TAPT: Adjunctive Cilostazol to Aspirin and Clopidogrel

The Role of Triple Antiplatelet Therapy in Patients with High Risk

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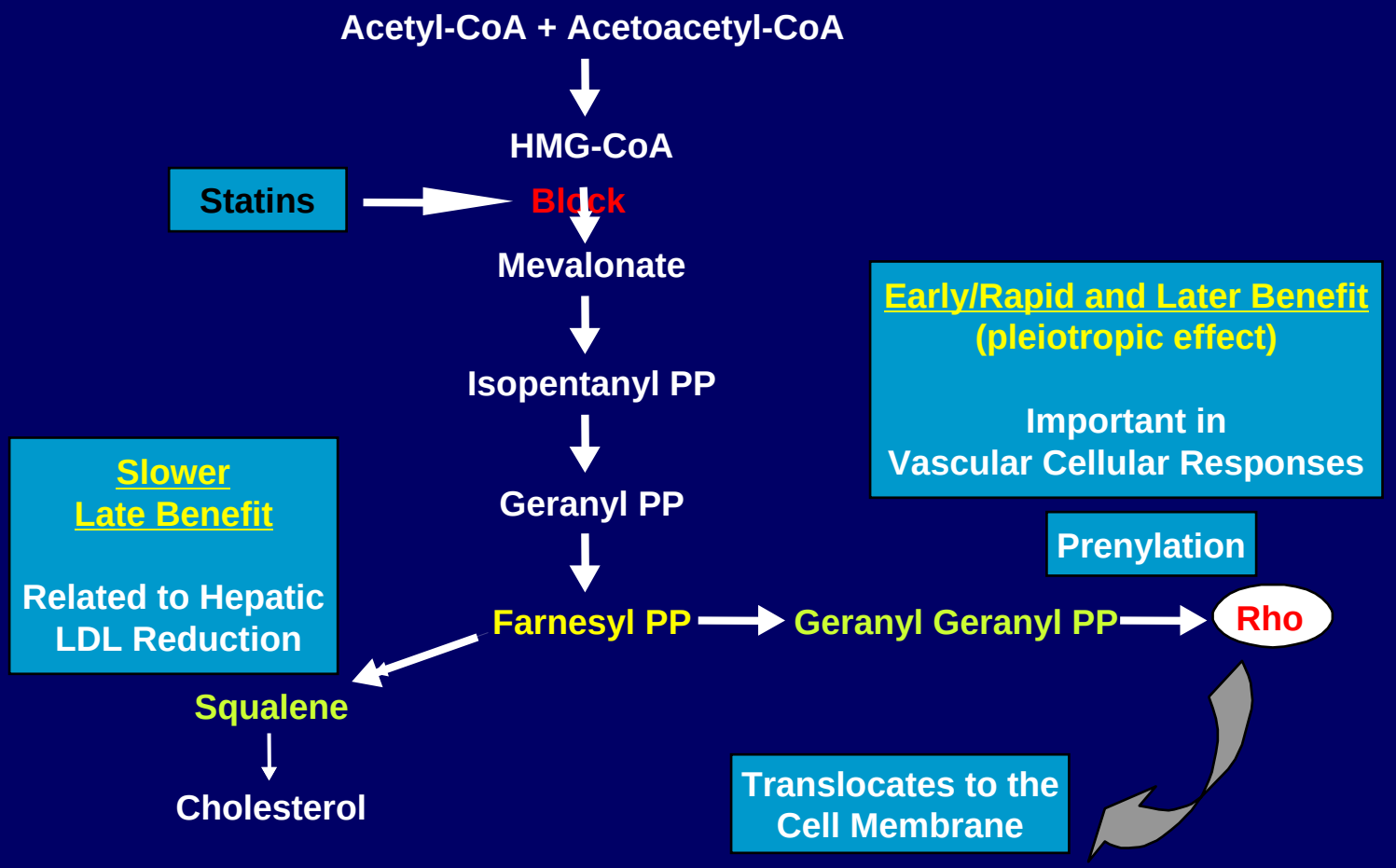
경상대학교병원
GYEONGSANG NATIONAL UNIVERSITY HOSPITAL

Metabolic Pathways blocked By Statins



PP = pyrophosphate.

Pleiotropic Effects of Statin

- Effects on VSMC growth
- Endothelial function (NO regulation)
- Atherosclerotic plaque stabilization
- Inhibition of LDL-C oxidation
- Reduced leukocyte adhesiveness
- Reduced ischemia-reperfusion injury (cardiac and cerebral)
- Enhanced angiogenesis
- Platelet inhibition and anti-thrombosis

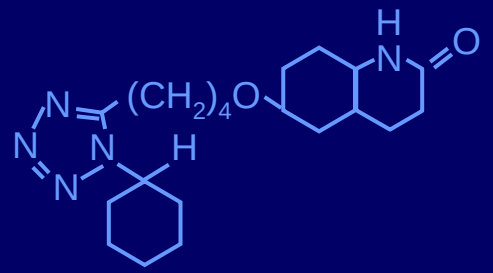
Rosensen R et al. *JAMA*. 1998;279:1643-1650; Gotto AM et al. *Curr Opin Lipidology*. 2001;12:391-394;
Maron DJ et al. *Circulation.* 2000;101:207-213; White CM. *J Clin Pharmacol*. 1999;39:111-118.

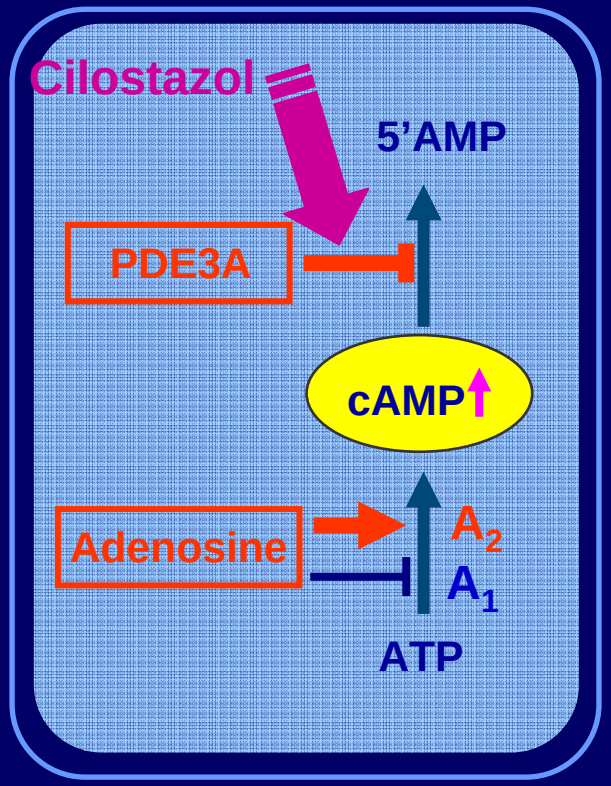
Pleiotropic Effects of *Cilostazol*

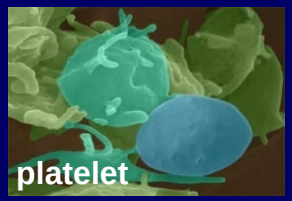
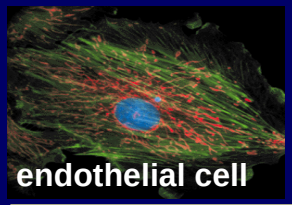
Atherosclerosis supplements 2006;6:1-52.

- **Inhibition of VSMC growth**
  Stimulation of p53 and p21 (Matsushita H. Hypertension 1998;31:493.)
- **Restoration of Endothelial dysfunction**
  Up-regulation of HGF (Aoki M. Diabetologia 2001;44:1034.)
- **Atherosclerotic plaque stabilization**
- **Reduced leukocyte adhesiveness**
  Inhibition of CAM expression (Otsuki M. Atherosclerosis 2001;158:121.)
- **Reduced ischemia-reperfusion injury (cardiac and cerebral)**
  Activation of PTEN (Kim KY, et al. JPET 2004;308:97.)
- **Enhanced angiogenesis**
- **Platelet inhibition and anti-thrombosis**

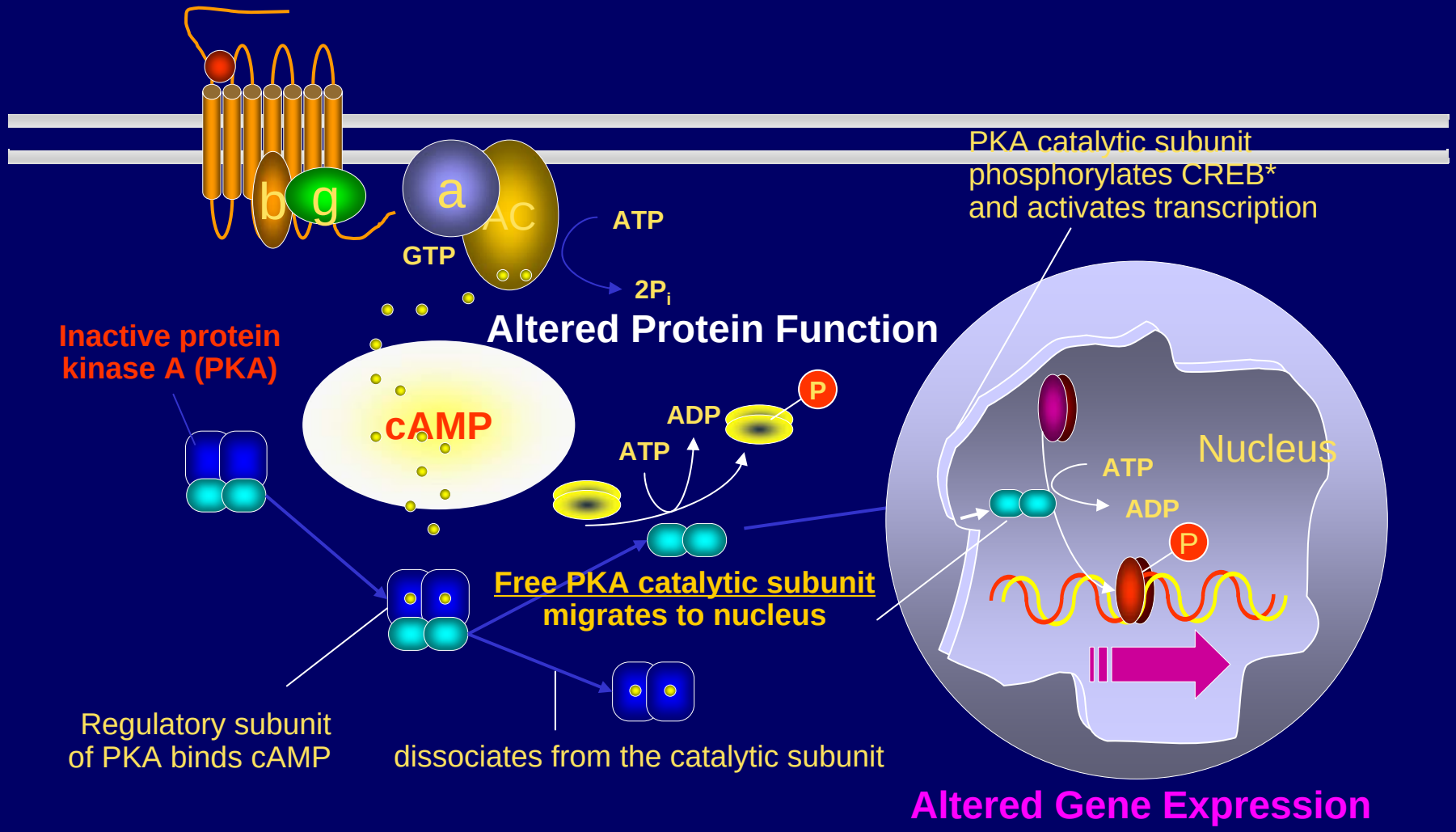
The Role of Cilostazol





Targets	cAMP actions (selected)
 platelet	• Inhibition of aggregation • Inhibition of expression of adhesion molecules
 endothelial cell	• Inhibition of expression of adhesion molecules • Angiogenesis
 smooth muscle cell	• Vasodilatory action • Inhibition of proliferation, migration and matrix synthesis • Headache
 cardiocyte	• Palpitation • Tachycardia

Role of cAMP / Protein Kinase A



- PKA can phosphorylate many different proteins depending on tissue type and status
- PKA can activate **enzymes or gene regulatory proteins**

Pleiotropic Effects of Cilostazol

Atherosclerosis supplements 2006;6:1-52.

