Clinical Application of Triple Antiplatelet Therapy: The Answer to Patients with CYP 2C19 Polymorphism and High Post-Treatment Platelet Reactivity After Clopidogrel?

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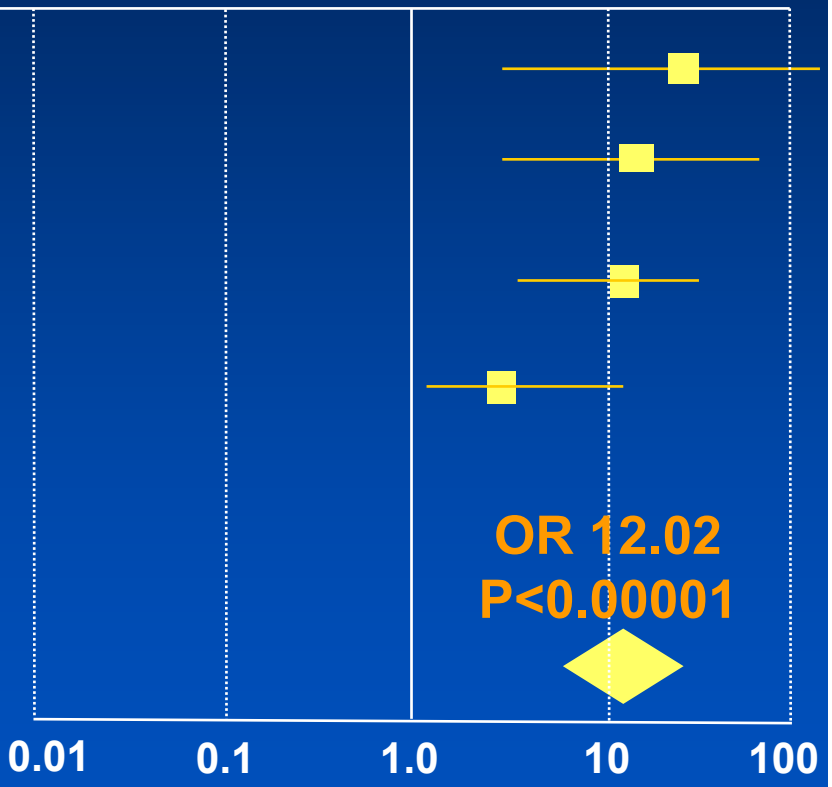
Clopidogrel resistance and Risk of CV event

Meta-analysis including pts treated with PCI in 25 studies (LTA, TEG, cytometry)

Clinical ischemic events (CV death, MI, stroke, revascularization, ST)

Study	CR	CS	Weight (%)
Matetzky	7/15	1/45	9.09
Cuisset (JTH)	9/23	3/83	14.08
Cuisset (JACC)	18/58	7/234	17.95
Geisler	5/22	19/357	16.63
Subtotal	**39/118**	**30/719**	**57.76**



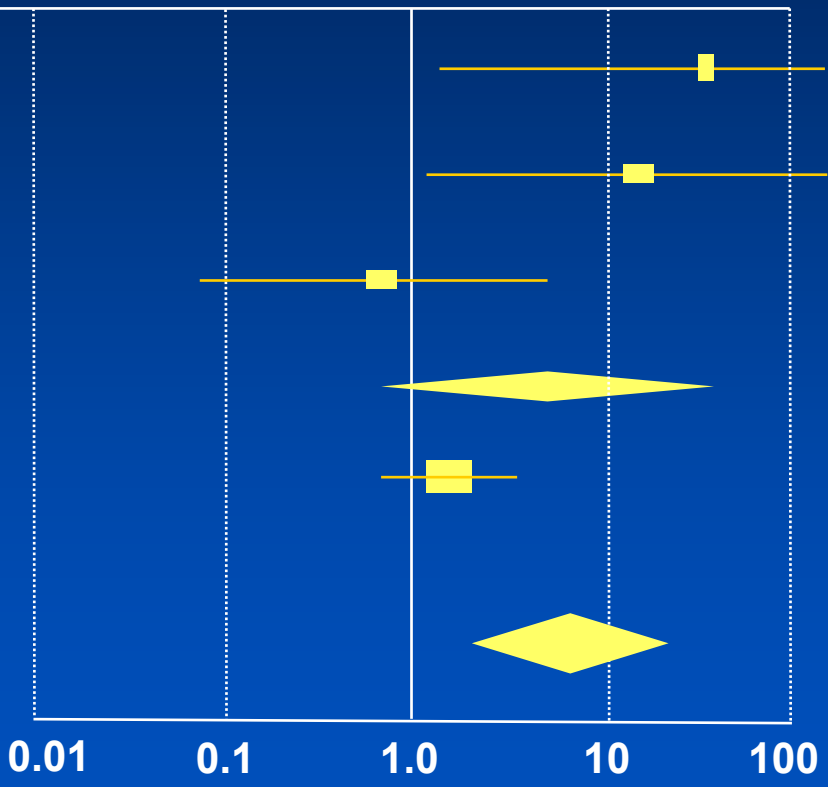
Snoep JD et al. Am Heart J 2007;154:221.

Clopidogrel resistance and Risk of CV event

Meta-analysis including 3688 pts in 25 studies (LTA, TEG, flow cytometry)

Subacute stent thrombosis

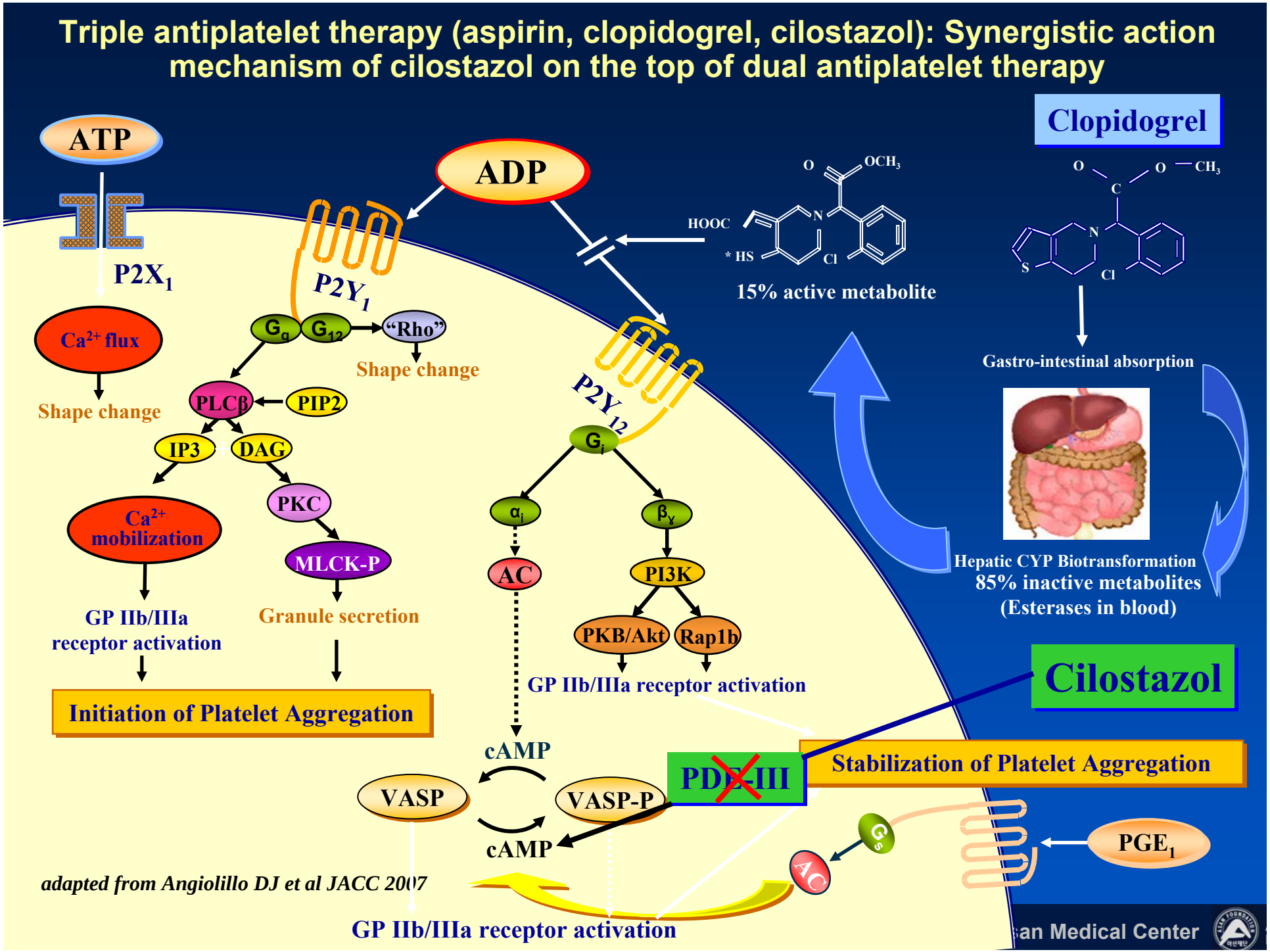
Study	CR	CS	Weight (%)
Muller	2/12	0/93	5.81
Klamroth	9/10	11/30	9.25
Wenaweser	1/4	22/69	8.65
Subtotal	12/26	33/192	23.72
Lev (myonecrosis)	11/36	19/114	18.53
Total	**26/440**	**184/634**	**100**



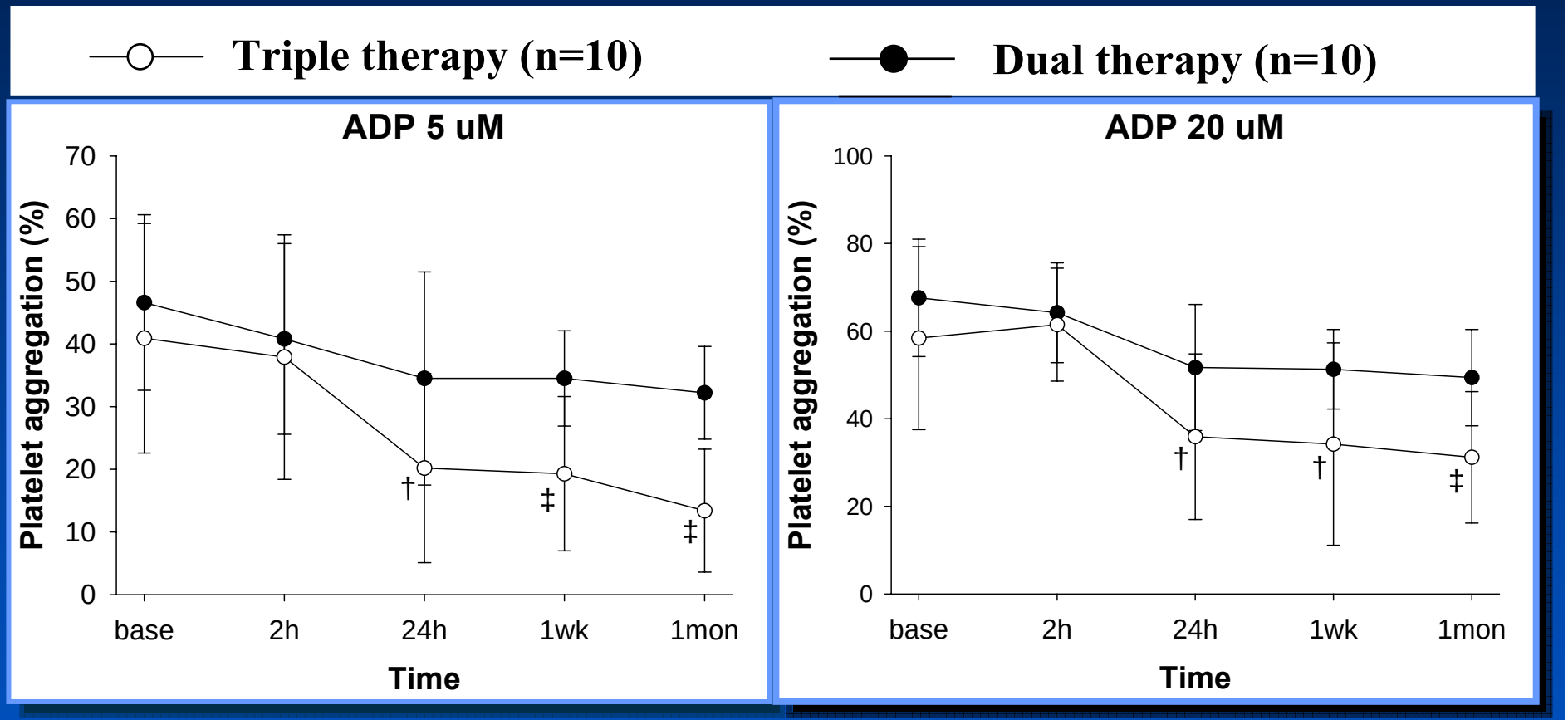
Snoep JD et al. Am Heart J 2007;154:221.

