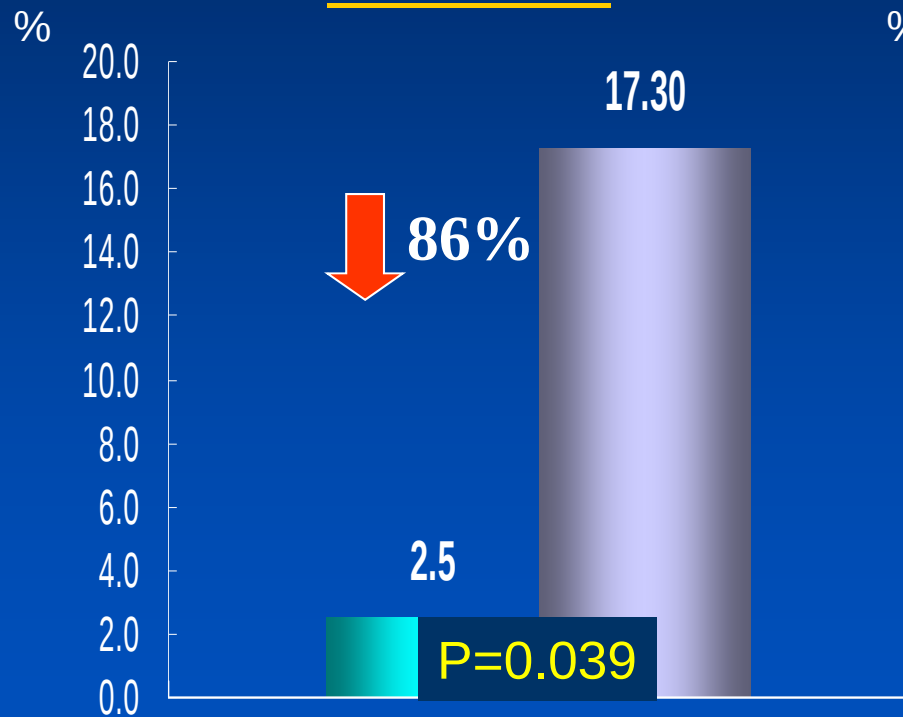


Insulin-DM restenosis rate

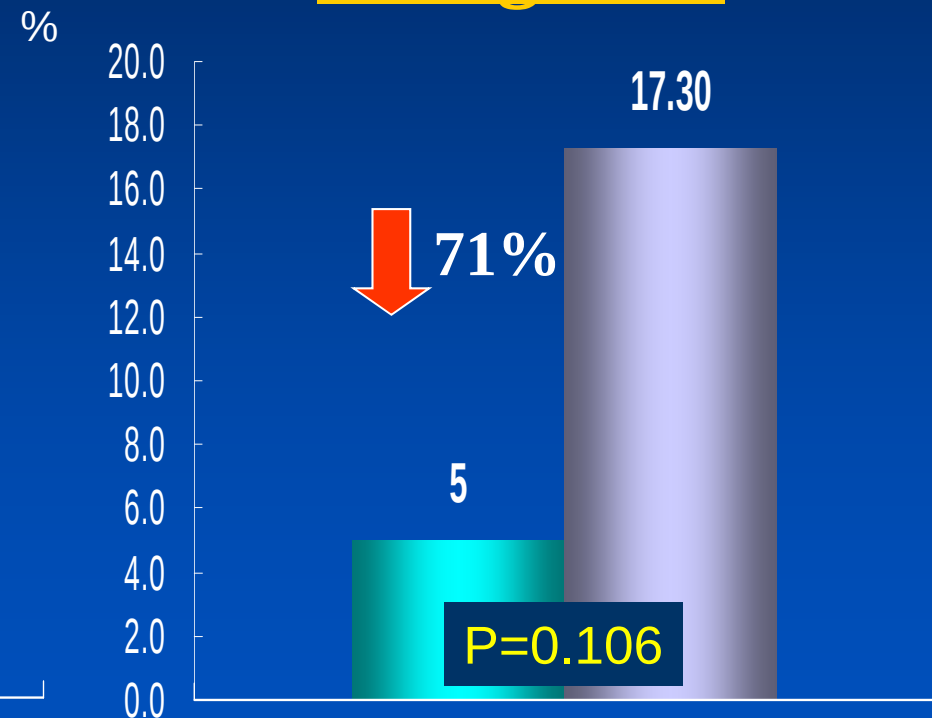
■ Triple (n=40)

■ Standard (n=52)