- **Inhibition of VSMC growth**
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- **Restoration of Endothelial dysfunction**
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- **Enhanced angiogenesis**
- **Platelet inhibition and anti-thrombosis**

Antiplatelet Therapy in ACS & PCI

DAPT is the standard therapy

- **Aspirin Resistance is rare. Low dose aspirin (- 162mg/d) achieves adequate inhibition of COX-1 pathway.**

Lordkipanidze M et al. EHJ 2007;28:1702.
Gurbel PA et al. Circulation 2007;115:3156.

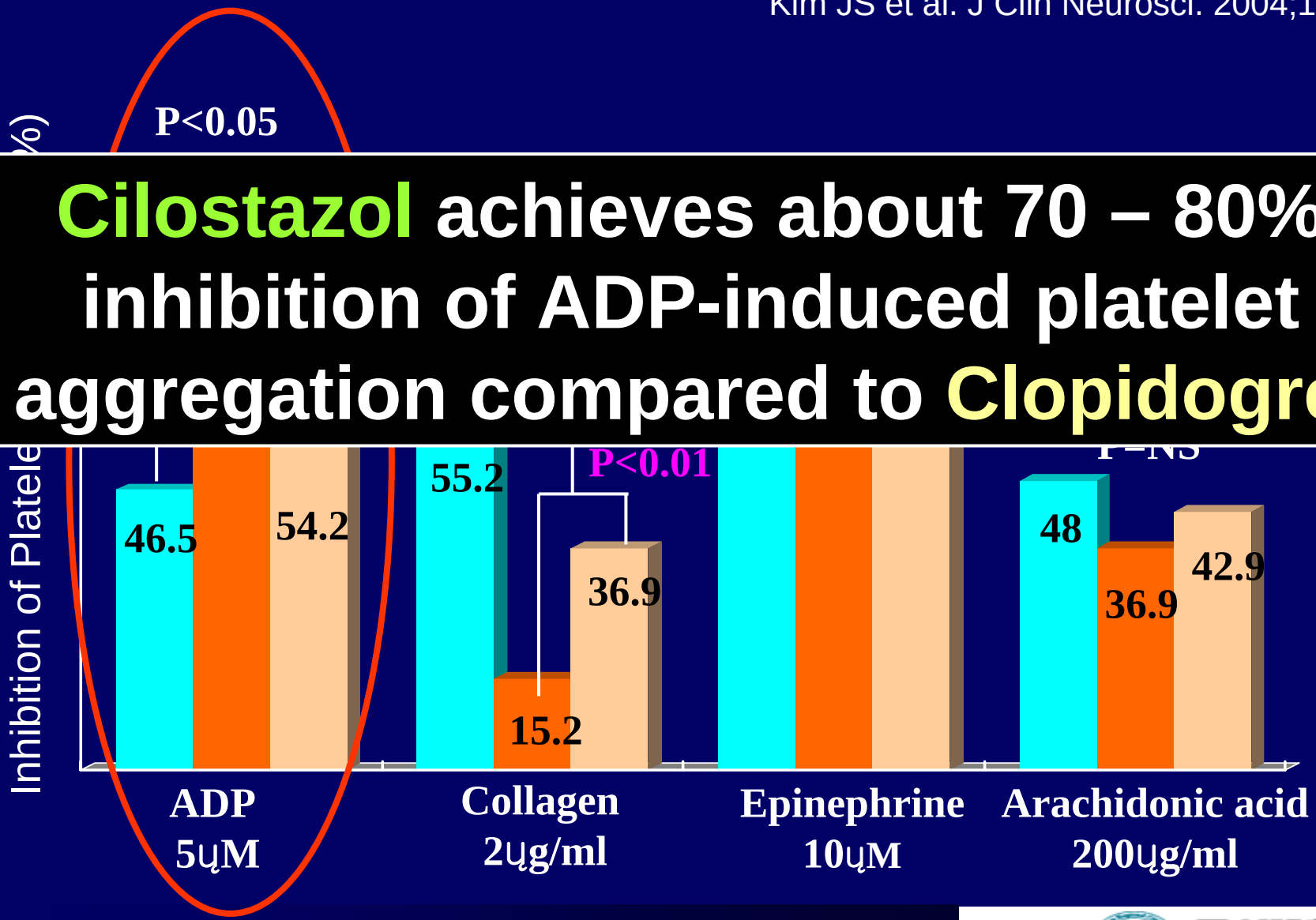
- **Clopidogrel variably inhibits ADP-induced platelet aggregation. Adequate platelet inhibition by potent P2Y12 antagonists may suppress the risk of ischemic events in pts with high risk.**

TRITON-TIMI 38. NEJM 2008;28:1702.

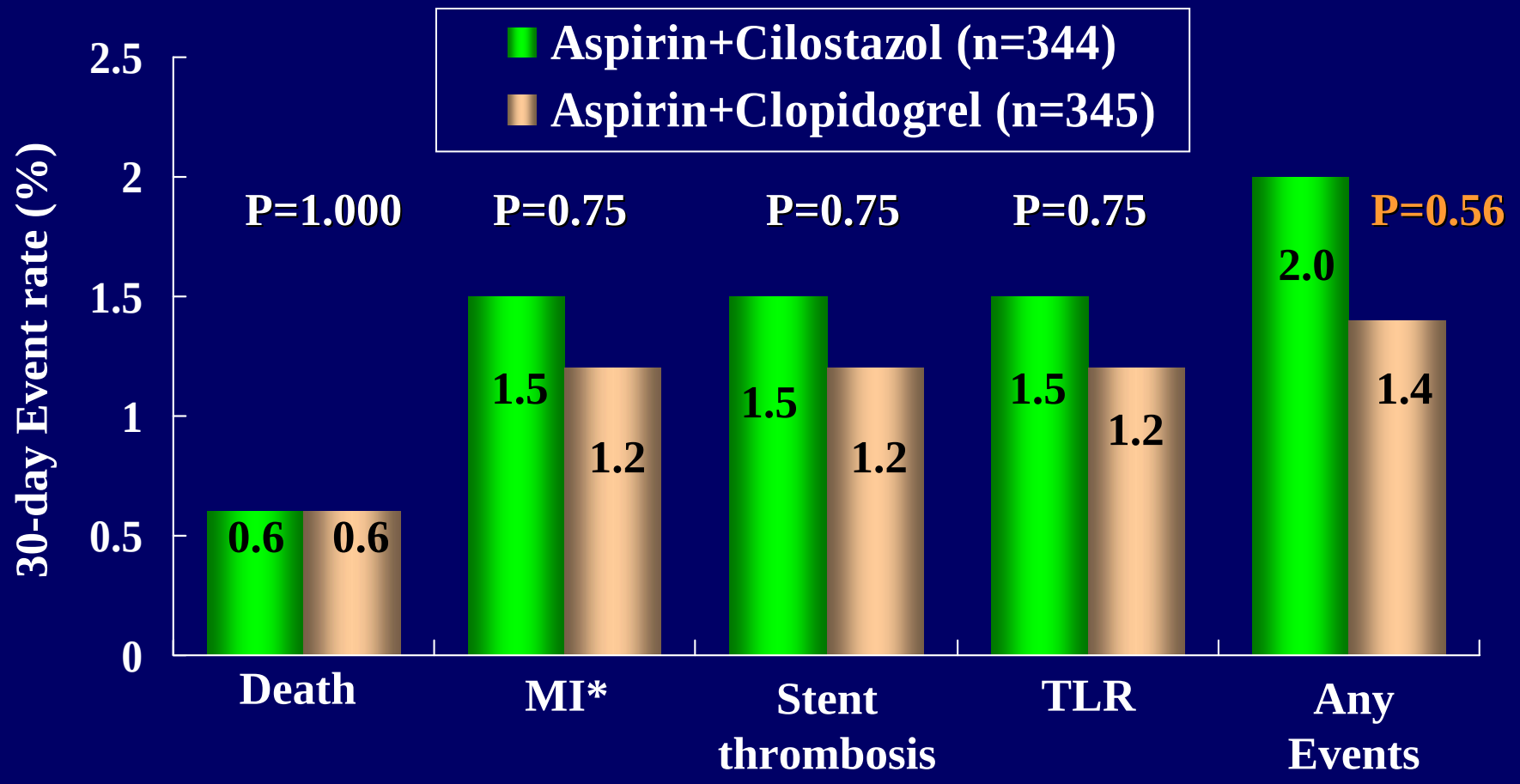
Platelet Inhibition: Asp vs CLPD vs CILO

Kim JS et al. J Clin Neurosci. 2004;11:600-2.

Cilostazol achieves about 70 – 80% inhibition of ADP-induced platelet aggregation compared to Clopidogrel



Cilostazol vs Clopidogrel Therapy After BMS Implantation



* AMI were due to stent thrombosis

Lee SW, Park SW et al. Am J Cardiol 2005;95:859.

Triple versus Dual Antiplatelet Therapy

TAPT reduces the risk of ST by 88% compared to DAPT.
It may be related with additive inhibition of ADP-induced platelet aggregation by Adjunct Cilostazol.

Predictors of stent thrombosis

1. Primary stenting for AMI
   (OR 7.9, 95% CI 2.0-30.8, p = 0.003)
2. TAPT (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.