Cilostazol has
different antiplatelet action mechanism
compare to Clopidogrel.

Triple antiplatelet therapy (aspirin, clopidogrel, cilostazol): Synergistic action mechanism of cilostazol on the top of dual antiplatelet therapy



Platelet aggregation
Triple vs. Dual therapy



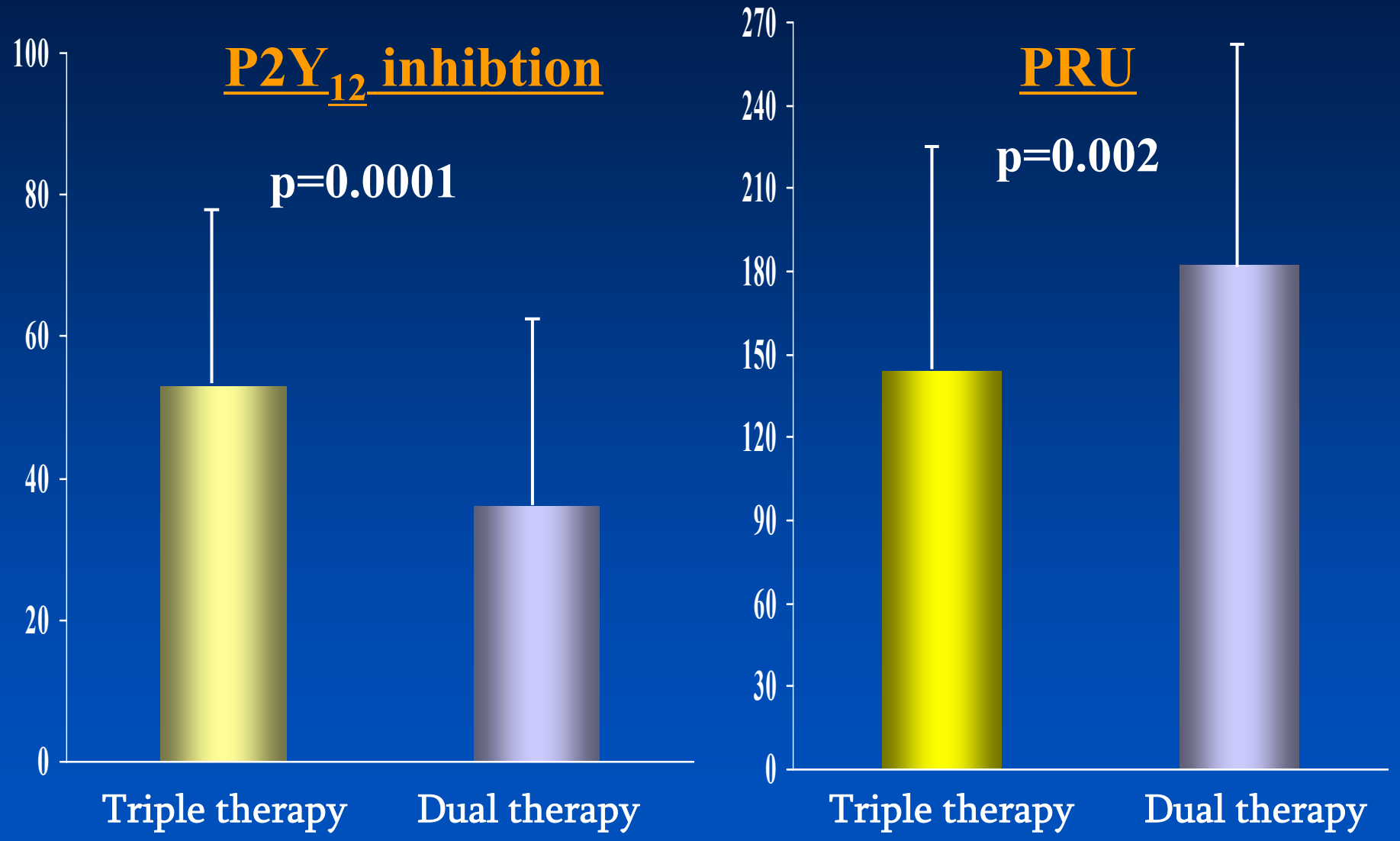
Results are expressed as the mean value ± SD.

† $p<0.05$, ‡ $p<0.01$ between two groups.

Lee BK, Lee SW, Park SW et al. Am J Cardiol. 2007;100:610-4

VerifyNow $P2Y_{12}$ Assay in DM

OPTIMUS-2



Angiolillo DJ et al. Eur Heart J. 2008;29:2202-11

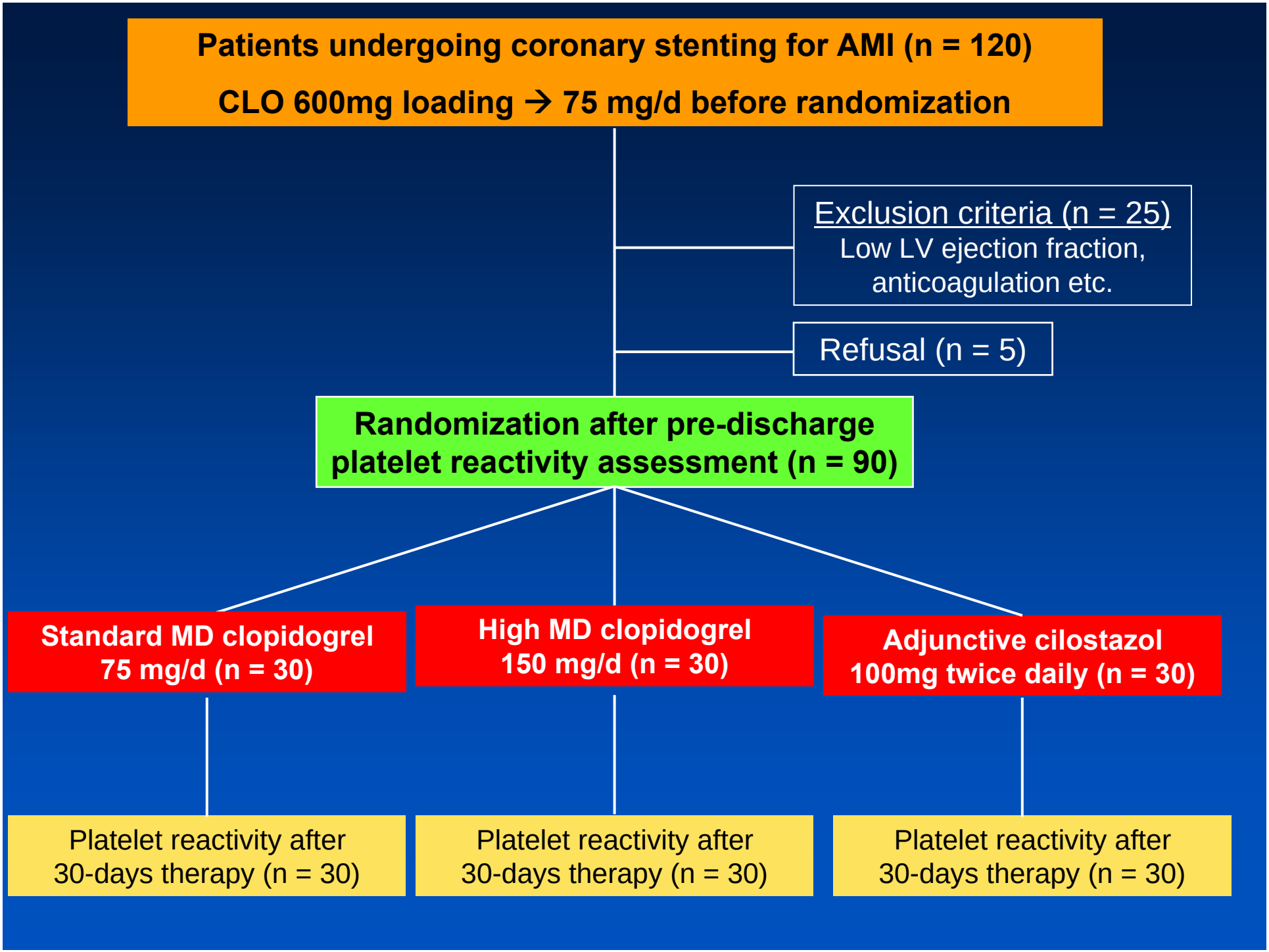
*A*djunctive Cilostazol to Dual Antiplatelet Therapy Achieves Greater Platelet Inhibition Compared with High Maintenance-dose Clopidogrel in Patients with AMI

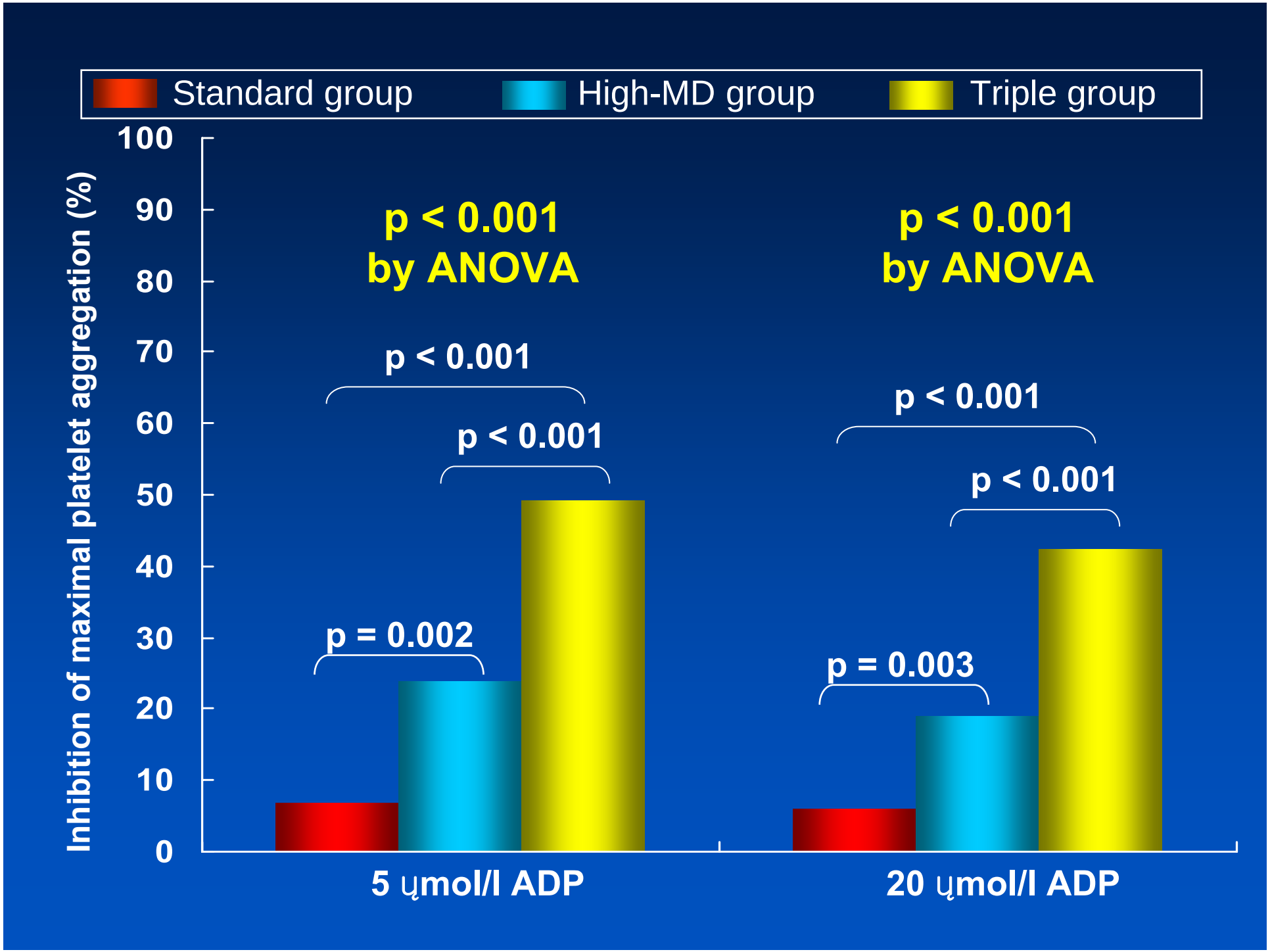
(*A*djunctive *C*ilostazol versus high MD *C*lopidogr*EL* in patients with **AMI**)