In-stent



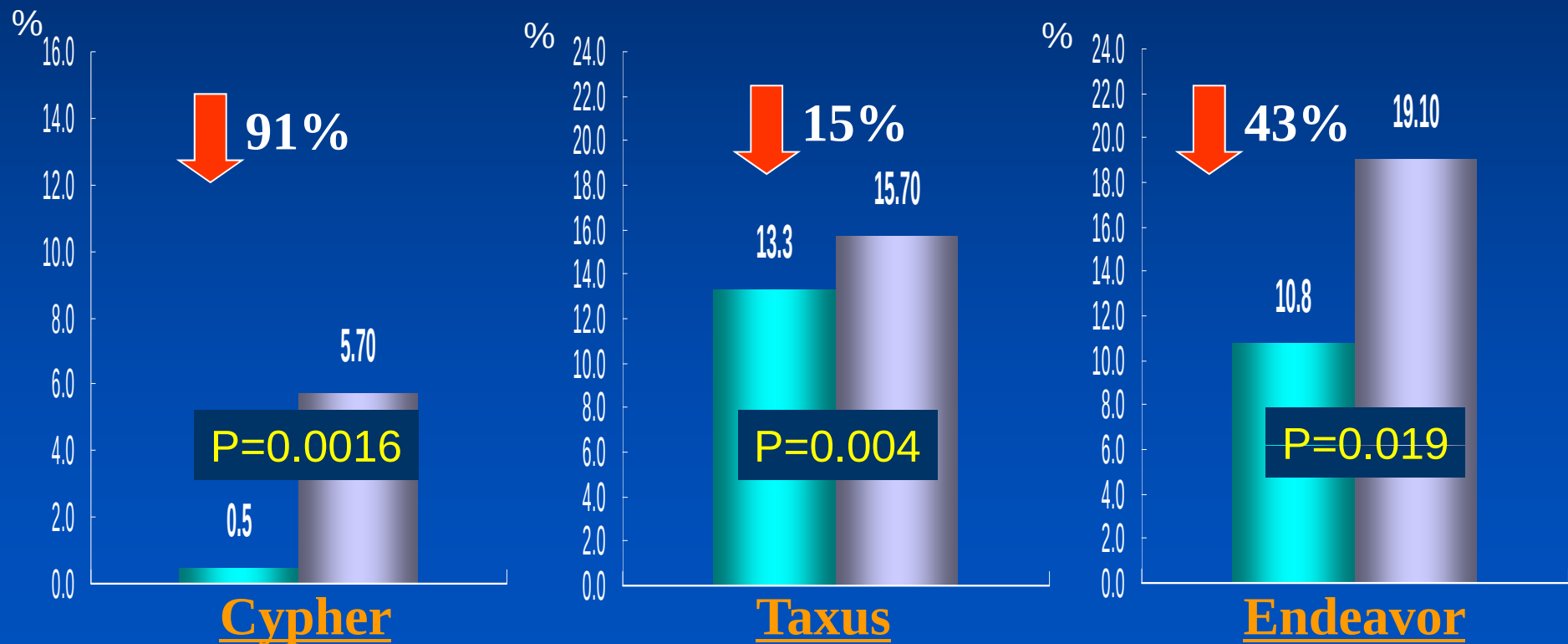
In-segment



DES In-Stent Restenosis rate

■ Triple (n=586) ■ Standard (n=587)