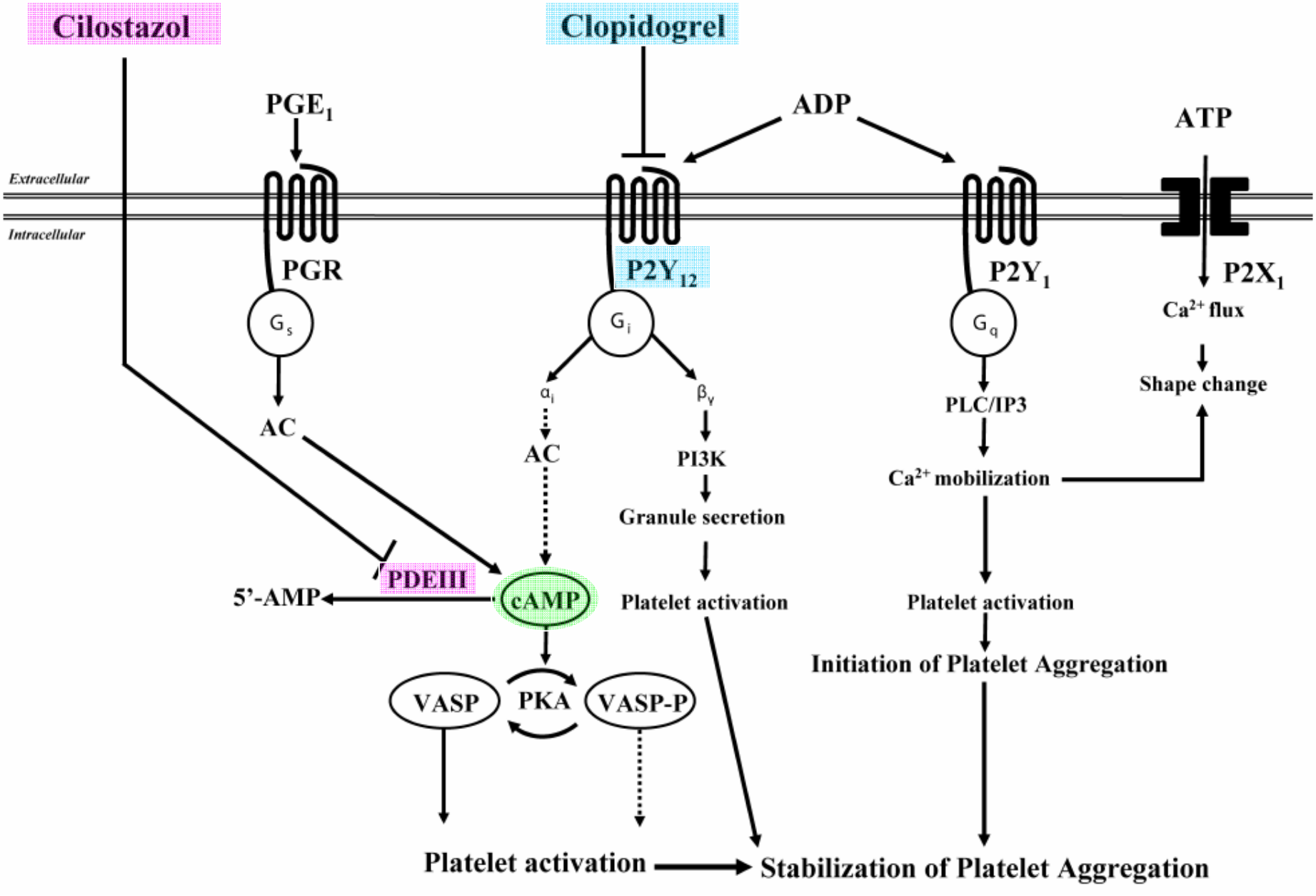
Safety of triple antiplatelet therapy

	DAPT (n=1597)	TAPT (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

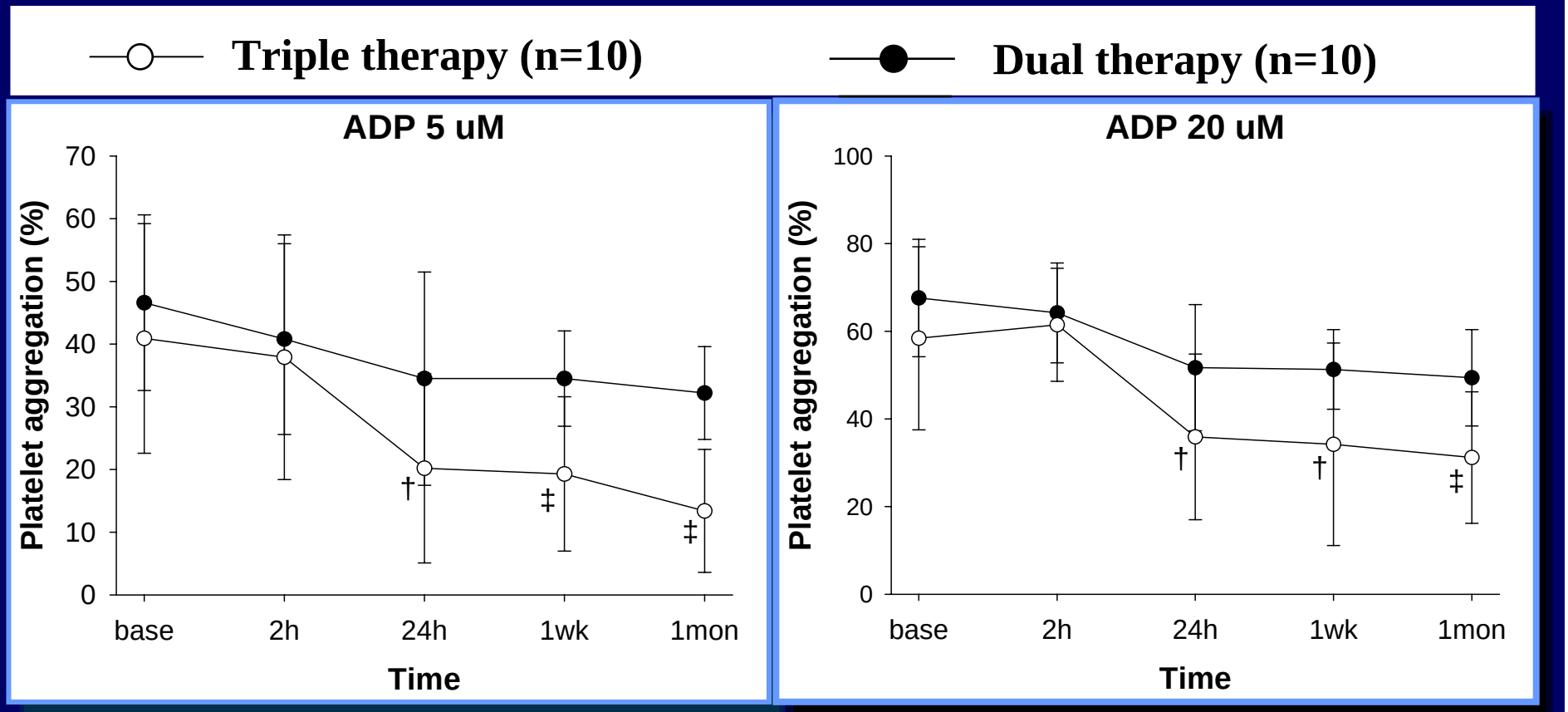
Lee SW, Park SW et al. J Am Coll Cardiol 2005;46:1833.

Postulated Modulation of P2Y12 Receptor Signalling

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



Platelet aggregation
Triple vs. Dual therapy

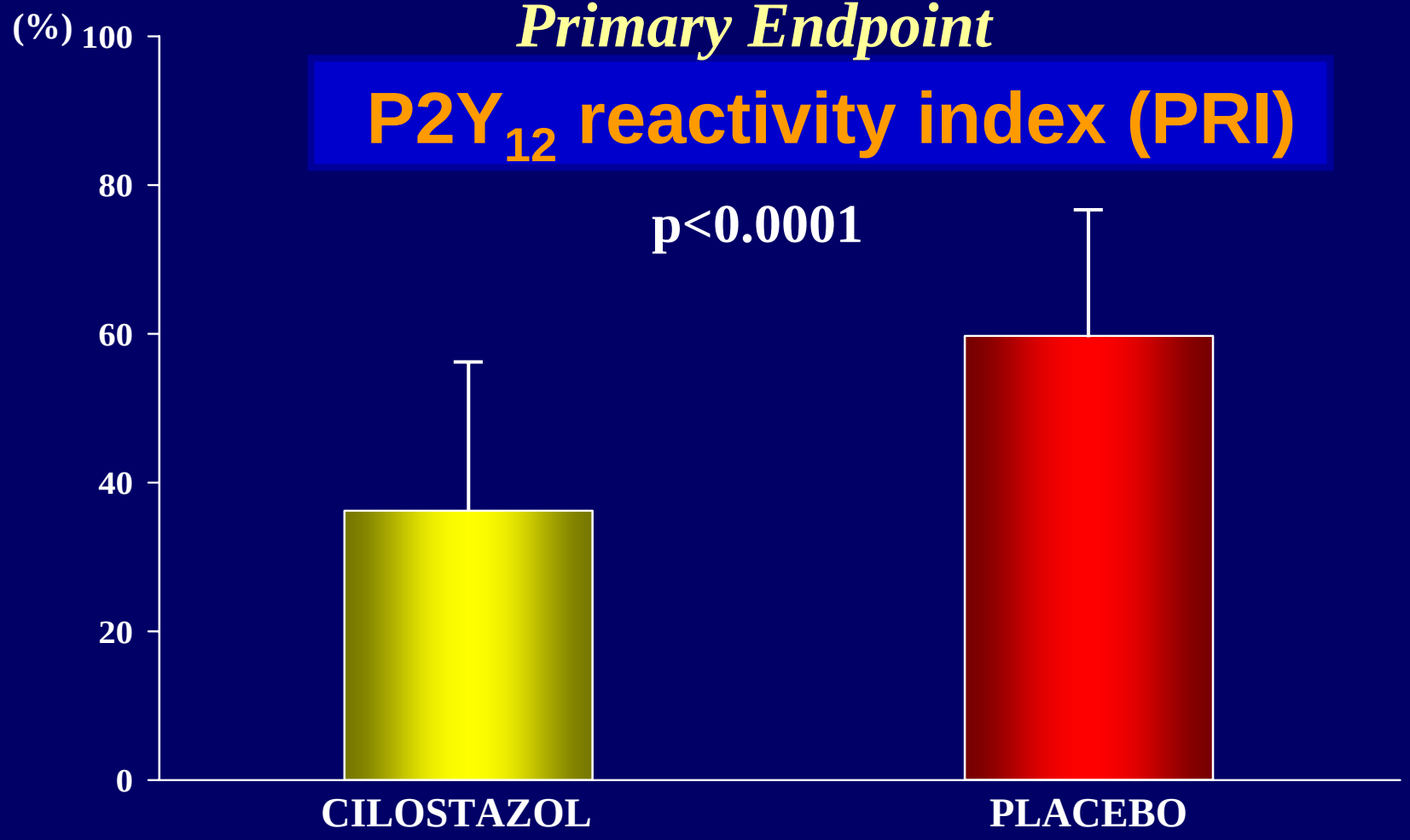


Results are expressed as the mean value ± SD.

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

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

OPTIMUS-2: *Impact of adjunctive cilostazol in Diabetes Mellitus patients on aspirin and clopidogrel*

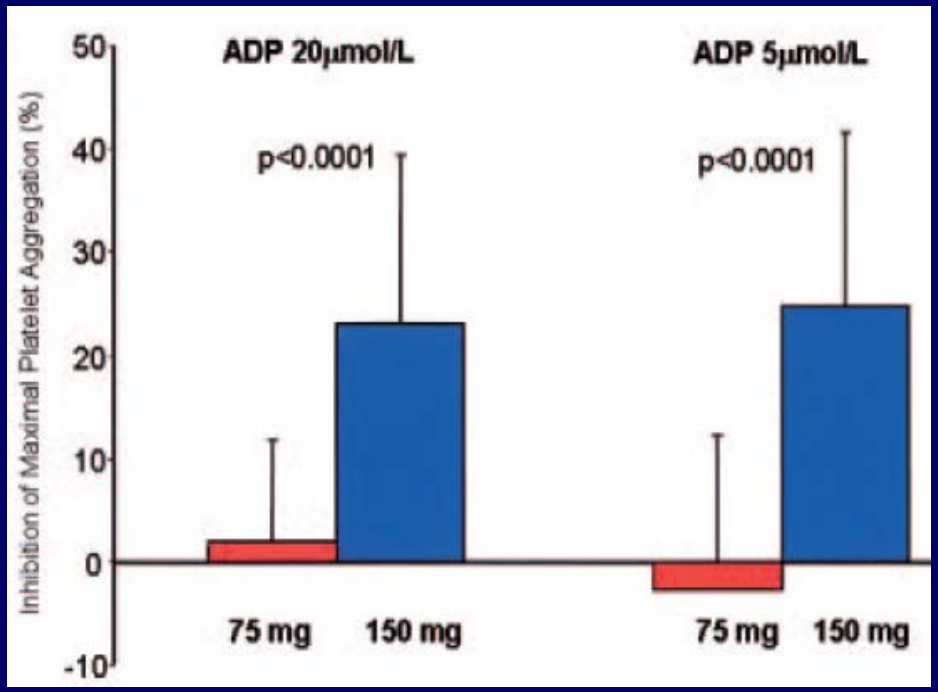


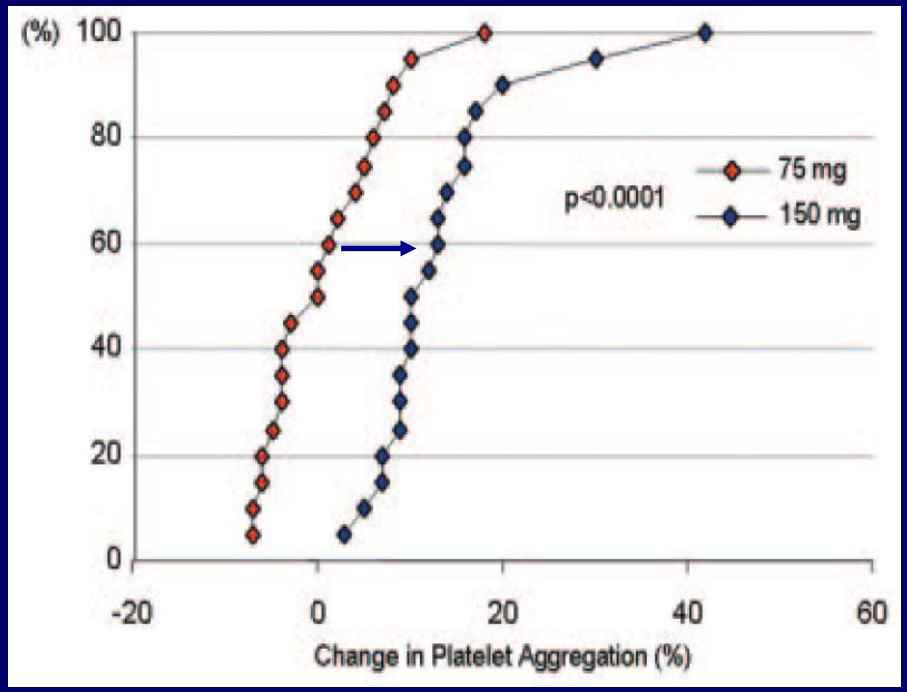
Angiolillo DJ et al. Eur Heart J 2008; 29:2202.