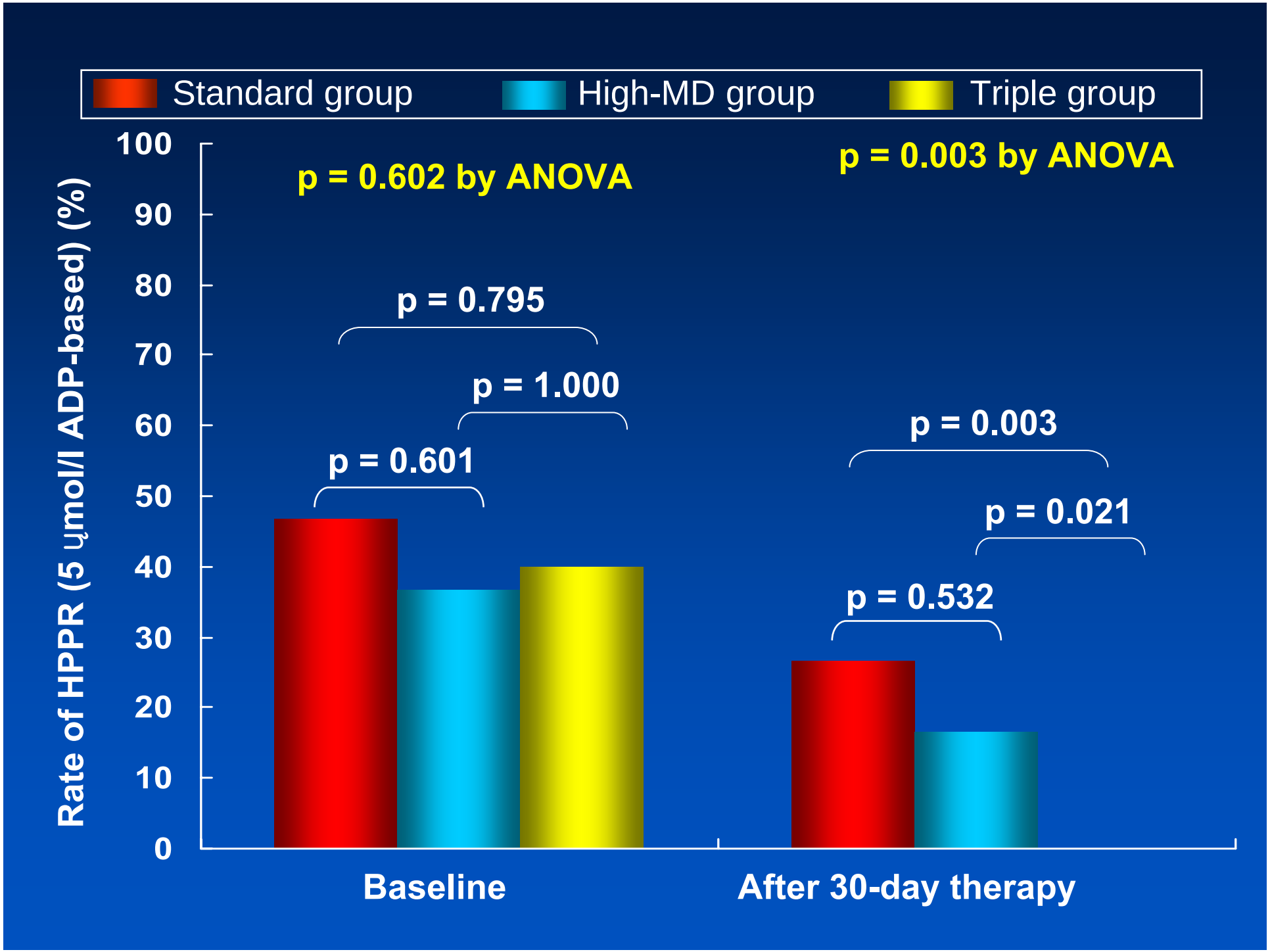
ACCEL-AMI

Young-Hoon Jeong,[1] Seung-Whan Lee,[2] Bong-Ryong Choi,[1] In-Suk Kim,[1] Choong Hwan Kwak,[1] Jin-Yong Hwang,[1] Seong-Wook Park,[2] For the ACCEL-AMI Investigators

1 Gyeongsang National University Hospital, Jinju, Korea.
2 Asan Medical Center, Seoul, Korea.


Patients undergoing coronary stenting for AMI (n = 120)
CLO 600mg loading → 75 mg/d before randomization
Exclusion criteria (n = 25)
Low LV ejection fraction, anticoagulation etc.
Refusal (n = 5)
Randomization after pre-discharge platelet reactivity assessment (n = 90)
Standard MD clopidogrel 75 mg/d (n = 30)
High MD clopidogrel 150 mg/d (n = 30)
Adjunctive cilostazol 100mg twice daily (n = 30)
Platelet reactivity after 30-days therapy (n = 30)
Platelet reactivity after 30-days therapy (n = 30)
Platelet reactivity after 30-days therapy (n = 30)


Standard group
High-MD group
Triple group
Inhibition of maximal platelet aggregation (%)
100
90
80
70
60
50
40
30
20
10
0
p < 0.001
by ANOVA
p < 0.001
by ANOVA
p < 0.001
p < 0.001
p < 0.001
p < 0.001
p = 0.002
p = 0.003
5 μmol/l ADP
20 μmol/l ADP


Standard group
High-MD group
Triple group
Rate of HPPR (5 μmol/l ADP-based) (%)
100
90
80
70
60
50
40
30
20
10
0
p = 0.602 by ANOVA
p = 0.003 by ANOVA
p = 0.795
p = 1.000
p = 0.601
p = 0.003
p = 0.021
p = 0.532
Baseline
After 30-day therapy

Randomized Comparison of Adjunctive Cilostazol versus High Maintenance-Dose Clopidogrel in Patients With Clopidogrel Hyporesponsiveness

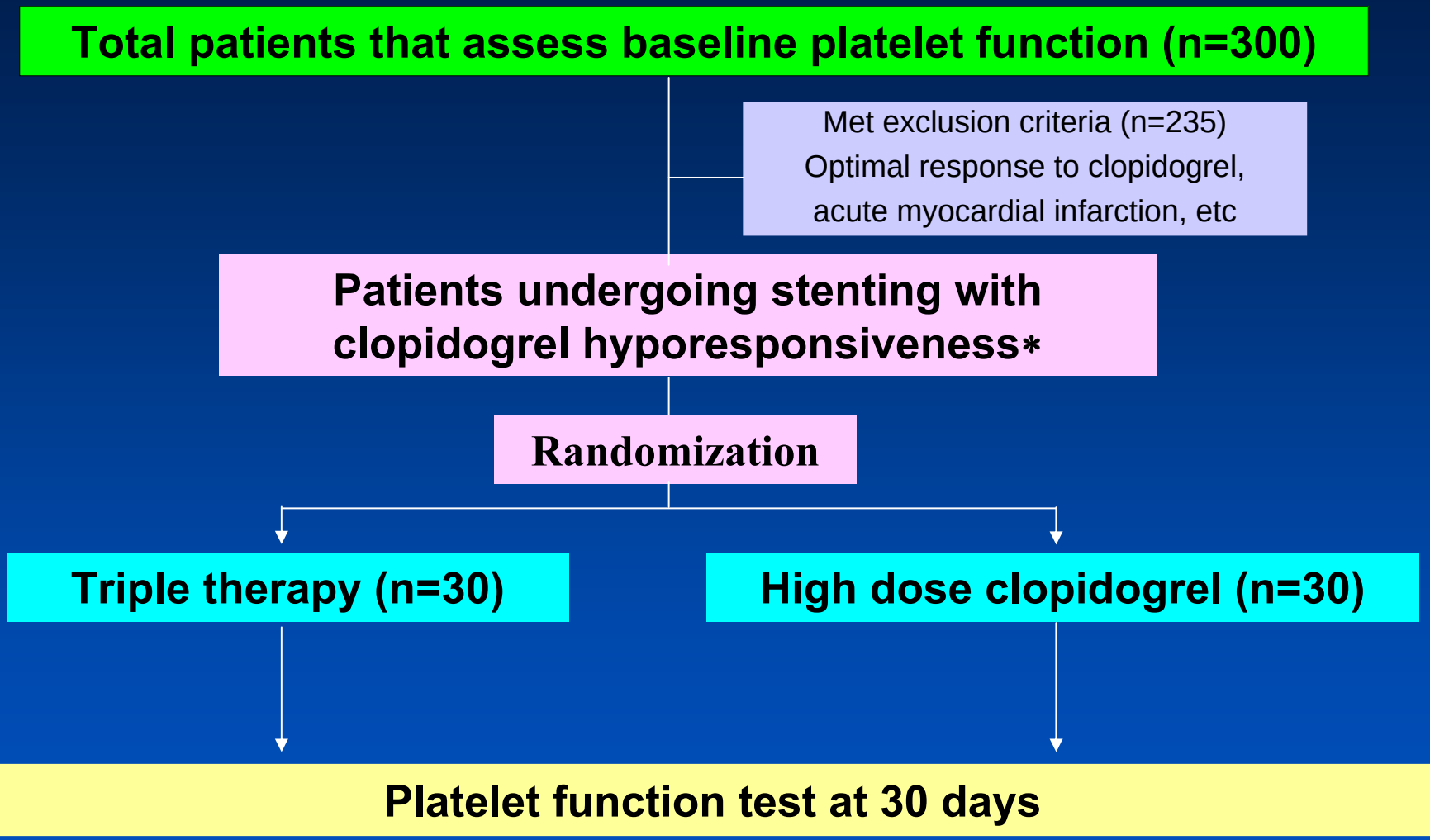
A*djunctive *C*ilostazol versus high MD *C*lopidogr*EL* for post-treatment platelet reactivity in patients with clopidogrel *RESISTANCE