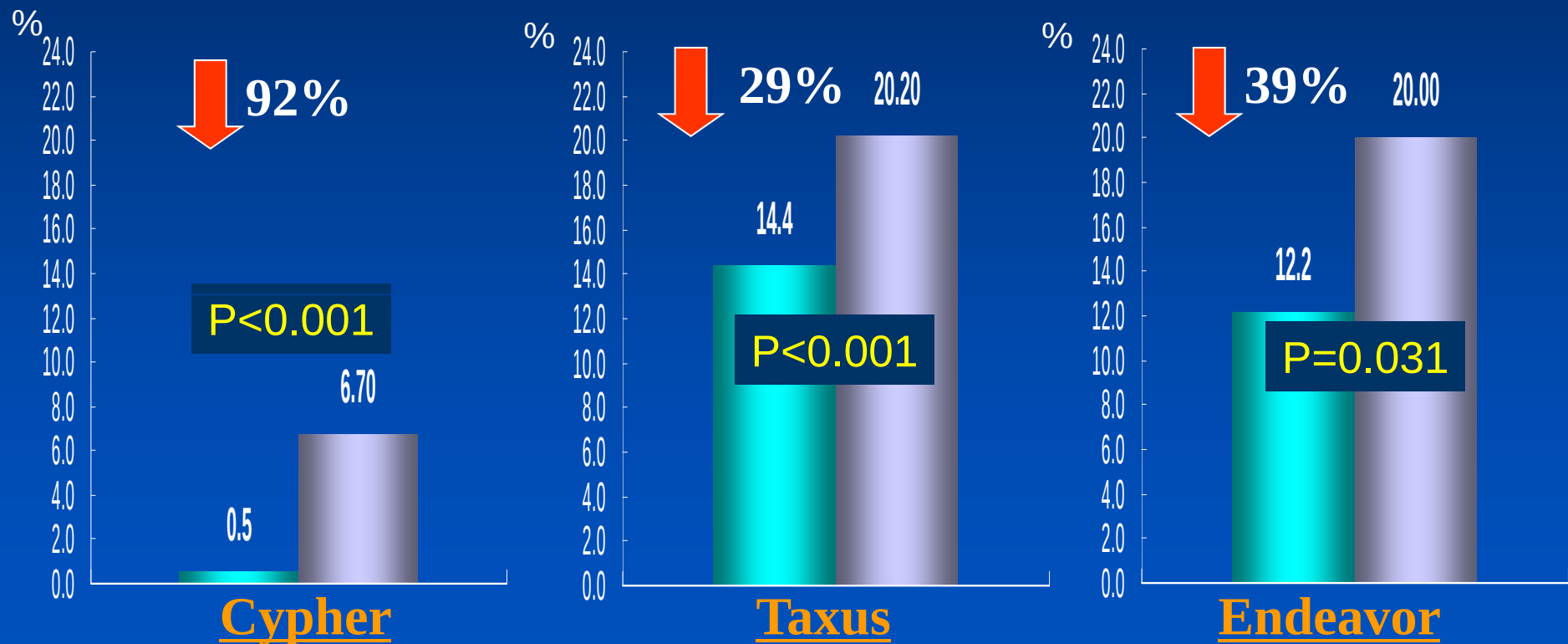
P value for interaction=0.027



DES In-Segment Restenosis rate

■ Triple (n=586) ■ Standard (n=587)