High MD Clopidogrel of 150mg/d in DM Pts

OPTIMUS-1 study

40 suboptimal responders (20μmol/L ADP-induced Agg_{max} > 50%) with DM





- A 150-mg MD of clopidogrel is associated with enhanced antiplatelet effects compared with 75-mg in high risk T2DM pts.
- Suboptimal clopidogrel response is still present in 60% pts of 150mg regimen.

Angiolillo DJ et al. Circulation 2007;115:708.

ADP-induced platelet inhibition in patients with high risk?

High MD CLPD vs. TAPT

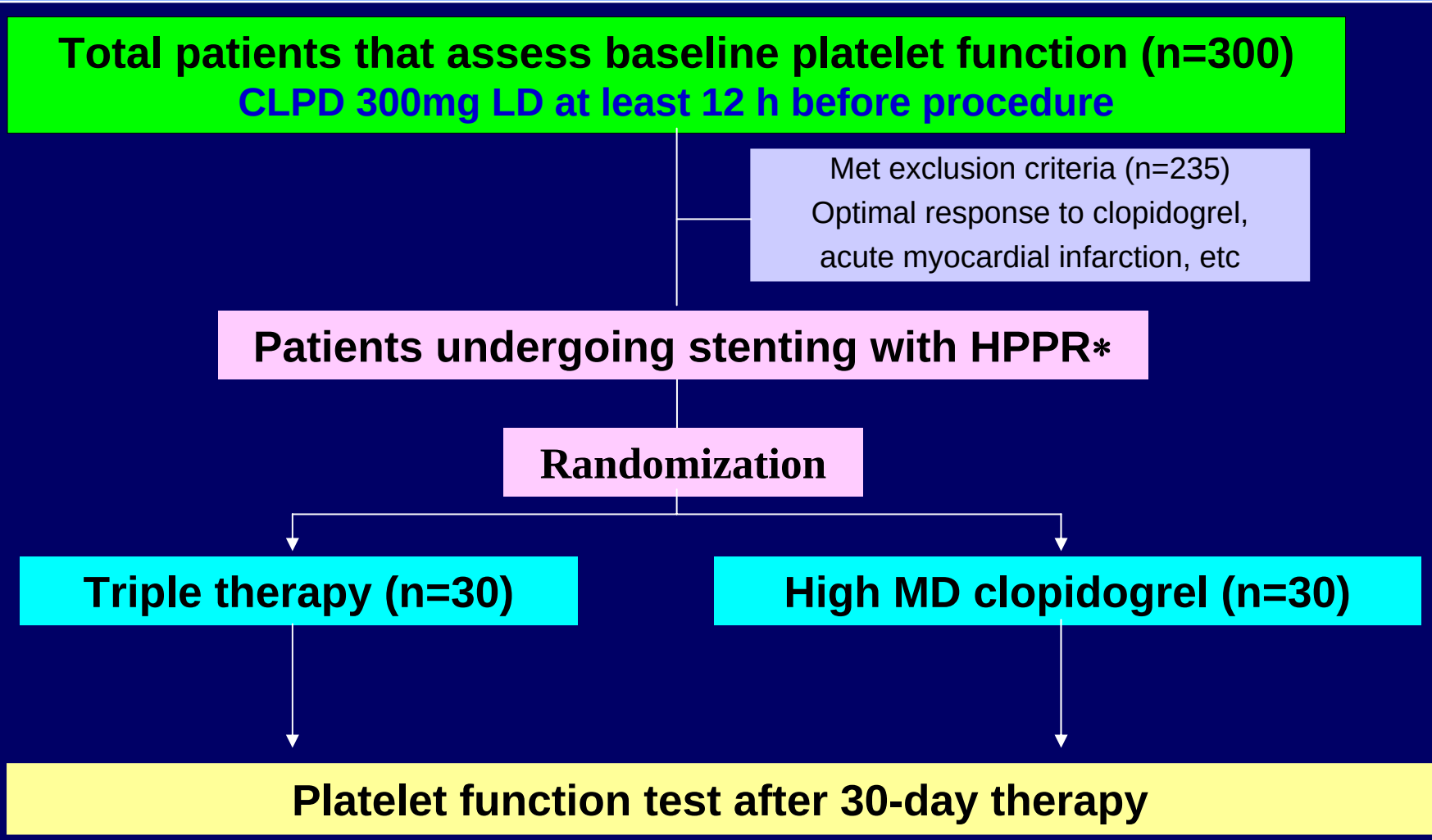
HPPR: High Post-treatment Platelet Reactivity

1. ADP-induced platelet inhibition in patients with HPPR?

High MD CLPD vs. TAPT

*A*djunctive *C*ilostazol vs. high-MD *C*lopidogr*EL* in HPPR (ACCEL study)

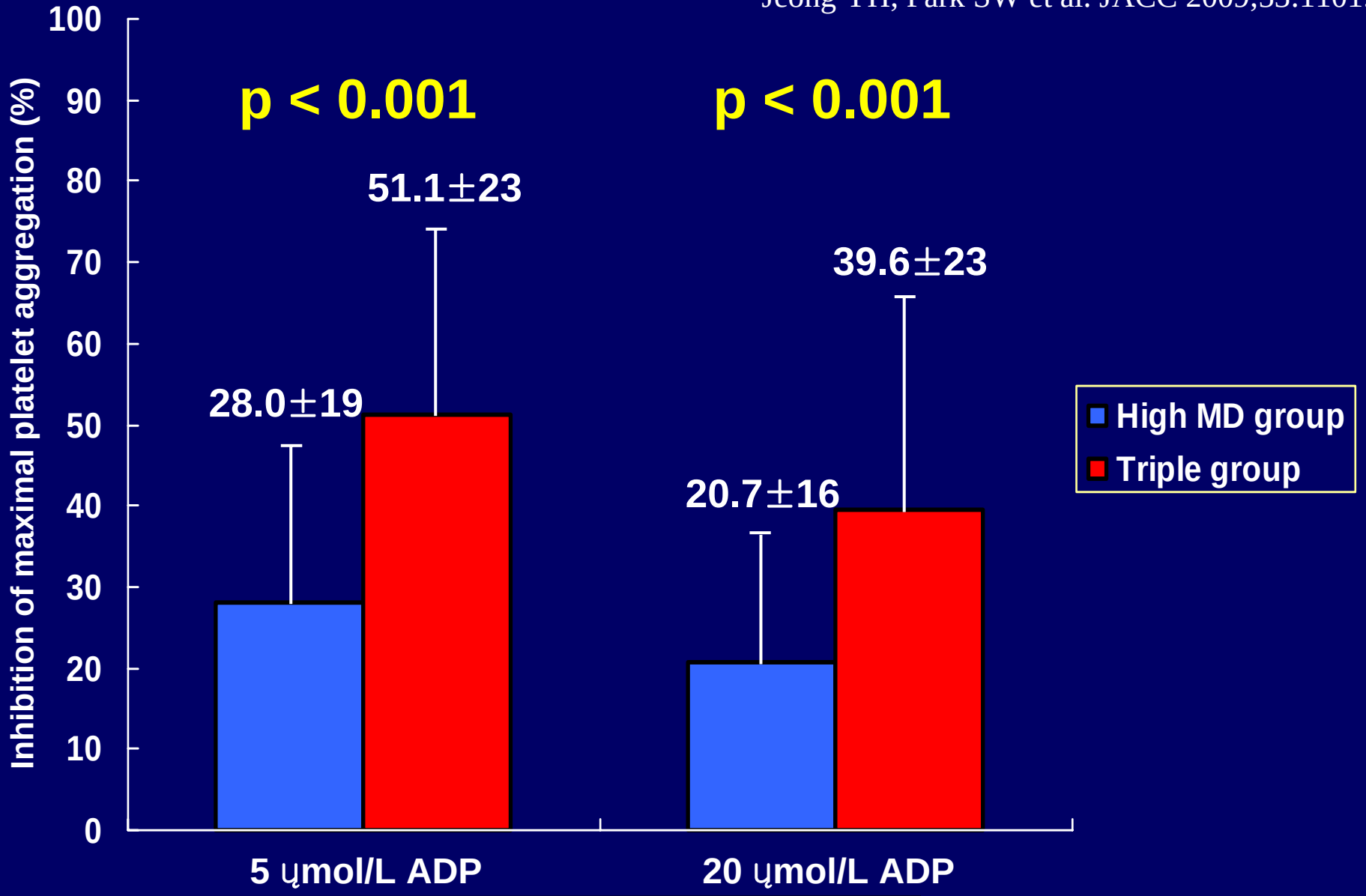
∗High Post-CLPD Platelet Reactivity (HPPR) : maximal aggregation > 50% with 5 ㎛M ADP



Jeong YH, Park SW et al. JACC 2009;53:1101.

IPA of Agg_{max}

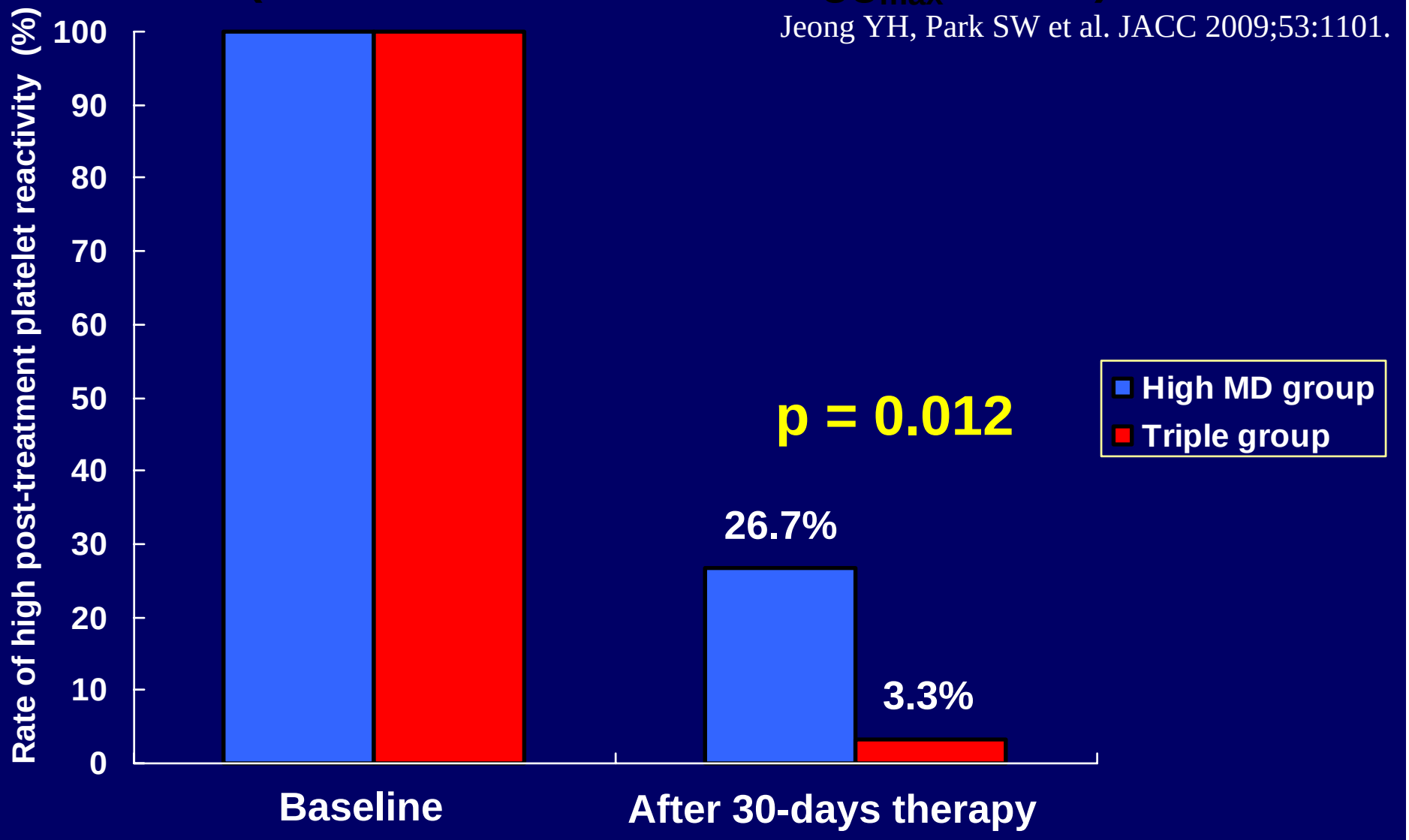
Jeong YH, Park SW et al. JACC 2009;53:1101.