ACCEL-RESISTANCE study

AMC and
Gyeongsang National University Hospital experience

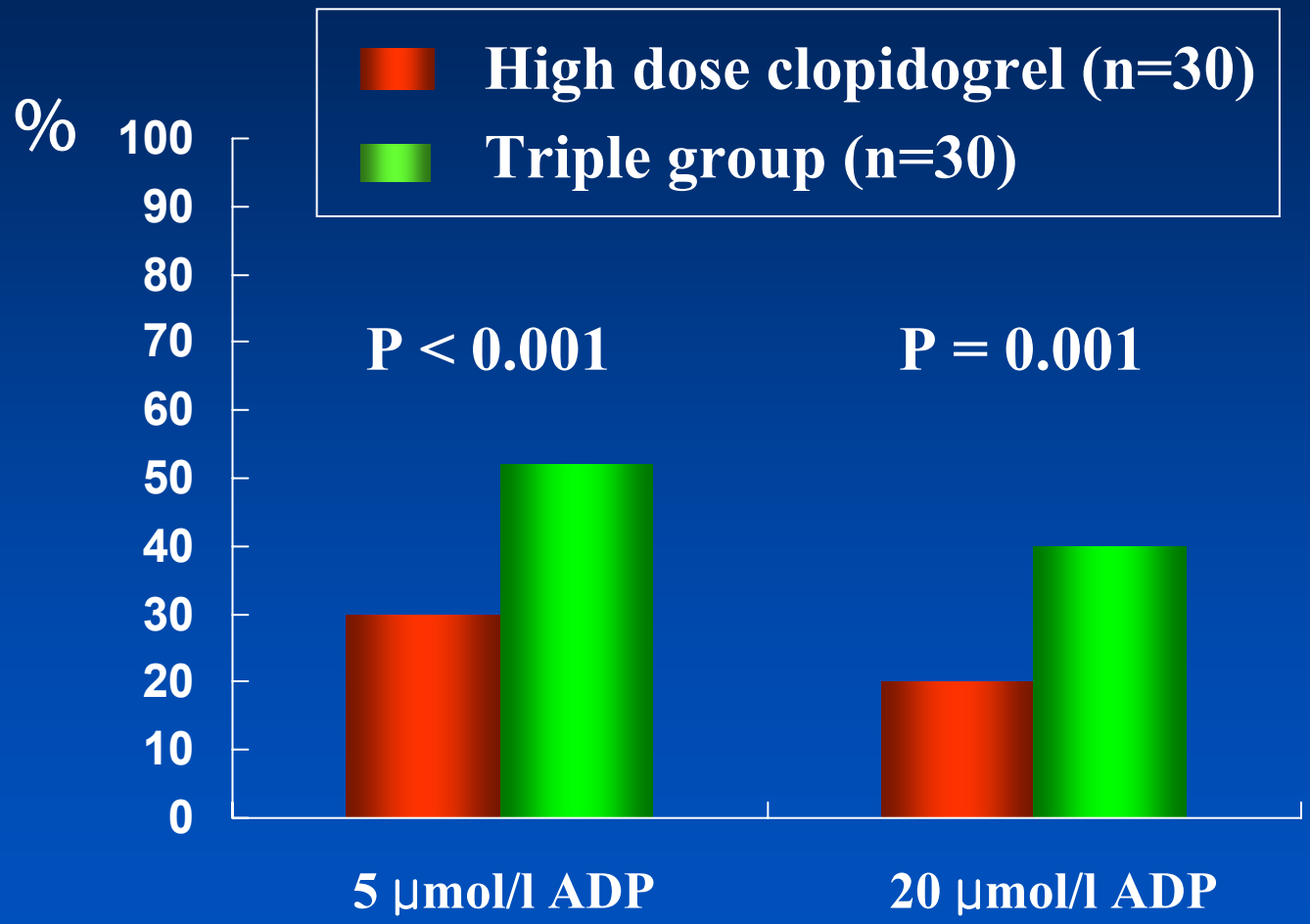
Jeong YH, Lee SW, Park SW et al. J Am Coll Cardiol 2009;53:1101-9

Trial Design



*Clopidogrel hyporesponsiveness : platelet aggregation > 50% with 5 ㎛ol/L ADP

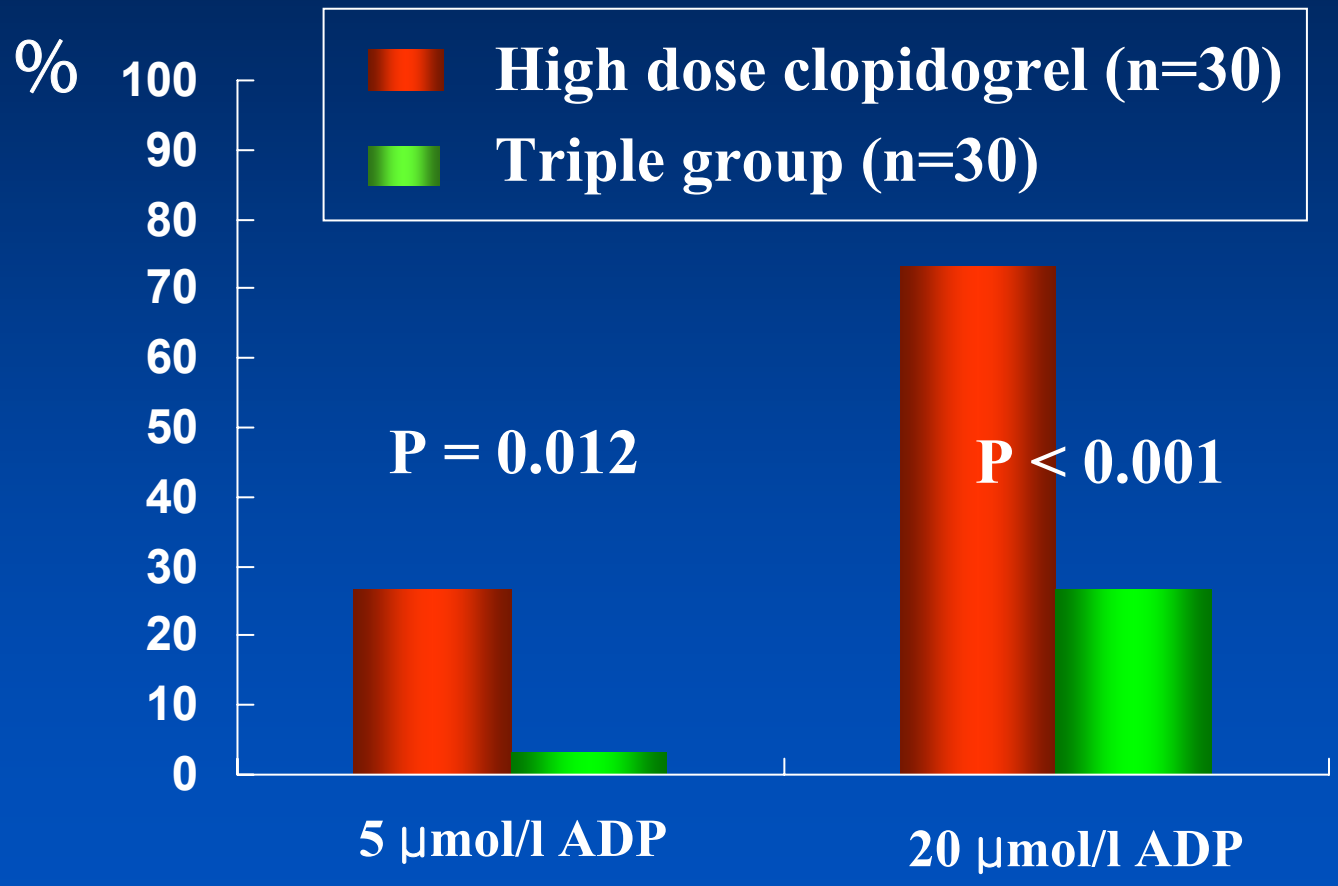
Inhibition of maximal platelet aggregation



Jeong YH, Lee SW, Park SW et al. J Am Coll Cardiol 2009;53:1101-9

Rate of clopidogrel hyporesponsiveness

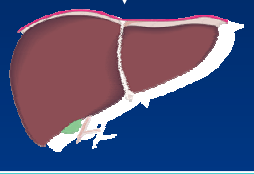
ADP-induced maximal platelet aggregation > 50%



Jeong YH, Lee SW, Park SW et al. J Am Coll Cardiol 2009;53:1101-9

Potential Sites for Response Variability

Intestinal absorption



Hepatic metabolism
Cytochrome P450 pathway

Active metabolite

$P2Y_{12}$ receptor
(irreversible inhibition)