P value for interaction=0.023

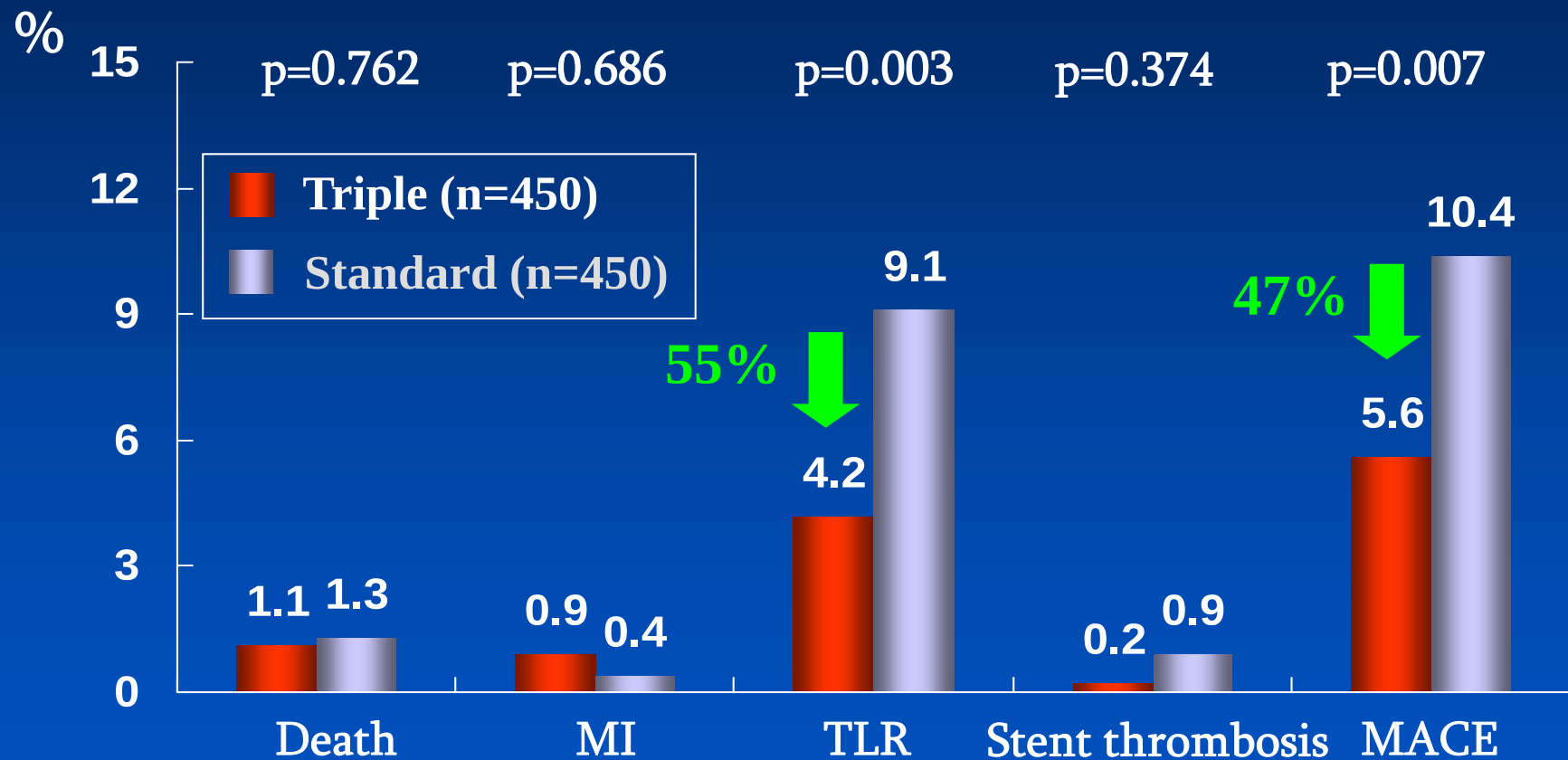


Independent Predictors of angiographic restenosis on multivariate analysis

	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

Two-year MACE

MACE: Death, MI, TLR



Lee SW, Park SW, et al. Am J Cardiol 2010;105:168

Summary I

- 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.

Summary II

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

Potential candidate of triple therapy in newer generation DES era

- Long lesions
- Diabetic population
- Restenotic lesion
- Bifurcation lesion.....

Triple versus Dual Antiplatelet Therapy After Successful coronary Stenting (BMS or DES)

1-month Stent Thrombosis

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

Major Cardiac Events at 1Mo

	Dual (n=3,253)	Triple (n=2,858)	<i>p</i>
Stent thrombosis	14 (0.4%)	3 (0.1%)	0.028
Acute	5 (0.2%)	0	NS
Subacute	9 (0.3%)	3 (0.1%)	NS
MI	15 (0.5%)	3 (0.1%)	0.021
Death	9 (0.3%)	5 (0.2%)	NS

Lee SW, Park SW et al. J Am Coll Cardiol 2005;46:1833-7.

Lee SW, Park SW, et al. Am Heart J 2010;159:284-291

Triple Antiplatelet Therapy (aspirin, clopidogrel and cilostazol) Significantly Reduces Ischemic Events after DES implantation in a broad range of population

:Drug-Eluting stenting followed by Cilostazol treatment Reduces Adverse Serious cardiac Events

The DECREASE registry

12-month Stent Thrombosis

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

DECREASE Study Design

The patients undergoing successful DES implantation

Operator decisions for adding cilostazol

Mean duration of cilostazol : 77.4 ± 88.1 days

Triple group (n=1443)

Dual group (n=1656)

Inverse-Probability-of-Treatment-Weighted (IPTW) for the Entire cohort

Propensity score matching (965 pairs)

Triple antiplatelet group (n=965)

Dual antiplatelet group (n=965)

Clinical follow-up at 12 months
(Death, MI, or stent thrombosis)

Twelve-month risk of Events after DES Implantation of Triple versus Dual antiplatelet therapy according to analytic methods

Variables	Crude		Inverse-probability-of-treatment weighted		Propensity-matched (965 pairs)	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Cardiac events						
Death	0.925 (0.521 -1.644)	0.7907	0.762 (0.401-1.448)	0.4062	0.644(0.300-1.381)	0.2584
MI	0.381 (0.138-1.048)	0.0617	0.233 (0.077-0.703)	0.0097	0.298 (0.082-1.086)	0.0665
Stent thrombosis	0.286 (0.081-1.013)	0.0524	0.136 (0.035-0.521)	0.0036	0.124 (0.016-0.996)	0.0496
Death/MI	0.761 (0.464-1.251)	0.2817	0.591 (0.3364-1.037)	0.0665	0.556 (0.287-1.075)	0.0811
Bleeding						
Major bleeding	0.850 (0.477-1.516)	0.5830	0.969 (0.443-2.119)	0.9372	0.683 (0.343-1.360)	0.2781
Minor bleeding	1.039 (0.757-1.426)	0.8125	1.062 (0.734-1.537)	0.7504	1.045 (0.703-1.555)	0.8267

Hazard ratios are for the triple group, as compared with the dual group.

Lee SW, Park SW, et al. Am Heart J 2010;159:284-291

Extended Cox analysis to adjust time-varying covariate

	Stent thrombosis		Myocardial infarction	
	HR(95% CI)	P	95% CI	P
On-triple therapy	0.07(0.005-0.90)	<0.05	0.02(0.003-0.18)	<0.05
Duration of triple therapy	0.06(0.003-0.92)	<0.05	0.75(0.57-0.98)	<0.05
On-clopidogrel	0.86(0.15-4.80)	0.86	0.11(0.03-0.37)	<0.05
Duration of clopidogrel	0.54(0.31-0.92)	<0.05	0.51(0.27-0.96)	<0.05

Lee SW, Park SW, et al. Am Heart J 2010;159:284-291

Triple versus Dual Antiplatelet Therapy in Patients with STEMI Undergoing Primary Stenting with DES