Rate of HPPR

(5 μmol/L ADP-induced Agg_{max} > 50%)

Jeong YH, Park SW et al. JACC 2009;53:1101.



Randomized Comparison of Adjunctive Cilostazol Versus High Maintenance Dose Clopidogrel in Patients With High Post-Treatment Platelet Reactivity

Results of the ACCEL-RESISTANCE (Adjunctive Cilostazol versus High Maintenance Dose Clopidogrel in Patients With Clopidogrel Resistance) Randomized Study

Young-Hoon Jeong, MD, PHD,* Seung-Whan Lee, MD, PHD,‡ Bong-Ryong Choi, MD,*
In-Suk Kim, MD, PHD,† Myung-Ki Seo, MD,* Choong Hwan Kwak, MD, PHD,*
Jin-Yong Hwang, MD, PHD,* Seong-Wook Park, MD, PHD‡

Jinju and Seoul, Korea

Objectives The purpose of this study was to determine the impact of adjunctive cilostazol in patients with high post-treatment platelet reactivity (HPPR) undergoing coronary stenting.

Adjunctive Cilostazol
reduces the rate of HPPR &
intensifies platelet inhibition
as compared with high-MD clopidogrel

Conclusion Adjunctive cilostazol reduces the rate of HPPR and intensifies platelet inhibition as compared with a high-MD clopidogrel of 150 mg/day. (J Am Coll Cardiol 2009;53:1101–9) © 2009 by the American College of Cardiology Foundation

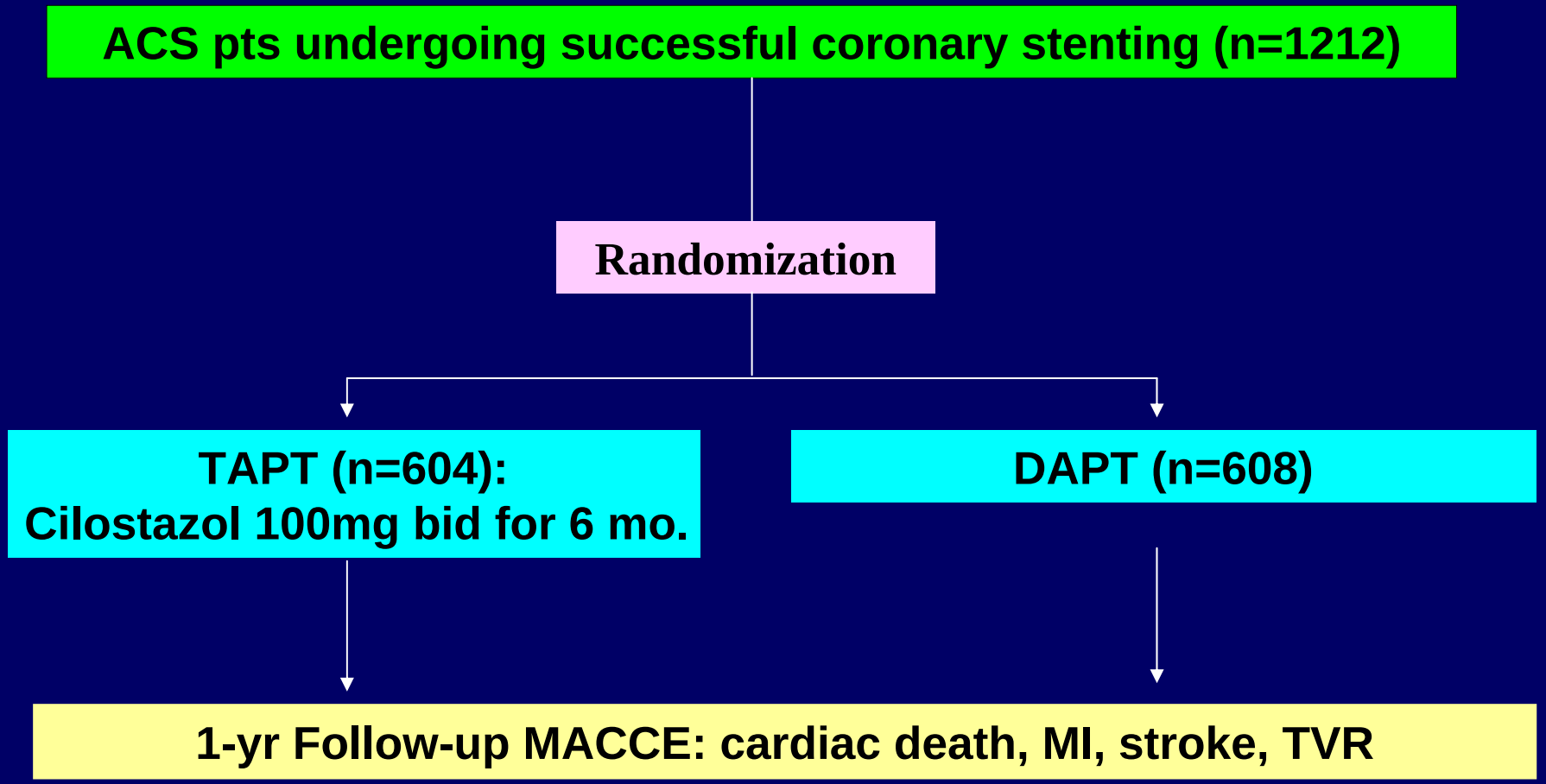
Summi

학교병원

2. ADP-induced platelet inhibition in patients with AMI?

High MD CLPD vs. TAPT

TAPT vs. DAPT in pts with ACS



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

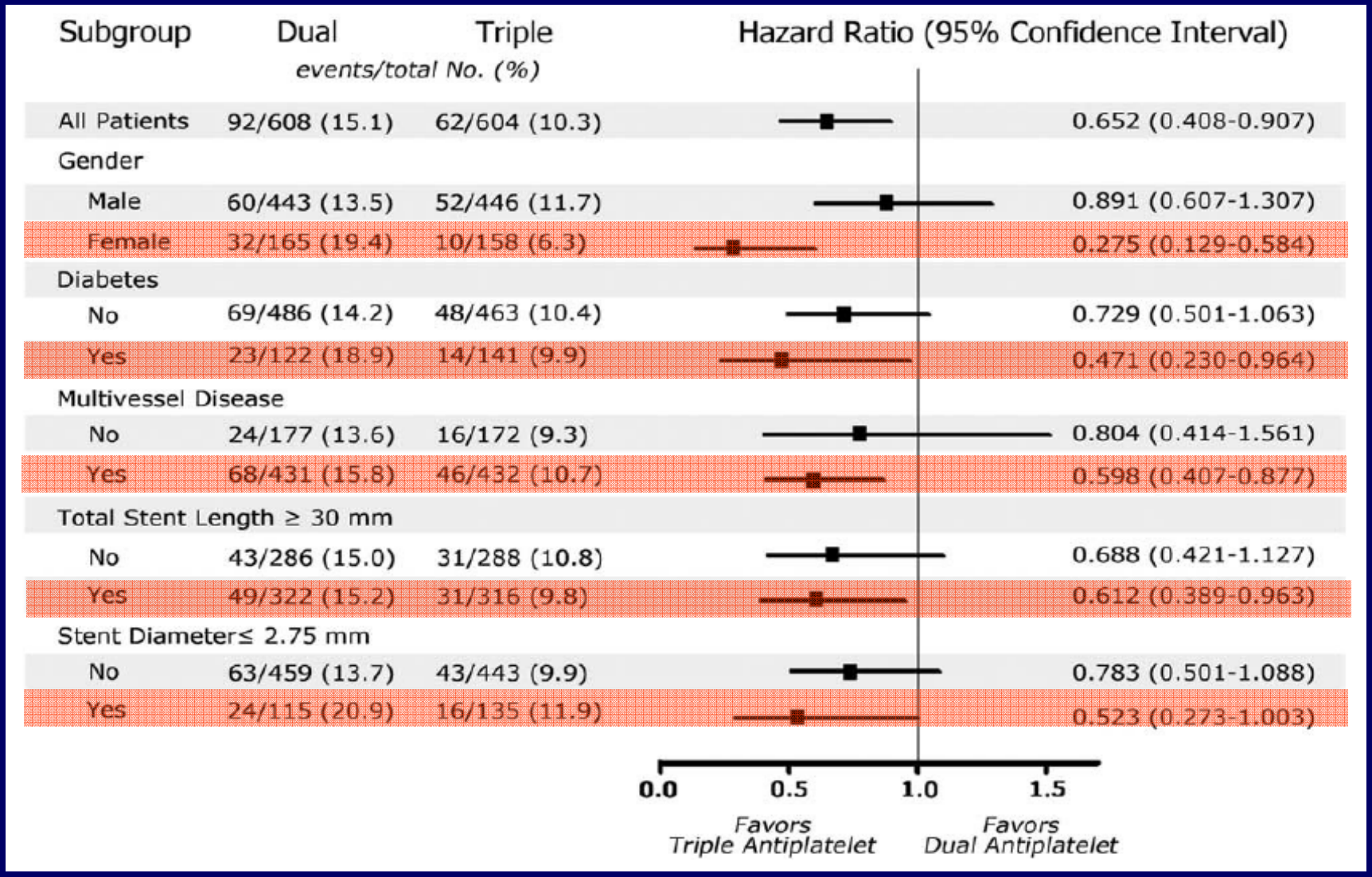
One-year Clinical Outcomes

	DAPT (n=608)	TAPT (n=604)	*p*
Cardiac death	20 (3.3%)	10 (1.7%)	0.067
MI	4 (0.7%)	2 (0.3%)	0.687
Stroke	10 (1.6%)	4 (0.7%)	0.109
TVR	63 (10.4%)	47 (7.8%)	0.118
Cardiac death, MI, stroke	**31 (5.1%)**	**16 (2.6%)**	**0.027**
MACCE	**92 (15.1%)**	**62 (10.3%)**	**0.011**

The rate of CV death, MI, stroke in ACS pts
TAPT vs. DAPT: 2.6% vs. 5.1%, OR 0.51

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

Key Subgroup Analysis



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

One-year Major Side Effects

	DAPT (n=608)	TAPT (n=604)	*p*
Major bleeding	**1 (0.2%)**	**0 (0%)**	**0.500**
GI disorder	3 (0.5%)	2 (0.3%)	1.000
Palpitation	2 (0.3%)	21 (3.5%)	<0.001
Headache	3 (0.5%)	17 (2.8%)	0.002
Skin rash	5 (0.8%)	14 (2.3%)	0.036
Discontinuation of Cilostazol	-	**16 (2.6%)**	-