GP IIb/IIIa receptor expression

Poor compliance

Inadequate administration

Variable absorption

Drug-drug interactions

Genetic polymorphisms CYP enzymes

Drug-drug interactions

Genetic polymorphisms $P2Y_{12}$ receptor

Alternate pathways of platelet activation

↑ release of circulating ADP

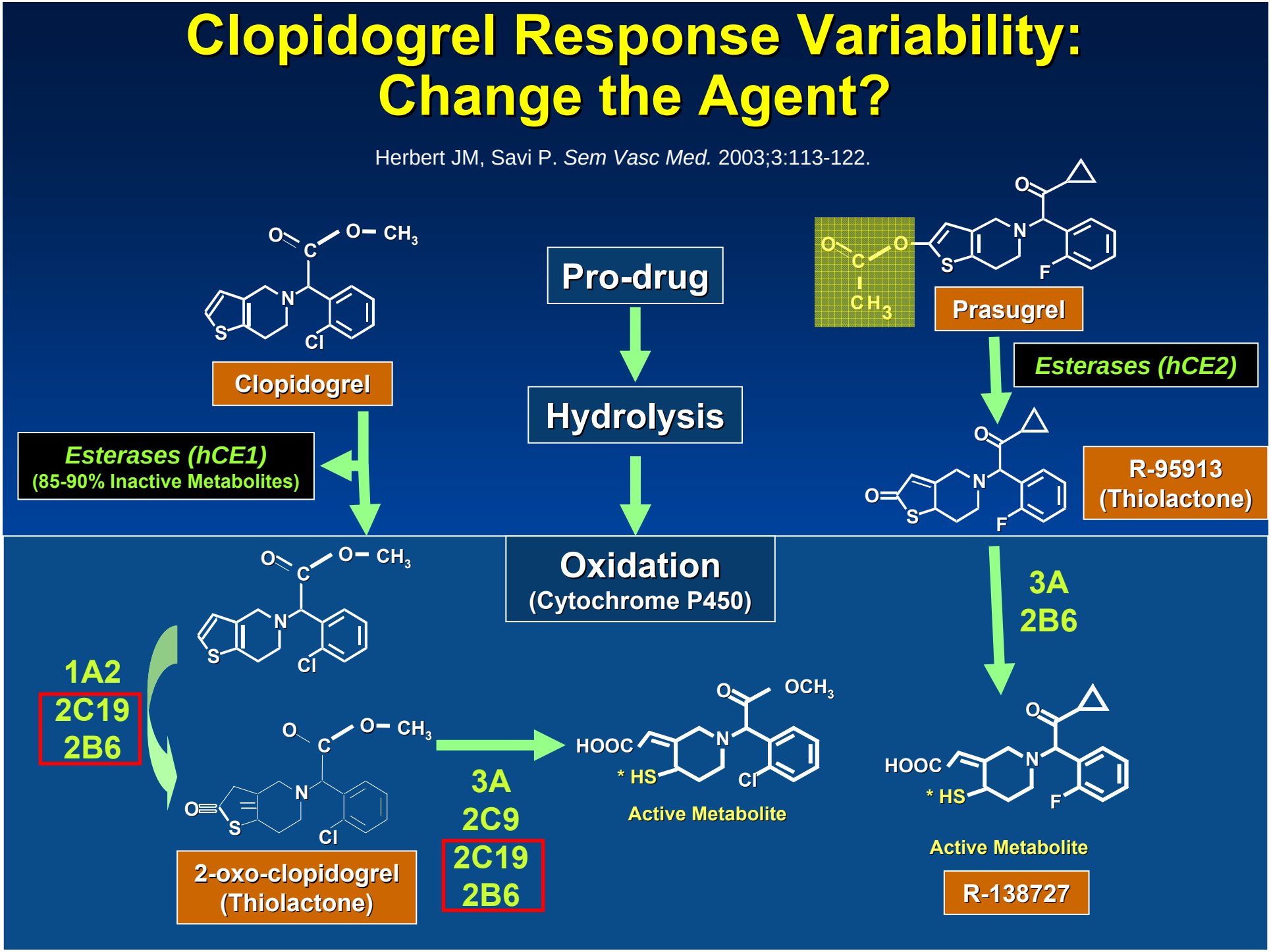
Higher baseline platelet reactivity

Genetic polymorphisms

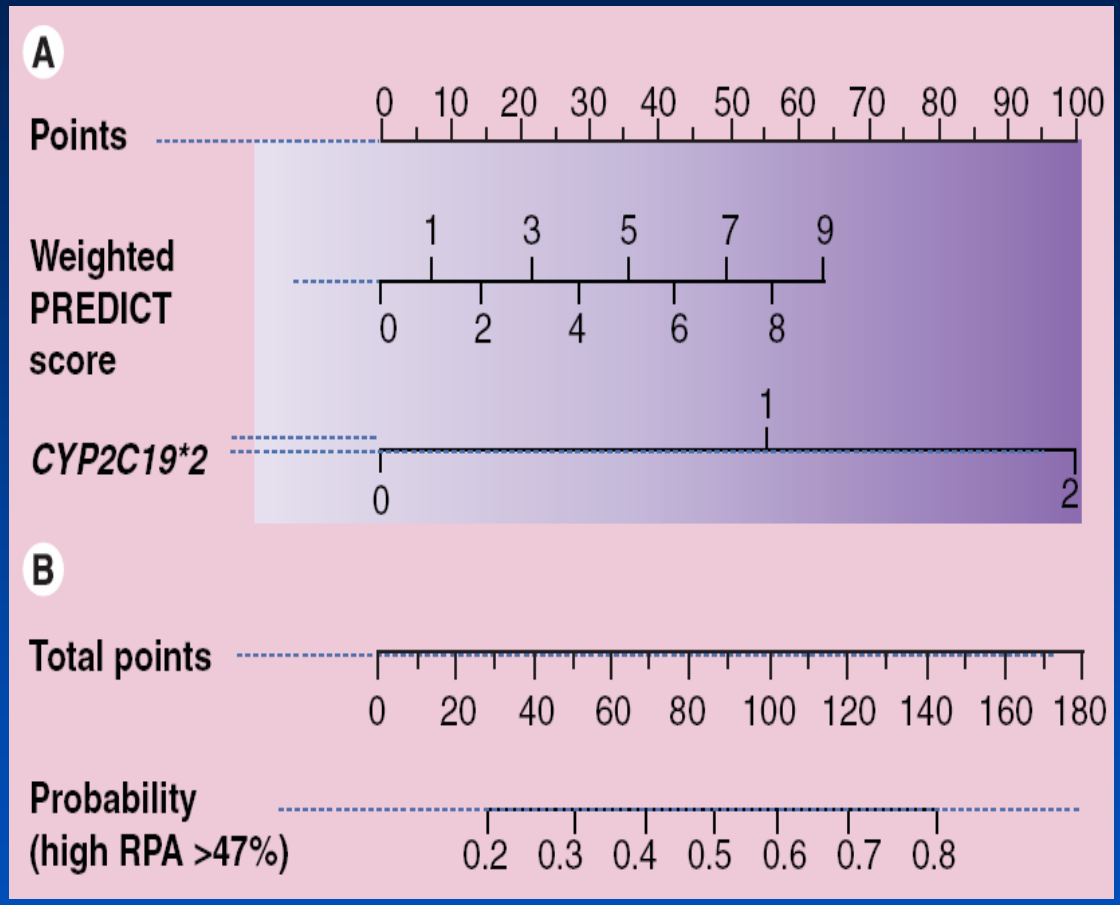
O'Donoghue M and Wiviott SD Circulation 2007

Clopidogrel Response Variability: Change the Agent?

Herbert JM, Savi P. *Sem Vasc Med.* 2003;3:113-122.



Risk of HPPR after clopidogrel loading 600mg
PREDICT score (n = 1092)



PREDICT score

1 = age > 65 yrs, ACS

2 = T2DM, CRF

3 = LV dysfunction

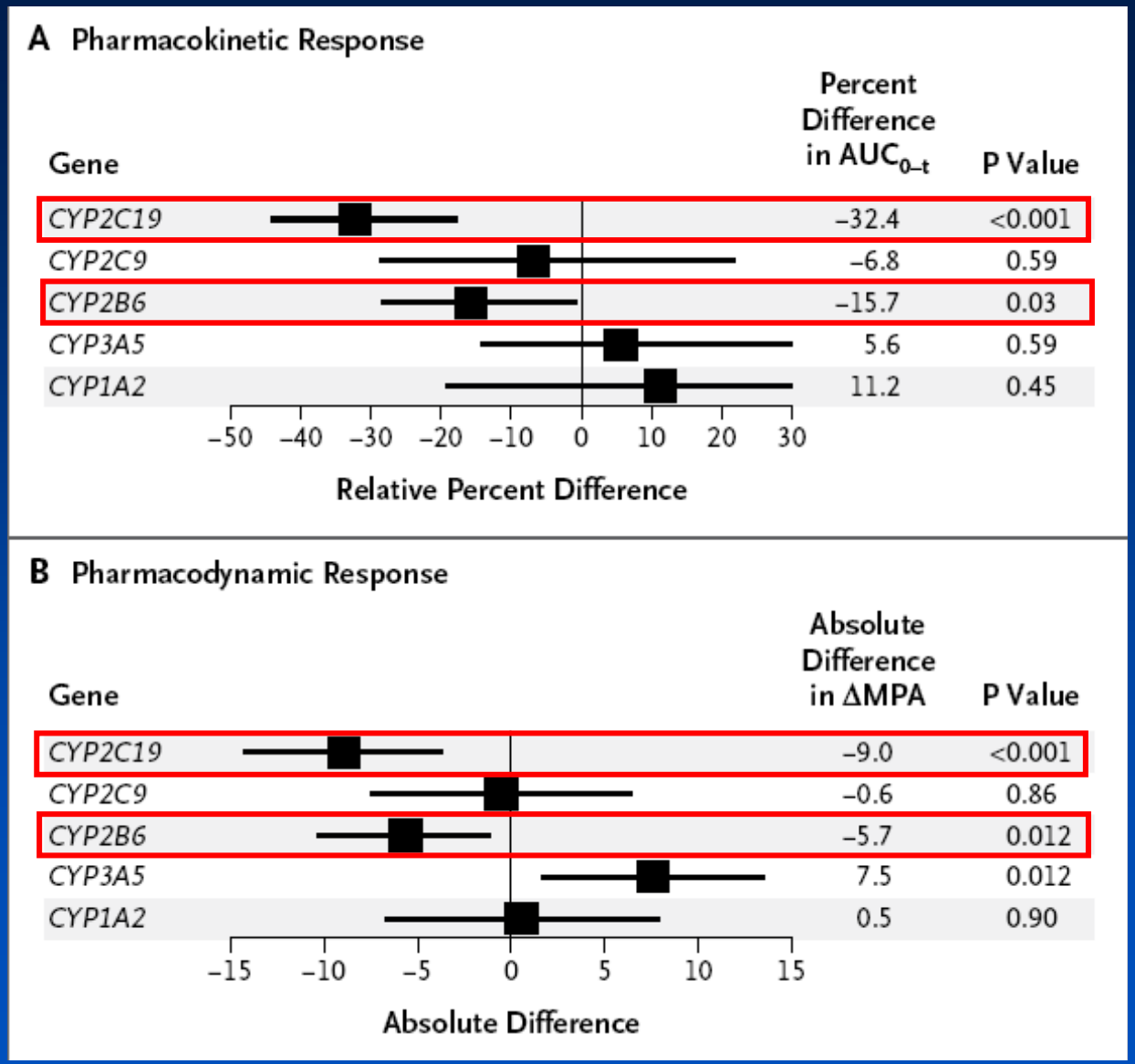
8 = one CYP2C19*2

14 = two CYP2C19*2

PREDICT score → Points → Probability of HPPR

Geisler T, et al. JTH 2008;6:54.: Pharmacogenomics 2008;9:1251.

Genetic Effects on Response to Clopidogrel



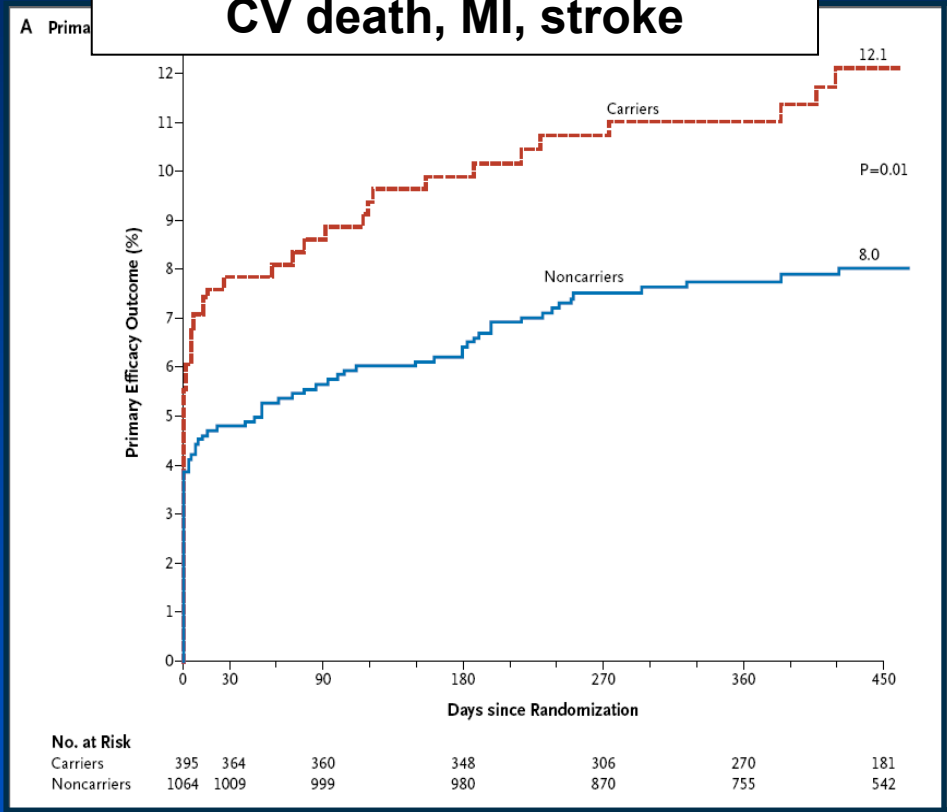
Mega JL, et al. NEJM 2009;360:354-62.