8-month Death and MACE

Chen KY et al. Circulation;119:3207-14



Study Groups

Prospective registry of STEMI patients:

1) Dual therapy group

(aspirin plus clopidogrel, n=2,569)

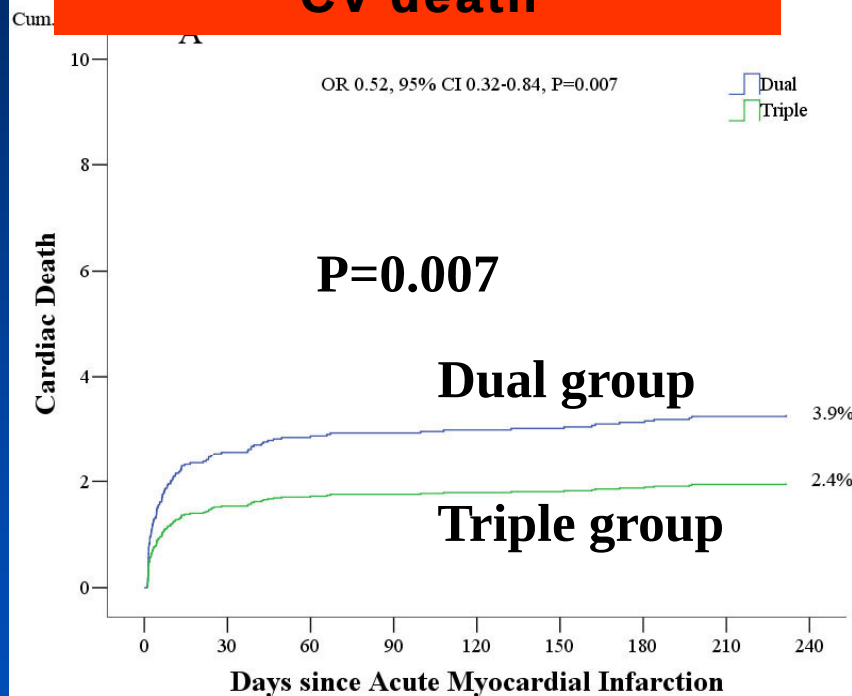
2) Triple therapy group (cilostazol for at least 1month)

(aspirin plus clopidogrel plus cilostazol, n=1,634)