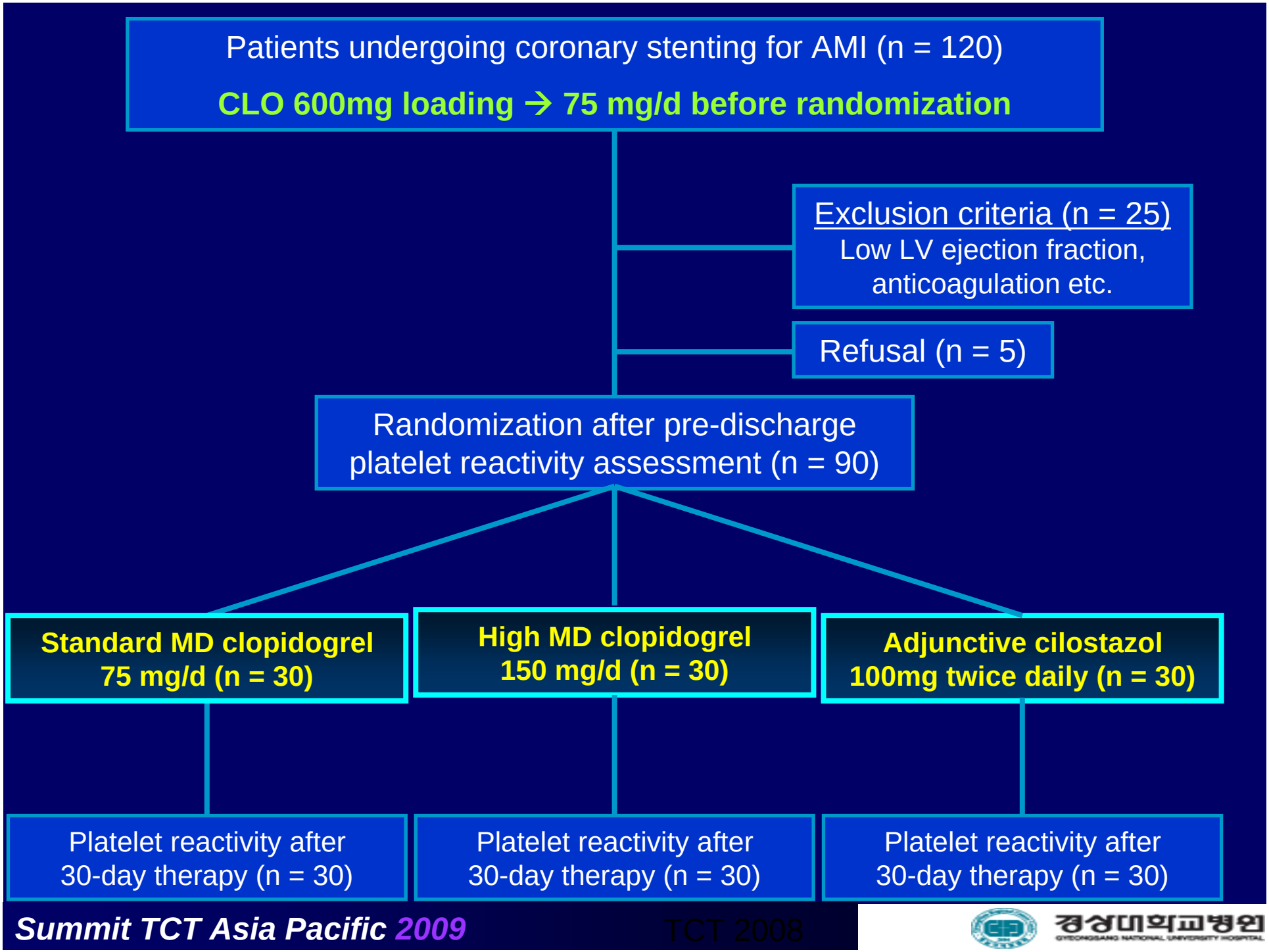
Han Y, et al. Am Heart J 2009;157:733.

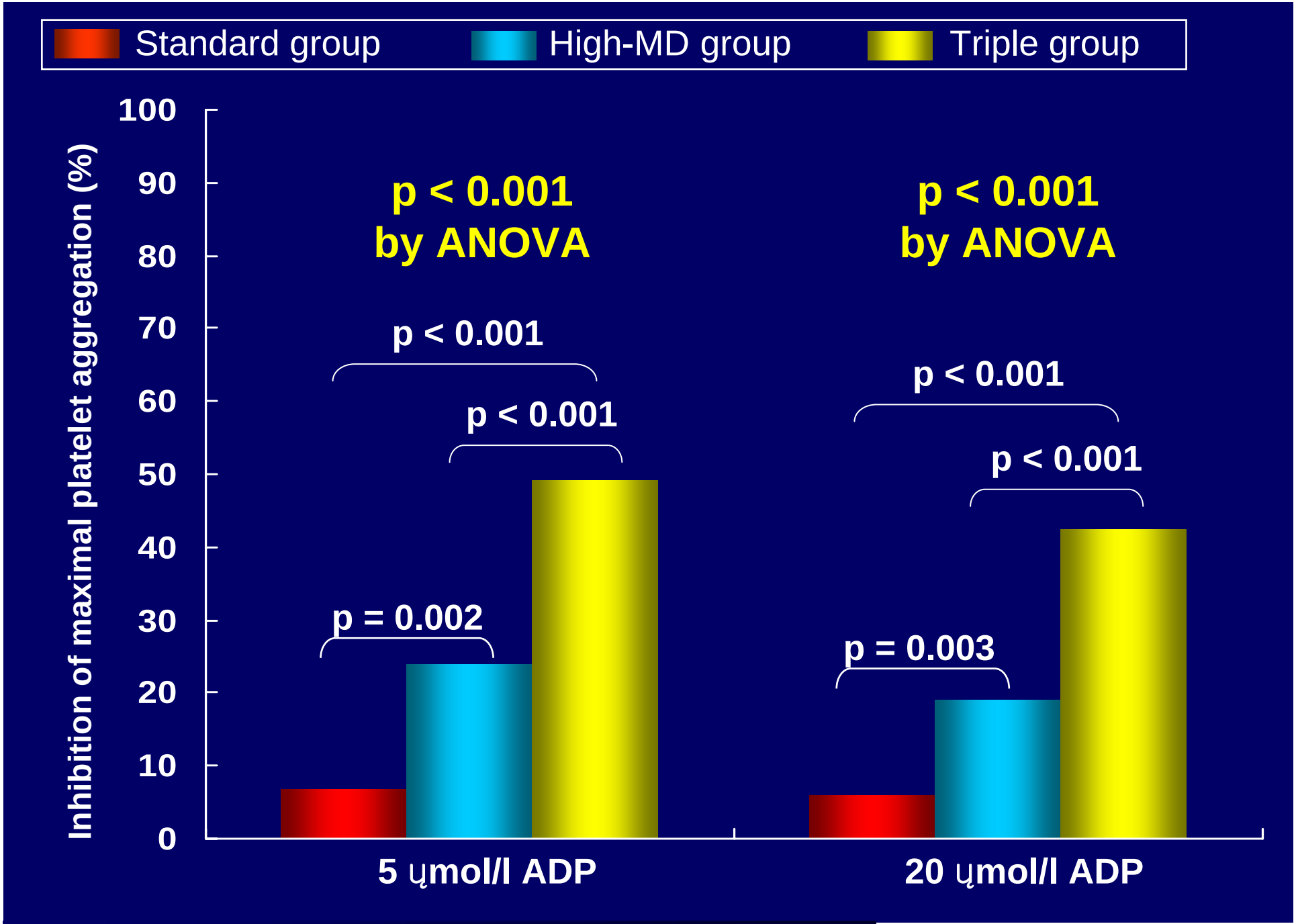
*A*dding Cilostazol to DAPT Achieves Greater Platelet Inhibition than High-MD Clopidogrel in Patients with AMI

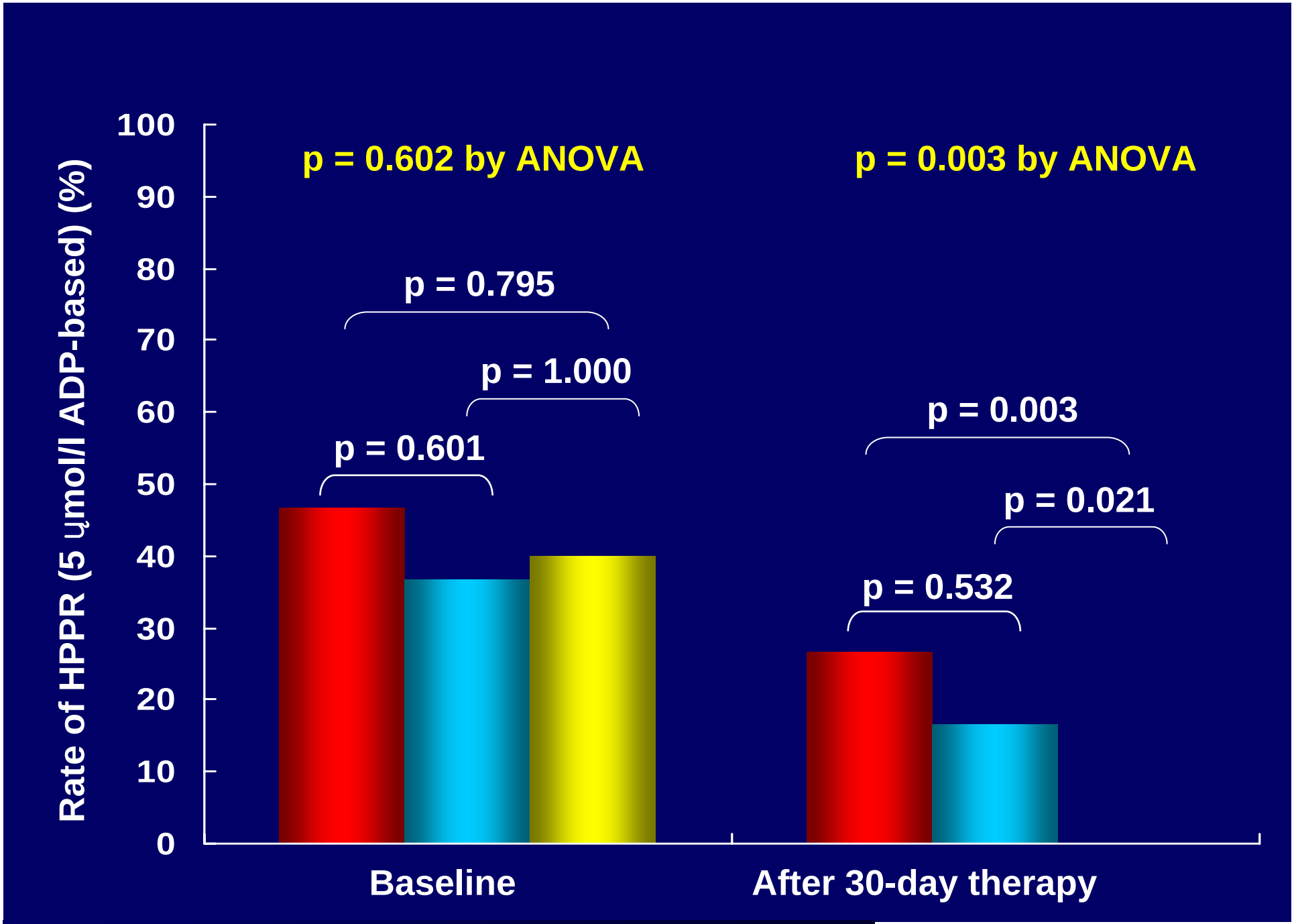
(***A***djunctive ***C***ilostazol versus high MD ***C***lopidogr***EL*** in patients with ***AMI***)

Young-Hoon Jeong,[1] Jin-Yong Hwang,[1] Younghwi Park,[1] Seok-Jae Hwang,[1] In-Suk Kim,[1] Choong Hwan Kwak,[1] Seung-Whan Lee,[2] 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-day therapy (n = 30)
Platelet reactivity after 30-day therapy (n = 30)
Platelet reactivity after 30-day 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 = 0.002
p < 0.001
p < 0.001
p = 0.003
5 μmol/l ADP
20 μmol/l ADP


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 = 0.795
p = 1.000
p = 0.601
p = 0.003 by ANOVA
p = 0.003
p = 0.021
p = 0.532
Baseline
After 30-day therapy

3. ADP-induced platelet inhibition in patients with Complex lesion or DM?

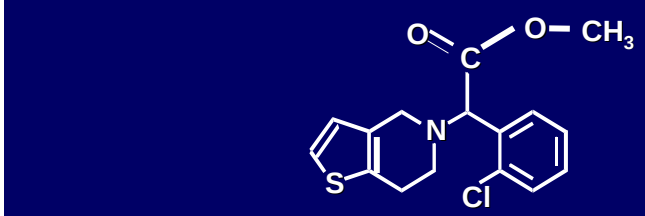
High MD CLPD vs. TAPT: Enrollment was completed

4. ADP-induced platelet inhibition in patients with 2C19 polymorphism?

High MD CLPD vs. TAPT

Clopidogrel Response Variability: Change the Agent?