The impact of CYP450 Polymorphism in ACS pts on-clopidogrel

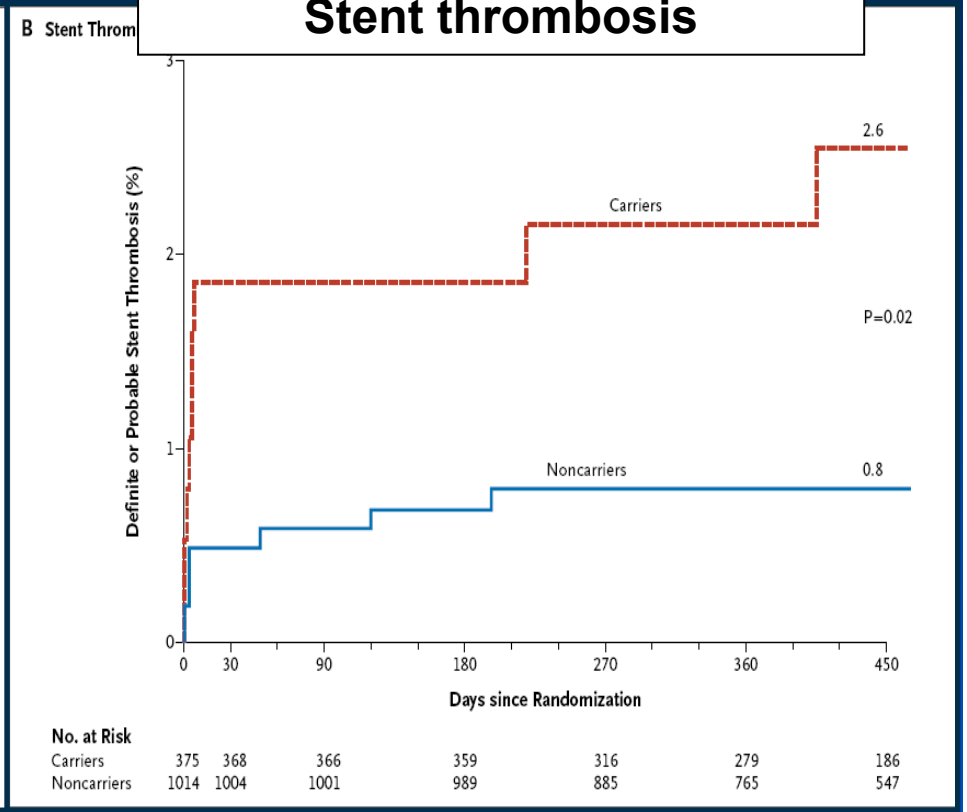
Substudy of TRITON-TIMI 38

2C19 polymorphism: Carrier vs. Non-Carrier

CV death, MI, stroke



Stent thrombosis



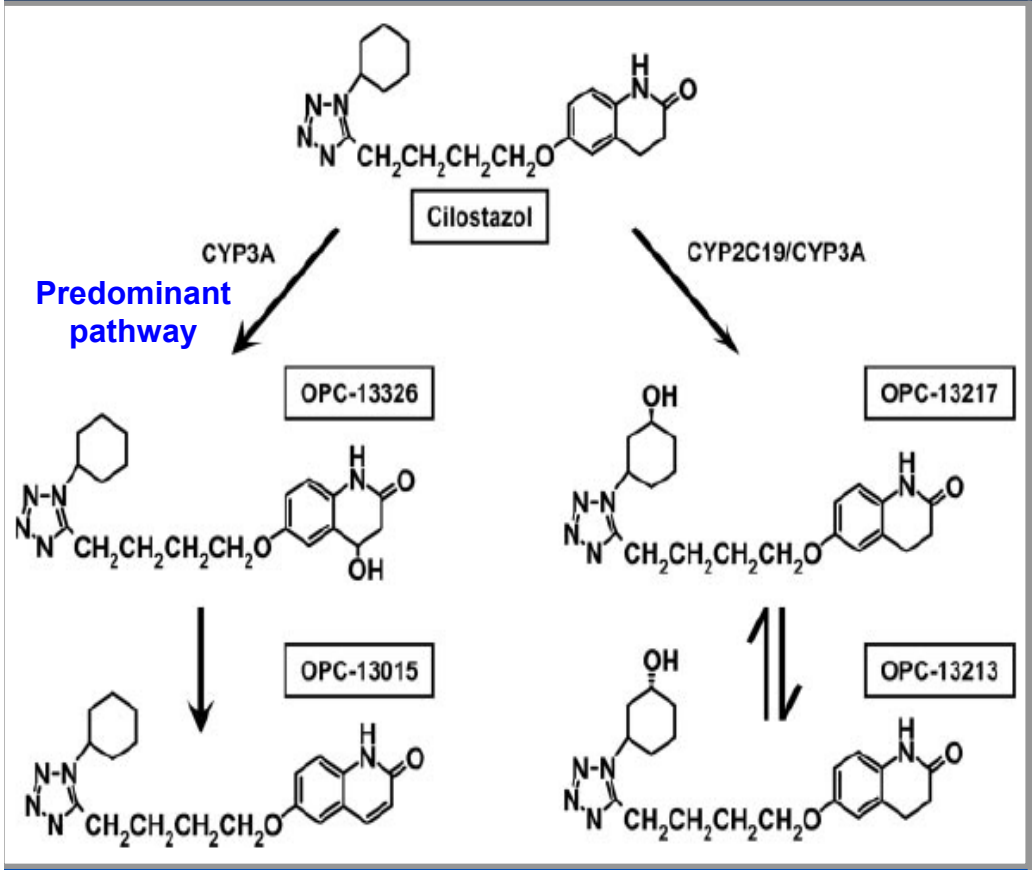
HR 1.53, 95% CI 1.07-2.19, P=0.01

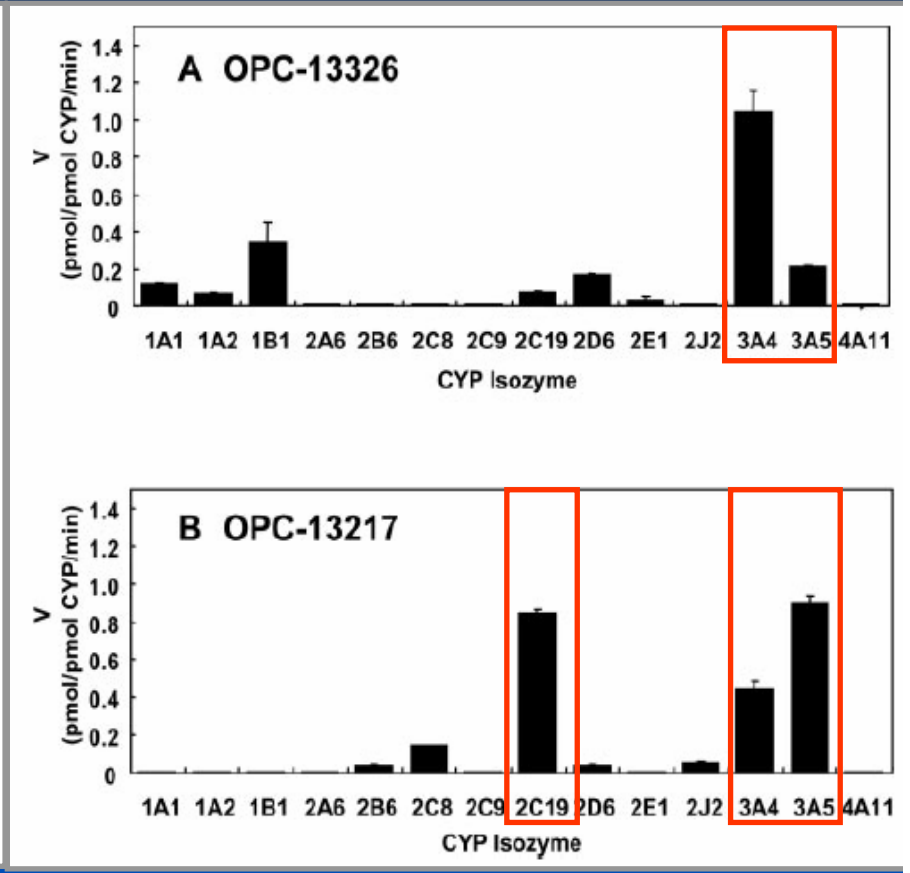
HR 3.09, 95% CI 1.19-8.00, P=0.02

Mega JL, et al. NEJM 2009;360:354-62.

Metabolic Pathway of Ciolstazol involving CYP450 Isozymes

Hiratsuka M, et al. Drug Metab Dispos 2007;35:1730.





3 times of cilostazol 1/3 times of cilostazol

The two major metabolites of cilostazol in vitro (OPC-13326 and OPC-13217) are mainly catalyzed by CYP3A4 and CYP3A5, respectively.

HPPR and Platelet Reactivity according to CYP2C19 genotyping

	Wild (*1/*1) **(n =57)**	One mutant (*1/*2, *1/*3) **(n=59)**	Two Mutant (*2/*2, *2/*3) **(n = 20)**	*P* value
	41.9%	**58.1%**		
Rate of HPPR	**16 (28.1%)**	**27 (45.8%)**	**12 (60.0%)**	***0.024***
LTA				
5μM ADP Agg_{max}	43±14	49±14	52±17	***0.012***
20μM ADP Agg_{max}	54±15	62±12	64±15	***0.002***
VerifyNow				
PRU	226±90	259±74	284±84	***0.018***
% platelet inhibition	28±23	20±18	13±16	***0.016***

HPPR: *5μmol/L ADP induced MPA >50%*

J Thromb Haemost 2009;E-pub.

Effect of High Dose Clopidogrel vs. Triple therapy according to CYP2C19 genotyping

92 patients undergoing elective coronary stenting (preliminary data)

Wild type of the CYP2C19 allele (*1/*1)

In carriers of CYP2C19 wild allele, similar inhibition of platelet reactivity and reduction of HPPR rate

Baseline platelet reactivity	48.0 ± 18.2%	49.5 ± 16.5%	0.827
30-day Platelet reactivity	28.5 ± 13.1%	24.7 ± 15.4%	0.500
Δ platelet reactivity	**19.5%**	**24.7%**	**0.432**
30-day rate of HPPR	**7.7%**	**6.7%**	**0.918**

Platelet reactivity: 5μmol/l ADP-induced maximal platelet aggregation (Agg_{max})
HPPR: 5μmol/l ADP-induced Agg_{max} > 50%

Effect of High Dose Clopidogrel vs. Triple therapy according to CYP2C19 genotyping

92 patients undergoing elective coronary stenting (preliminary data)

Mutant type of the CYP2C19 allele (*2 or *3)

In carriers of CYP2C19 mutant allele, Triple therapy shows greater reduction of platelet reactivity and the rate of HPPR compared to high-dose clopidogrel

30-day Platelet reactivity	42.4 ± 10.3%	29.7 ± 11.8%	0.001
Δ platelet reactivity	11.6%	22.6%	0.004
30-day rate of HPPR	30.0%	5.9%	0.018

Platelet reactivity: 5μmol/l ADP-induced maximal platelet aggregation (Agg_{max})
HPPR: 5μmol/l ADP-induced Agg_{max} > 50%

Triple versus Dual Antiplatelet Therapy After Successful Bare Metal Stenting: Impact on the Stent Thrombosis

AMC experience

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

Major Cardiac Events at 1Mo

	Dual (n=1597)	Triple (n=1415)	*p*
Stent thrombosis	9 (0.5%)	1 (0.1%)	0.024
Acute	3 (0.2%)	0	NS
Subacute	6 (0.3%)	1 (0.1%)	NS
MI*	9 (0.5%)	1 (0.1%)	0.024
TLR	9 (0.5%)	1 (0.1%)	0.024
Death	5 (0.6%)	3 (0.2%)	NS
MACE	13(0.8%)	4 (0.3%)	0.085

* AMI due to stent thrombosis

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

Predictors of Stent Thrombosis
by multivariate analysis

Primary stenting for AMI

OR=7.9, 95% CI=2.0-30.8, p=0.003

Triple antiplatelet therapy

OR=0.12, 95% CI=0.015-0.98, p=0.048

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

Safety of triple antiplatelet therapy

	Dual (n=1597)	Triple (n=1415)	*p*
Major bleeding	10 (0.6%)	11 (0.8%)	NS
Vascular complication	9 (0.5%)	4 (0.3%)	
Adverse side effect			
Leukopenia	3(0.2%)	2(0.1%)	NS
Thrombocytopenia	4(0.2%)	2(0.1%)	NS
Elevated LFT	2(0.1%)	1(0.1%)	NS
GI trouble	8 (0.5%)	3 (0.2%)	NS
Skin rash	8 (0.5%)	15 (1.1%)	0.079