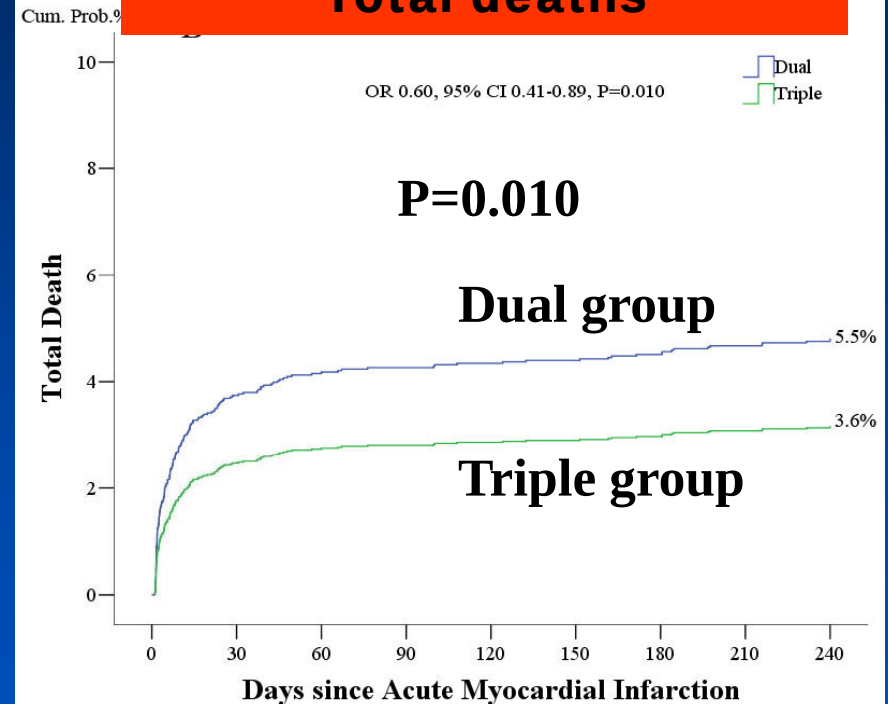
Chen KY et al. Circulation;119:3207-14

8-month mortality

CV death



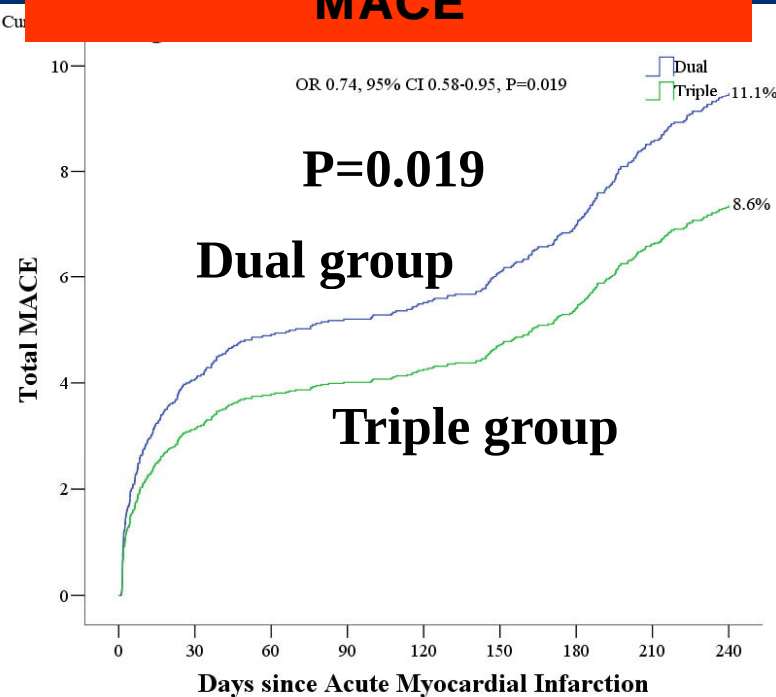
Total deaths



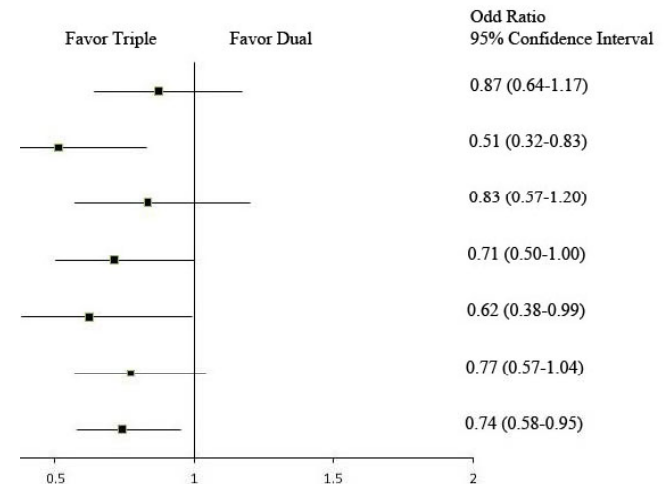
Chen KY et al. Circulation;119:3207-14

8-month death/MI/repeat revascularization

MACE



Non-DM
DM
Age < 65
Age ≥ 65
Female
Male
All patients



MACE at 8 months

Chen KY et al. Circulation;119:3207-14

**Cilostazol in addition to aspirin and
clopidogrel improves long-term
outcomes after PCI (BMS or DES) in
patients with acute coronary syndrome:
A randomized, controlled study**

12-month MACCE

Han Y, et al. Am Heart J 2009;157:733-9



Study Groups

Prospective randomized trial in ACS patients

1) Dual antiplatelet therapy group

(aspirin plus clopidogrel, n=608)

2) Triple antiplatelet therapy group (6 months)

(aspirin plus clopidogrel plus cilostazol, n=604)

The primary end point : composite of cardiac death, nonfatal MI, stroke, or TVR at 1 year