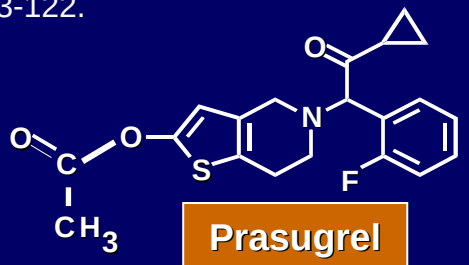
Herbert JM, Savi P. *Sem Vasc Med.* 2003;3:113-122.



Clopidogrel

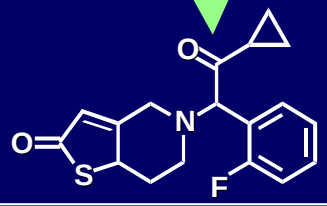
Pro-drug

Hydrolysis



Prasugrel

Esterases (hCE2)



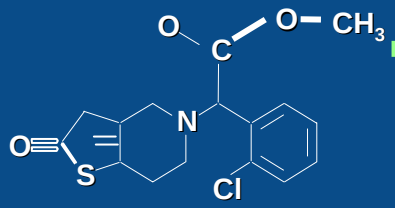
R-95913 (Thiolactone)

Esterases (hCE1) **(85-90% Inactive Metabolites)**

Oxidation **(Cytochrome P450)**

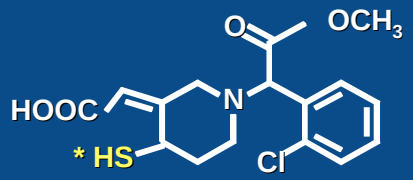
3A
2B6

1A2
2C19
2B6

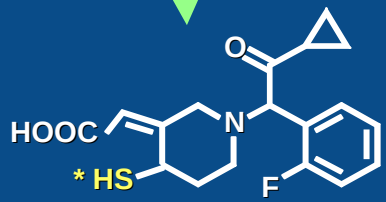


2-oxo-clopidogrel (Thiolactone)

3A
2C9
2C19
2B6



Active Metabolite



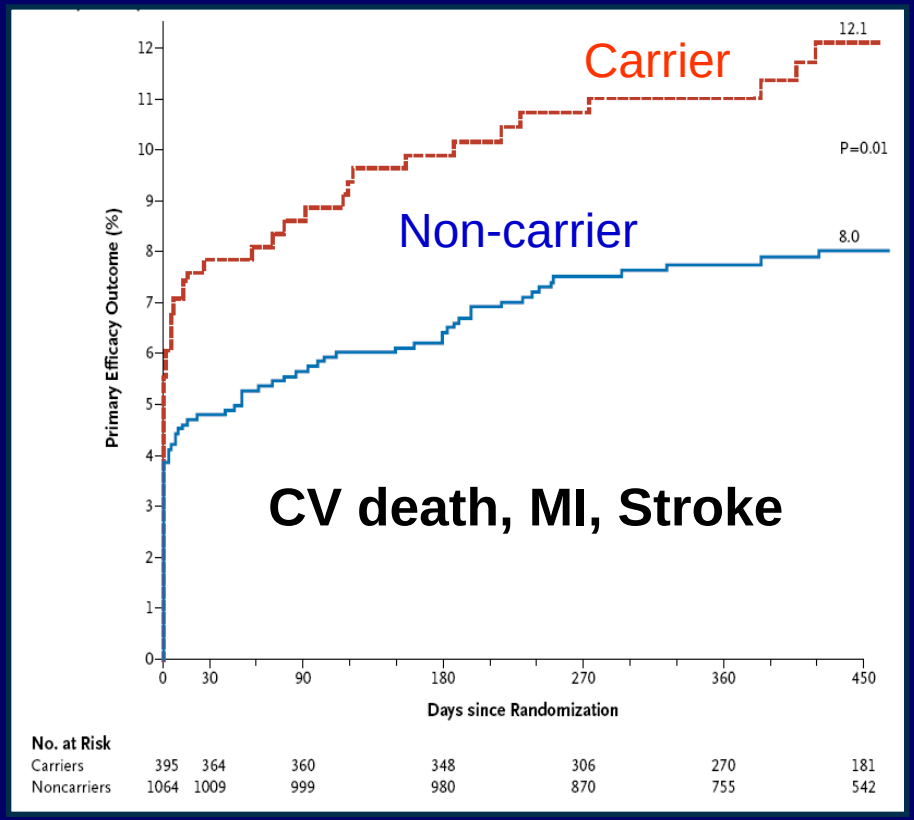
Active Metabolite

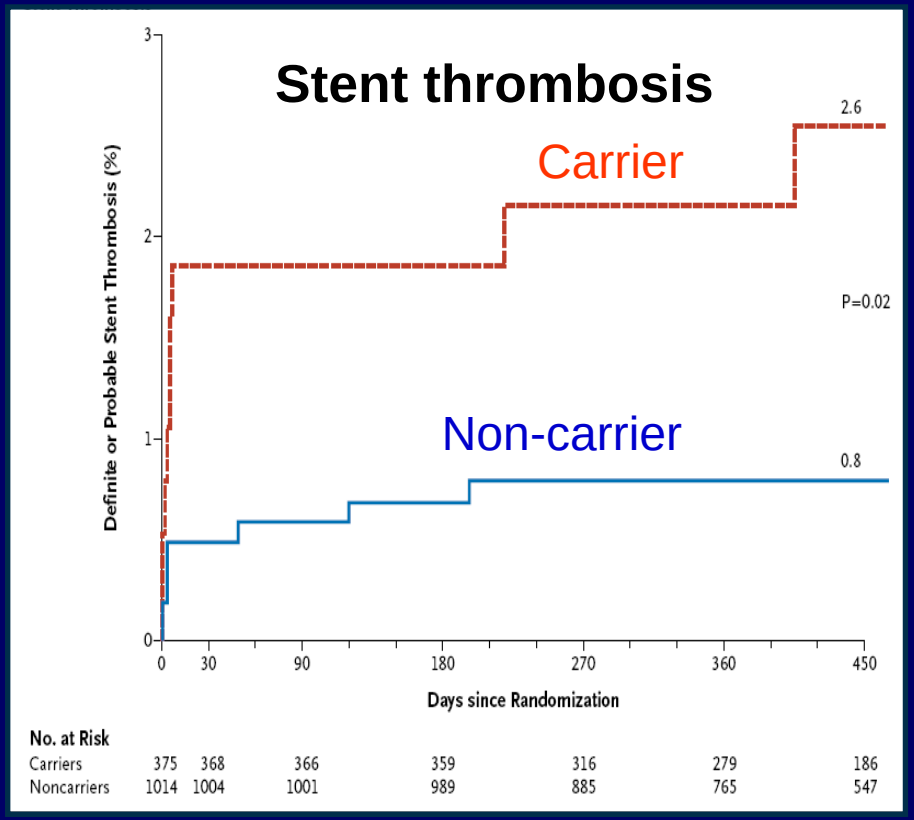
R-138727

The impact of CYP450 Polymorphism in ACS pts on-clopidogrel

Substudy of TRITON-TIMI 38

2C19 mutant allele: Carrier vs. Non-Carrier





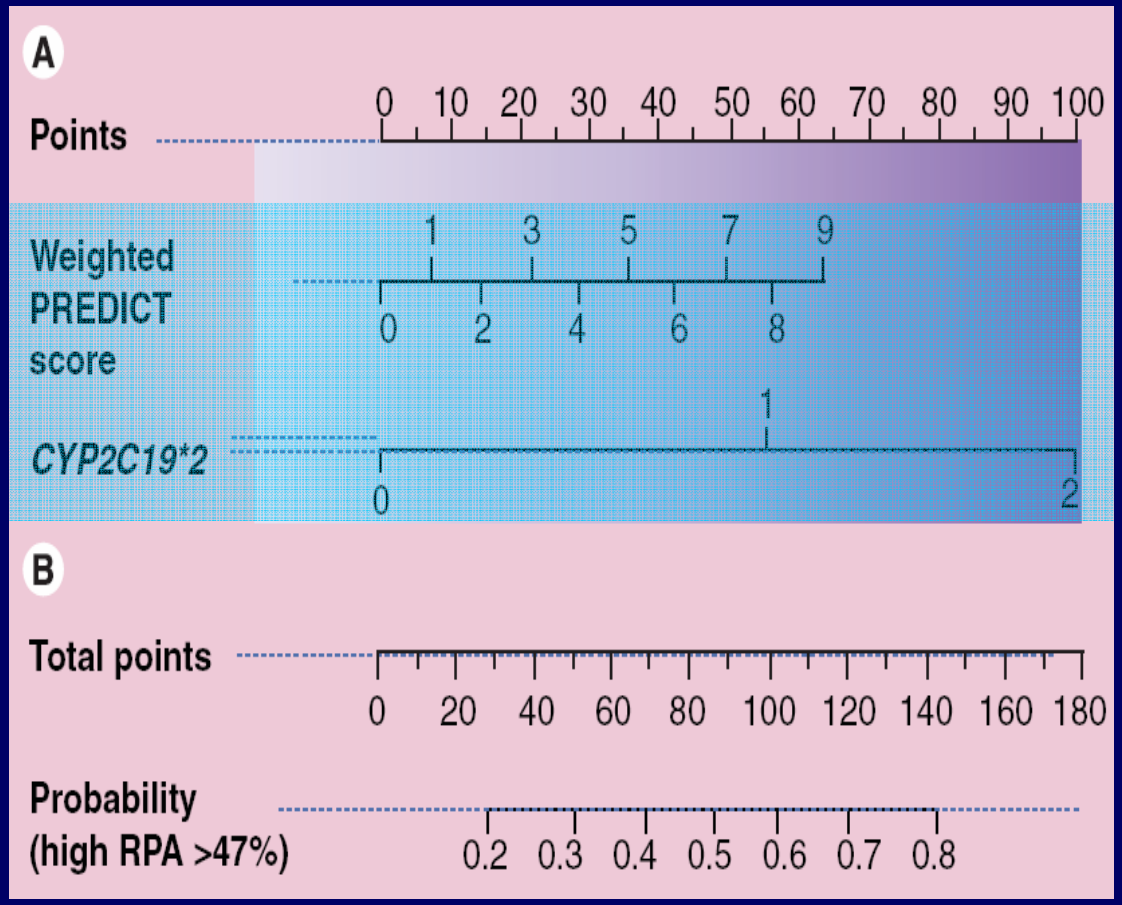
HR 1.53, 95% CI 1.07-2.19, P=0.01

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

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

Risk of HPPR after CLPD LD 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.

*The CYP2C19*2* and *CYP2C19*3* polymorphisms are associated with high post-clopidogrel platelet reactivity in acute myocardial infarction

Kim IS,* Jeong YH,† et al.

***Department of Laboratory Medicine,**
†Division of Cardiology, Department of Internal Medicine,
Gyeongsang National University Hospital, Jinju

J Thromb Haemost 2009;E-pub.