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

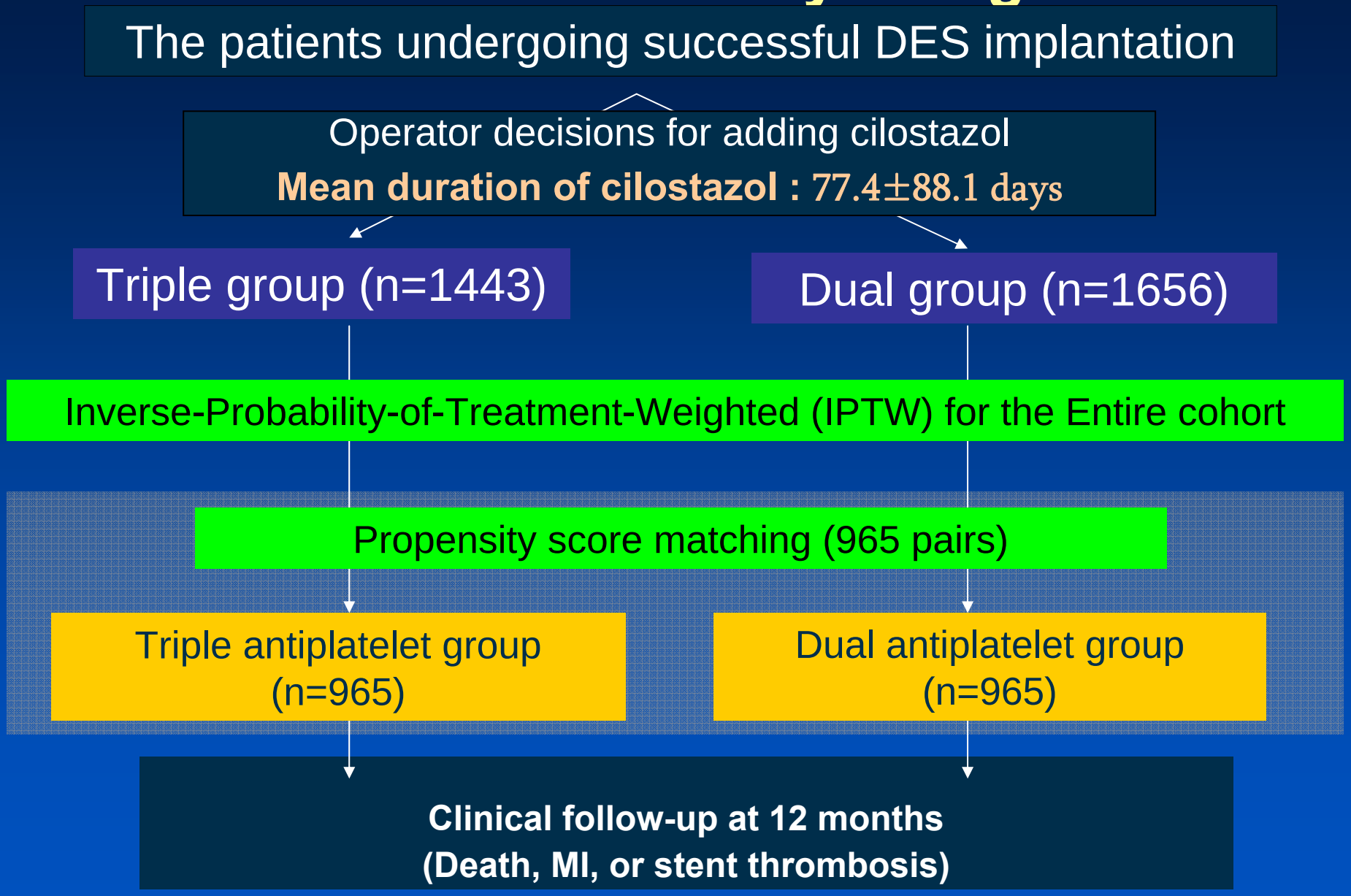
Triple Antiplatelet Therapy (asprin, clopidogrel and cilostazol) Significantly Reduces Ischemic Events after Drug-eluting stent implantation in a broad range of population

:*D*rug-*E*luting stenting followed by *C*ilostazol treatment *RE*duces *A*dverse *S*erious cardiac *E*vents

The DECREASE registry

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

DECREASE Study Design



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.

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

Triple versus Dual Antiplatelet Therapy in Patients with Acute Myocardial Infarction Undergoing Percutaneous Coronary Intervention (BMS or DES)

Circulation (in press)

Study Groups

Prospective registry of NSTEMI and STEMI patients:

1) Dual antiplatelet therapy group

(aspirin plus clopidogrel, n=2,986)

2) Triple antiplatelet therapy group (cilostazol 1month)

(aspirin plus clopidogrel plus cilostazol, n=1,924)

Circulation (in press)

Adjusted Clinical Outcomes at 8 Months for Triple Antiplatelets Therapy

Variables	Unadjusted OR (95% CI)	*P* value	Adjusted OR * (95% CI)	*P* value
Cardiac death	0.80 (0.57-1.13)	0.209	0.86 (0.58-1.25)	0.416
Total death	0.79 (0.58-1.09)	0.155	0.83 (0.59-1.17)	0.287
Recurrent MI	0.51 (0.26-1.02)	0.057	0.55 (0.27-1.11)	0.096
CABG	0.62 (0.33-1.15)	0.130	0.69 (0.41-1.24)	0.215
Re-PCI	0.91 (0.65-1.26)	0.559	0.86 (0.61-1.22)	0.395
TLR	0.82 (0.58-1.24)	0.242	0.95 (0.58-1.56)	0.846
Total MACE	0.79 (0.64-0.97)	0.031	0.79 (0.63-0.98)	0.034

Circulation (in press)

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

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

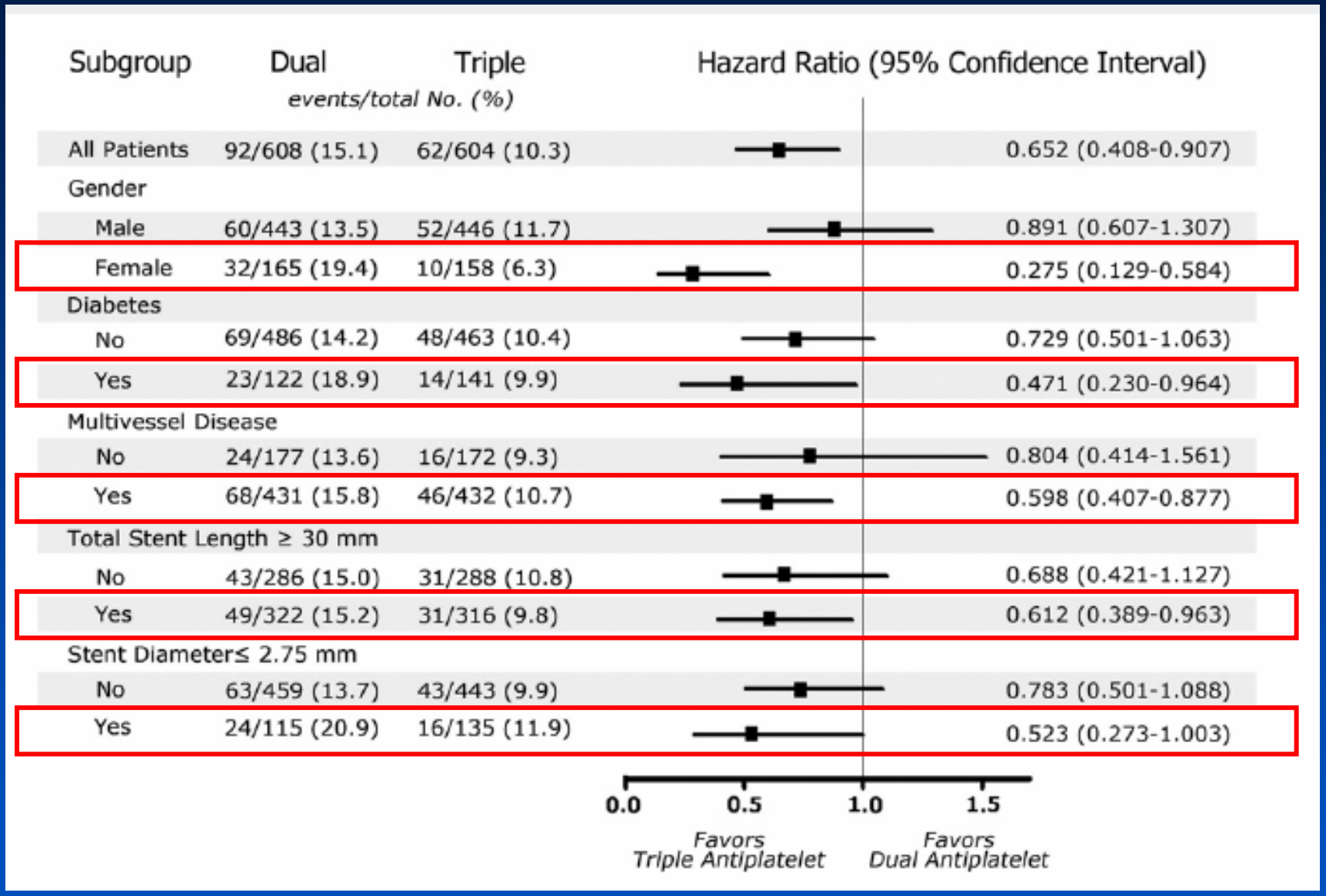
Han Y, et al. Am Heart J 2009;157:733-9

Clinical Outcomes at 12 Months for Triple Antiplatelet Therapy

	Dual (n=608)	Triple (n=604)	*p*
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

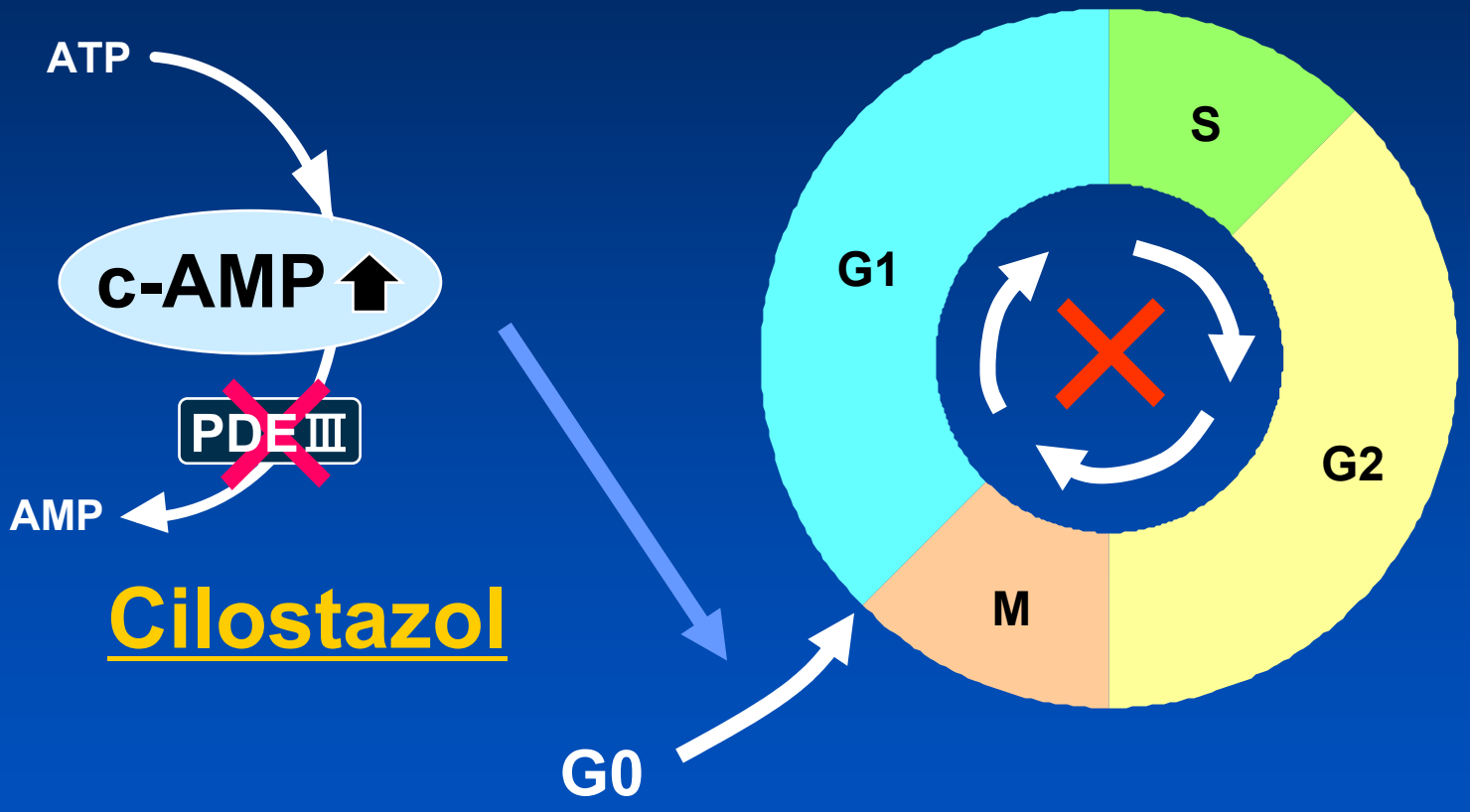


Han Y, et al. Am Heart J 2009;157:733-9

Cilostazol

Antiproliferative effect after DES

Cilostazol has inhibitory effects on smooth muscle cell proliferation too…



Journal of the American College of Cardiology
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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)