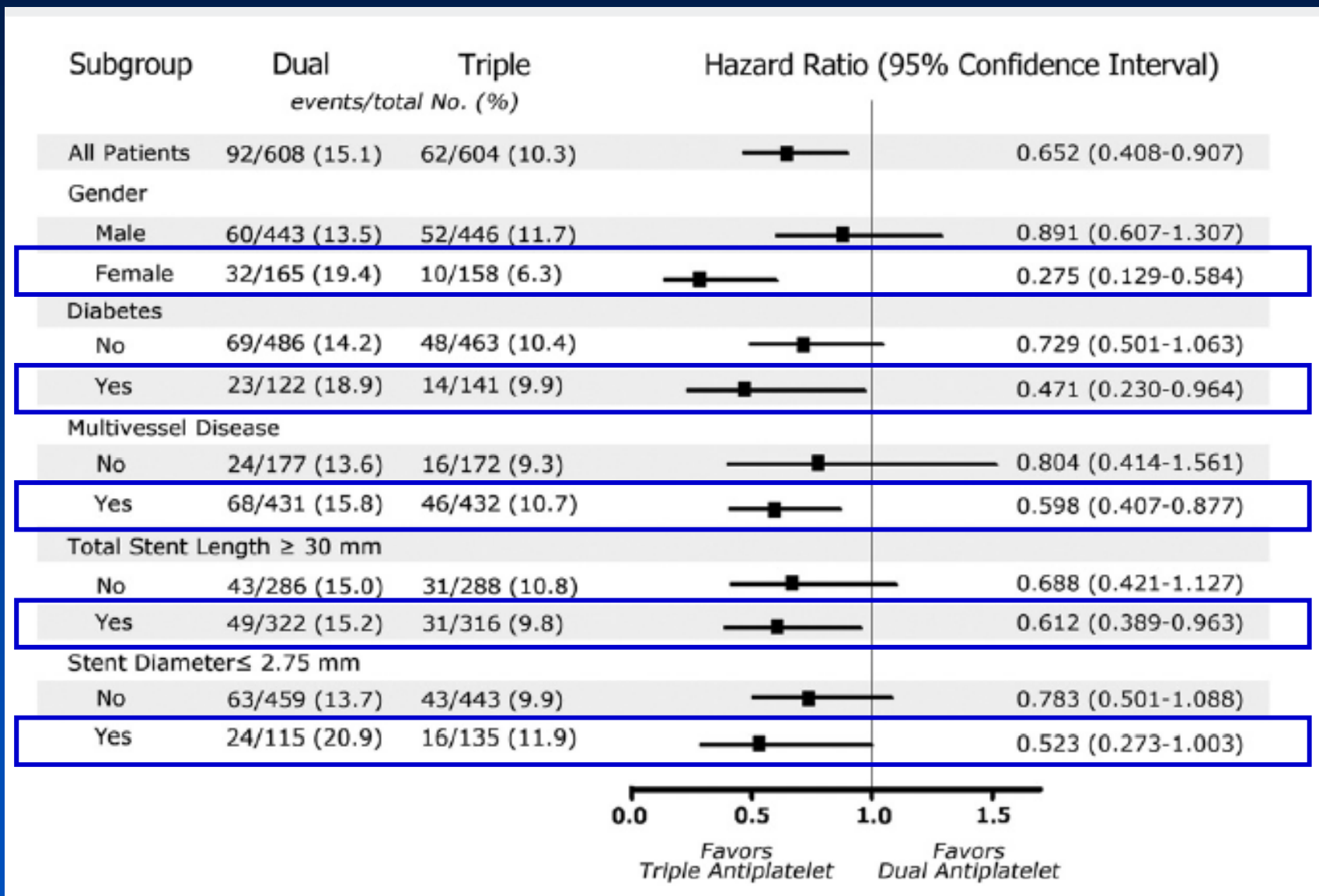
Han Y, et al. Am Heart J 2009;157:733-9

Clinical Outcomes at 12 Months for Triple Antiplatelet Therapy

	Dual (n=608)	Triple (n=604)	<i>p</i>
All death	4.1%	2.6%	0.159
CV death	3.3%	1.7%	0.067
MI	0.7%	0.3%	0.687
Stroke	1.6%	0.7%	0.109
Cardiac death/MI/Stroke	5.1%	2.6%	0.027
TVR	10.4%	7.8%	0.118
MACCE	15.1%	10.3%	0.011

Han Y, et al. Am Heart J 2009;157:733-9

Subgroup analysis



Han Y, et al. Am Heart J 2009;157:733-9

Recommended duration of triple antiplatelet therapy

- For stent thrombosis/MI, 1 month at minimum
- For restenosis, 6 months at minimum