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

Comparison of Triple Versus Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation (from the DECLARE–Long Trial)

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

Pooled analysis of DECLARE-DM and LONG

Antiplatelet Regimen

Triple Regimen :
Aspirin 100mg/d + Clopidogrel 75mg/d
+ Cilostasol 200mg/d for 6 months

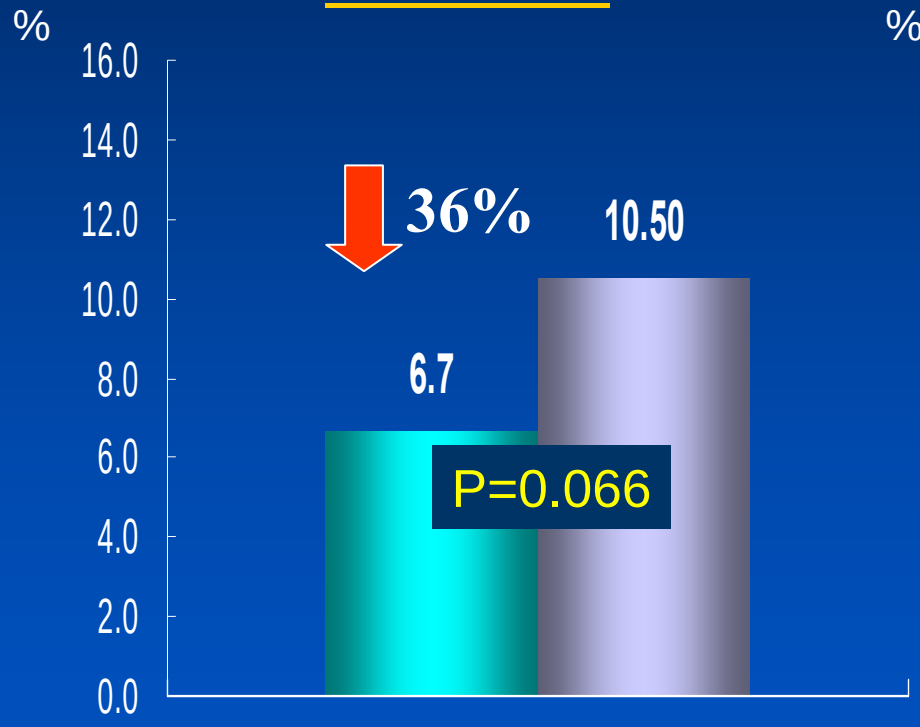
Standard dual antiplatelet therapy :
Aspirin 100mg/d + Clopidogrel 75mg/d
for at least 6 months

Restenosis rate after DES

From DECLARE-DM, LONG

Triple (n=373) Standard (n=372)

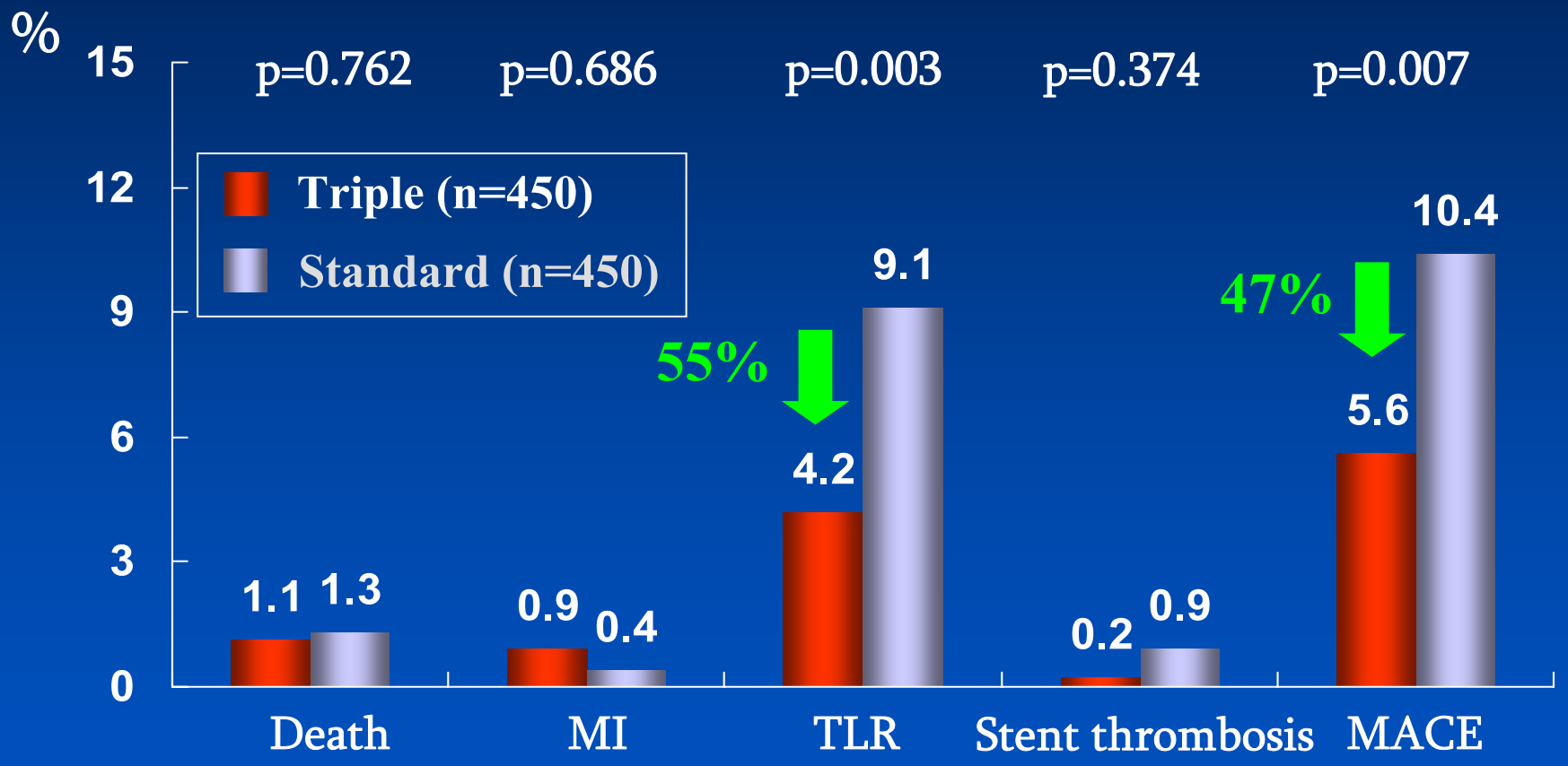
In-stent



In-segment

Lee SW, Park SW et al. J Am Coll Cardiol March, 2008;52:727-33
Lee SW, Park SW et al. Am J Cardiol. 2007;100:1103-8

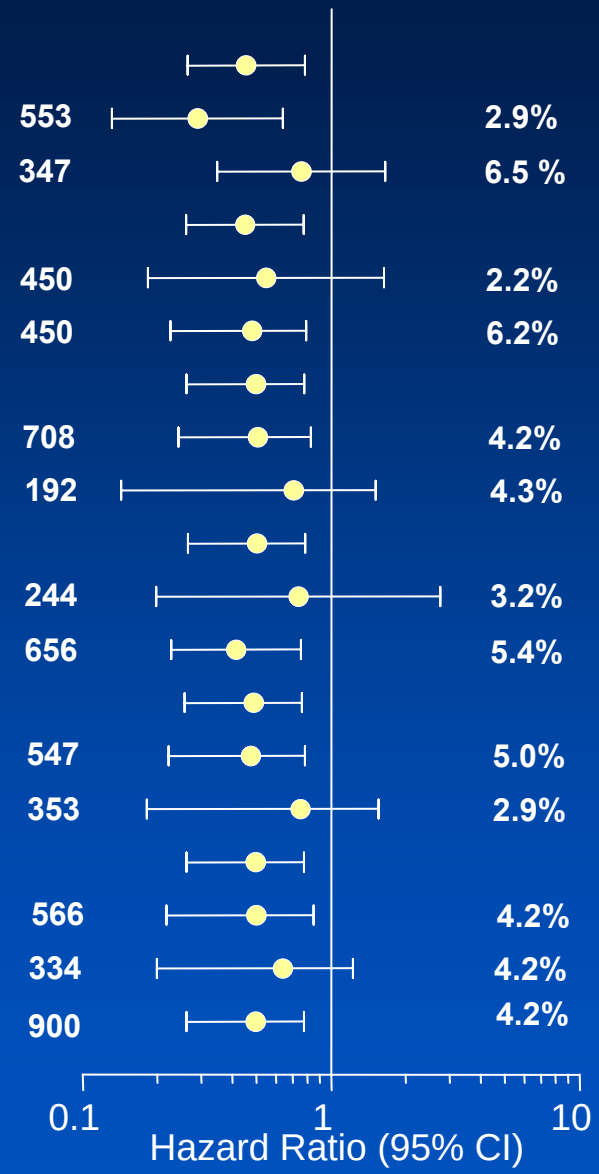
Two-year MACE



MACE: Death, MI, TLR

Subgroup Analyses of 2-yr TLR

	Patients (No.)	Triple	Standard	HR (95% CI)	*P value*	*P* value for homogeneity
Gender				0.454 (0.264, 0.783)	0.005	0.090
Male	553	2.9%	9.5%	0.290 (0.131, 0.640)	0.002	
Female	347	6.5 %	8.5%	0.758 (0.348, 1.650)	0.485	
DES				0.450 (0.261, 0.776)	0.004	0.692
SES	450	2.2%	4.0%	0.547 (0.183, 1.631)	0.279	
PES	450	6.2%	14.2%	0.424 (0.226, 0.794)	0.007	
Lesion length				0.452 (0.262, 0.779)	0.004	0.958
≥ 25mm	708	4.2%	9.1%	0.449 (0.243, 0.829)	0.010	
< 25mm	192	4.3%	9.1%	0.465 (0.143, 1.510)	0.203	
Vessel size				0.456 (0.265, 0.786)	0.005	0.434
≥ 3mm	244	3.2%	4.2%	0.739 (0.198, 2.752)	0.652	
< 3mm	656	5.4%	10.4%	0.415 (0.227, 0.757)	0.004	
LAD				0.443 (0.257, 0.763)	0.003	0.708
LAD	547	5.0%	11.6%	0.417 (0.222, 0.785)	0.007	
Non-LAD	353	2.9%	5.5%	0.529 (0.181, 1.549)	0.246	
DM				0.452 (0.262, 0.778)	0.004	0.810
DM	566	4.2%	9.6%	0.430 (0.218, 0.849)	0.015	
Non-DM	334	4.2%	8.3%	0.494 (0.199, 1.224)	0.128	
Overall	900	4.2%	9.1%	0.452 (0.262, 0.778)	0.004	



← Favors Triple vs. Standard Antiplatelet Treatment →

Conclusions

- Triple antiplatelet therapy significantly reduced the platelet activation in patients with CYP 2C19 polymorphism and high post-treatment platelet reactivity after clopidogrel treatment.

- Triple antiplatelet therapy significantly reduced stent thrombosis in the BMS or DES era in a broad range of population (DECREASE registry).

Conclusions

- Triple antiplatelet therapy for at least 1 month improved mid term clinical outcomes after PCI in ACS patients.
- Triple antiplatelet therapy for 6 months significantly reduced angiographic restenosis, mid-term and long-term (2-year) TLR and MACE (death, MI, and TLR) after DES implantation in patients at high risk of restenosis without a increased risk of bleeding complications, compared to dual antiplatelet therapy.
- Benefit of Triple antiplatelet therapy is prominent in patients with high risk profile.

Conclusions

- Therefore, Triple antiplatelet therapy is valuable option in patients with genetic polymorphism, poor responder to clopidogrel treatment, and high risk profile in terms of angiographic restenosis and adverse cardiac outcomes after PCI.