Potential candidate of triple therapy in newer generation DES era

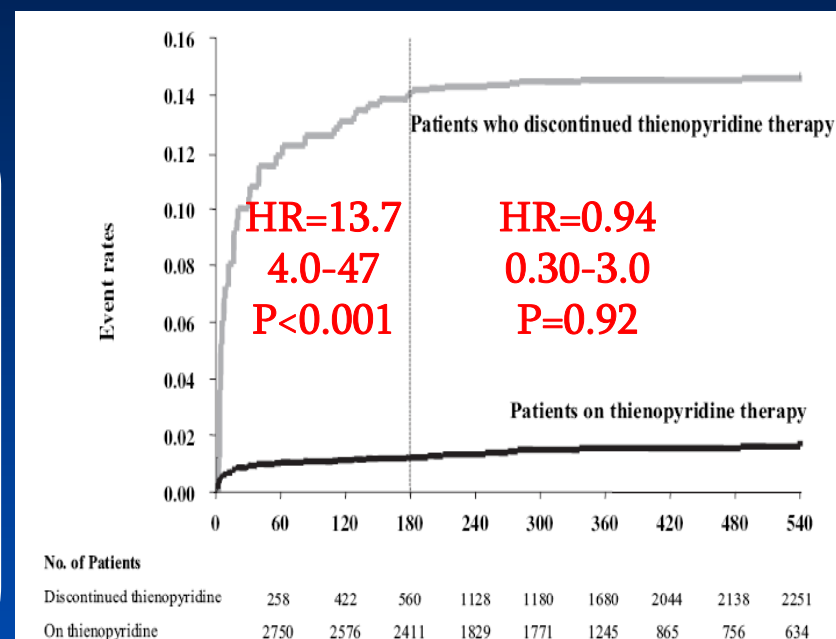
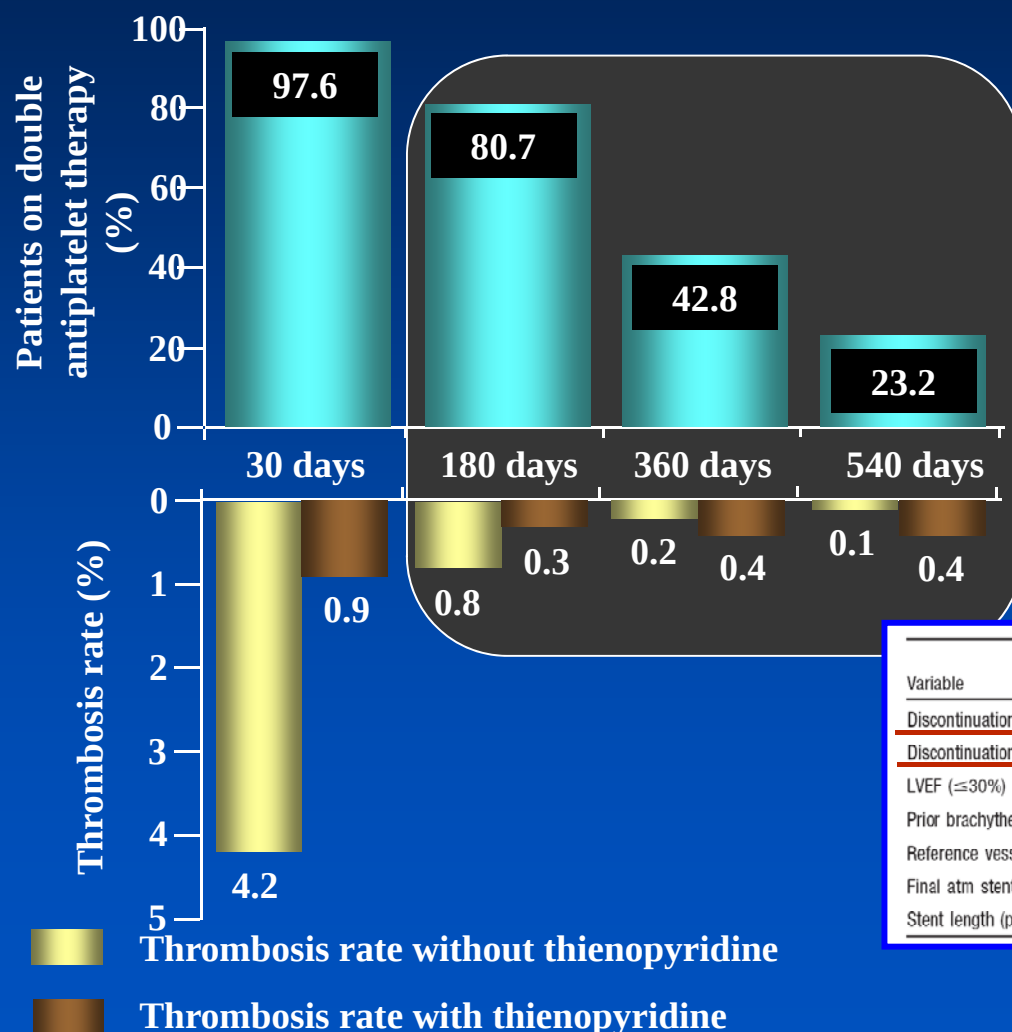
- Long lesions
- Diabetic population
- Restenotic lesion
- Bifurcation lesion
- Multi-vessel stenting
- STEMI
- ACS....

Complex PCI patients would be potential candidate of triple antiplatelet therapy even in new generation DES era

Thank you for your attention



The Observational Data from Europe (Milan-Helios Group)



Variable	No. of Patients	HR	95% Lower Confidence Limit	95% Upper Confidence Limit	P
Discontinuation of thienopyridine (0-6 months)*	583	13.74	4.04	46.68	<0.001
Discontinuation of thienopyridine (6-18 months)*	1737	0.94	0.30	2.98	0.92
LVEF (≤30%)	96	3.72	1.50	9.27	0.005
Prior brachytherapy	31	9.70	2.99	31.44	<0.001
Reference vessel diameter (per 1 mm)†	...	0.27	0.06	1.13	0.07
Final atm stent implantation (per 1 atm)†	...	0.39	0.18	0.85	0.02
Stent length (per 10 mm)†	...	2.75	1.55	4.88	<0.001

Airolidi F et al. Circulation, 2007;116:745