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%**		

Racial difference of CYP2C19 polymorphism

- **Few CYP2C19*3 gene in whites**
- **Whites 20-30% vs. East Asian 55-65%**

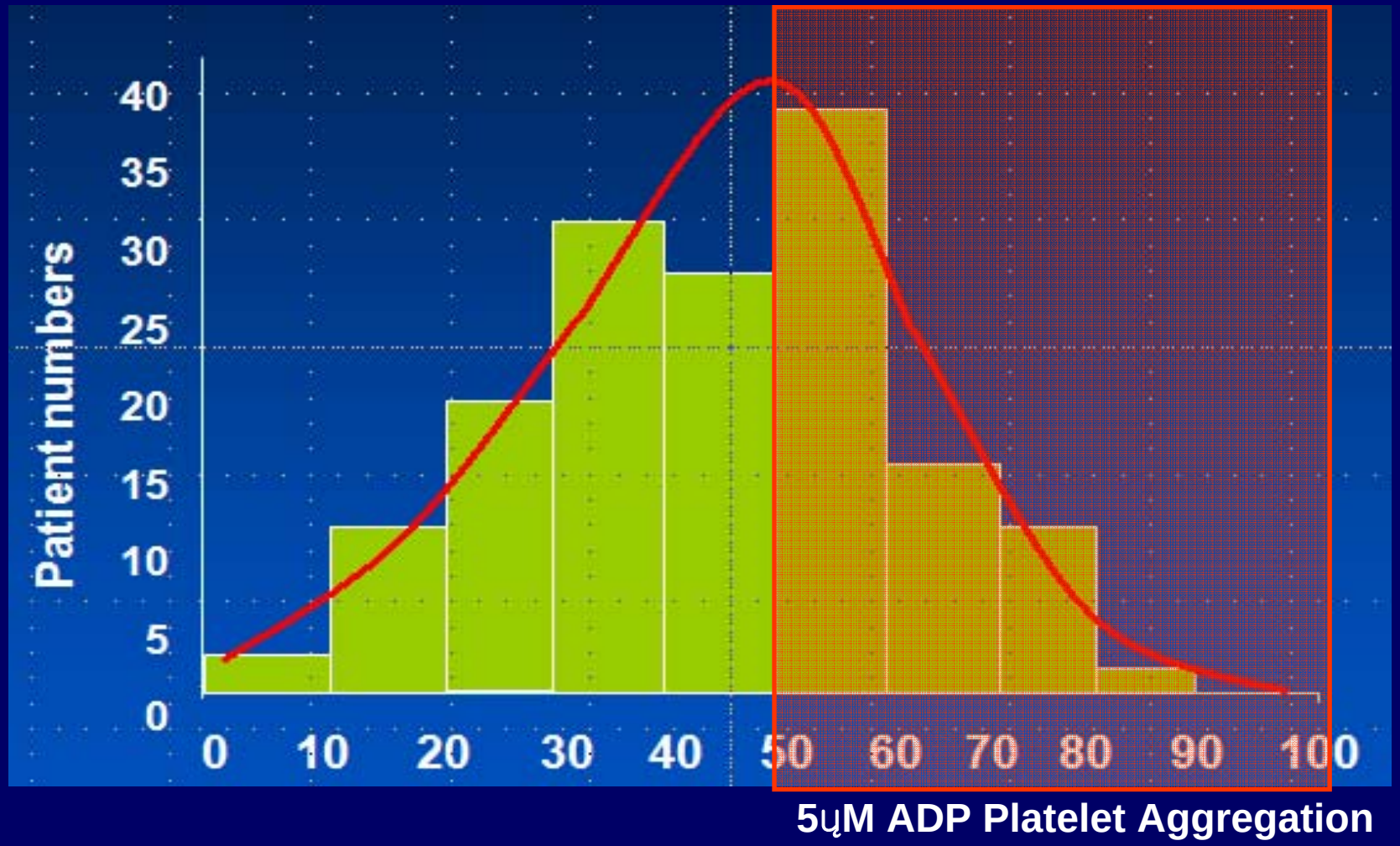
♣ **Higher prevalence of HPPR in East Asian People ?**

HPPR: *5μmol/L ADP induced MPA >50%*

J Thromb Haemost 2009;E-pub.

Variability of Platelet aggregation in chronic CLPD of 75mg/d (≥ 6 mo.)

East Asian patients with Coronary artery stent (n = 164)



- **Up to 42% of pts** taking Plavix® have suboptimal inhibition.

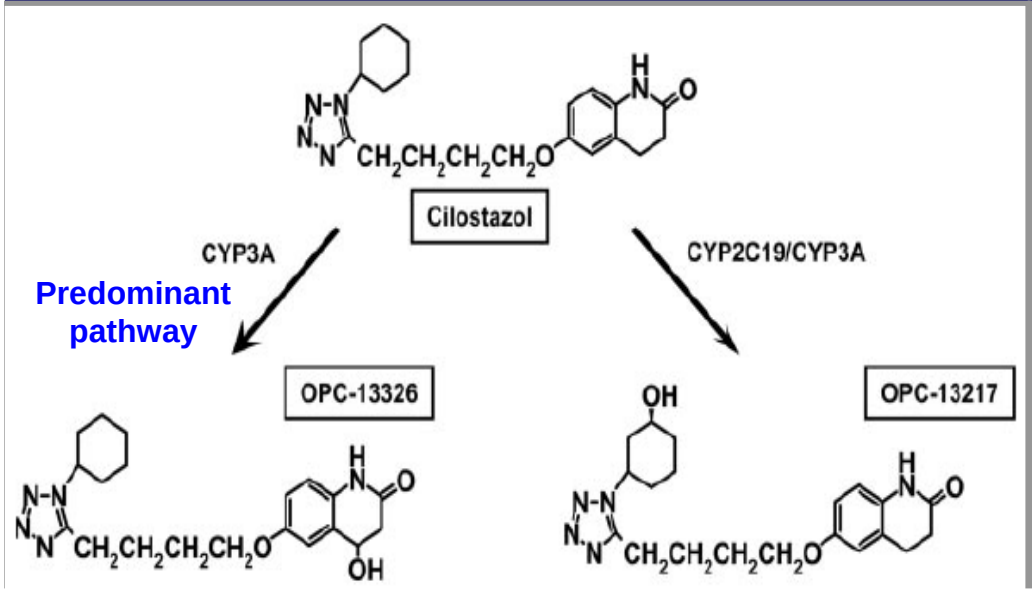
How to overcome the effect of the loss-of-function 2C19 mutant allele ?

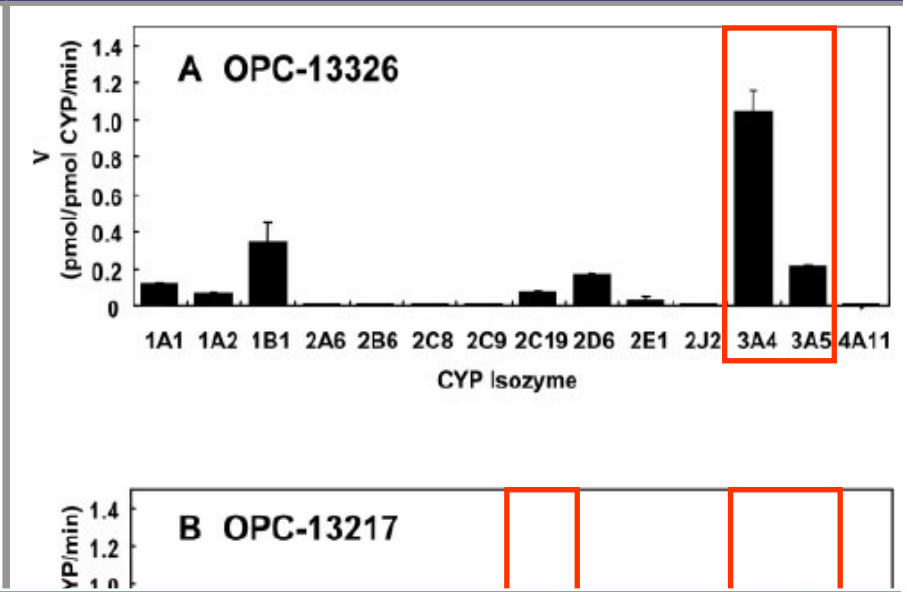
1. High MD CLPD

2. Novel P2Y12 antagonist

3. Adjunctive cilostazol (TAPT)

Metabolic Pathway of Ciolstazol





Cilostazol are mainly activated by CYP3A4/5 System

Potency of OPC 13015: X 3 of cilostazol

Potency of OPC 13213: X 1/3 of cilostazol

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

Effect of High MD CLPD vs. TAPT according to CYP2C19 genotyping

92 patients undergoing elective coronary stenting (preliminary data)

Non-carrier of CYP2C19 mutant allele (*1/*1)

	High MD CLPD	TAPT	P value
30 day rate of HPPR	11%	67%	0.018

In non-carriers of CYP2C19 mutant allele, TAPT and high-MD CLPD significantly enhance inhibition of platelet reactivity and reduce the rate of HPPR

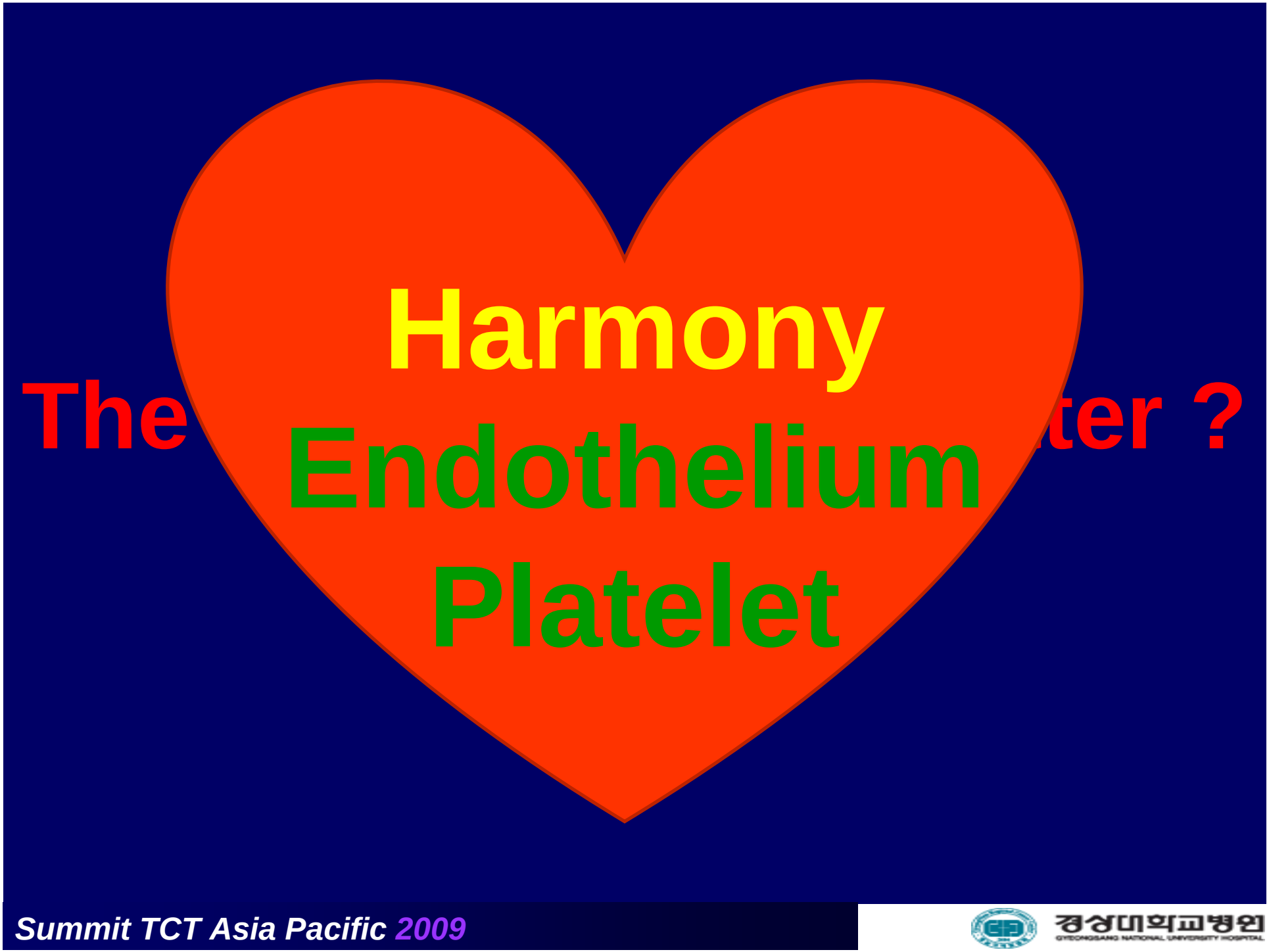
Platelet reactivity: 5μmol/l ADP-induced maximal platelet aggregation (Agg_{max})
HPPR: 5μmol/l ADP-induced Agg_{max} > 50%

Effect of High MD CLPD vs. TAPT according to CYP2C19 genotyping

92 patients undergoing elective coronary stenting (preliminary data)

In carriers of CYP2C19 mutant allele, TAPT can and High-MD CLPD cannot overcome the effect of the loss-of-function CYP2C19 mutant allele.

TAPT achieves optimal platelet inhibition with lesser ischemic and bleeding events, especially in East Asian patients with a higher frequency of CYP2C19 Polymorphism


The
Harmony
Endothelium
Platelet
ter ?

Pleiotropic Effects of Cilostazol

Cilostazol may give your patients RAINBOW against Atherosclerosis

Adjunctive Cilostazol to DAPT (TAPT)

Proven Efficacy and Safety in Pts with High Risk

(HPPR, ACS, CYP2C19 polymorphism and so on)

Neuroprotective Effect

Improvement of Lipid Metabolism

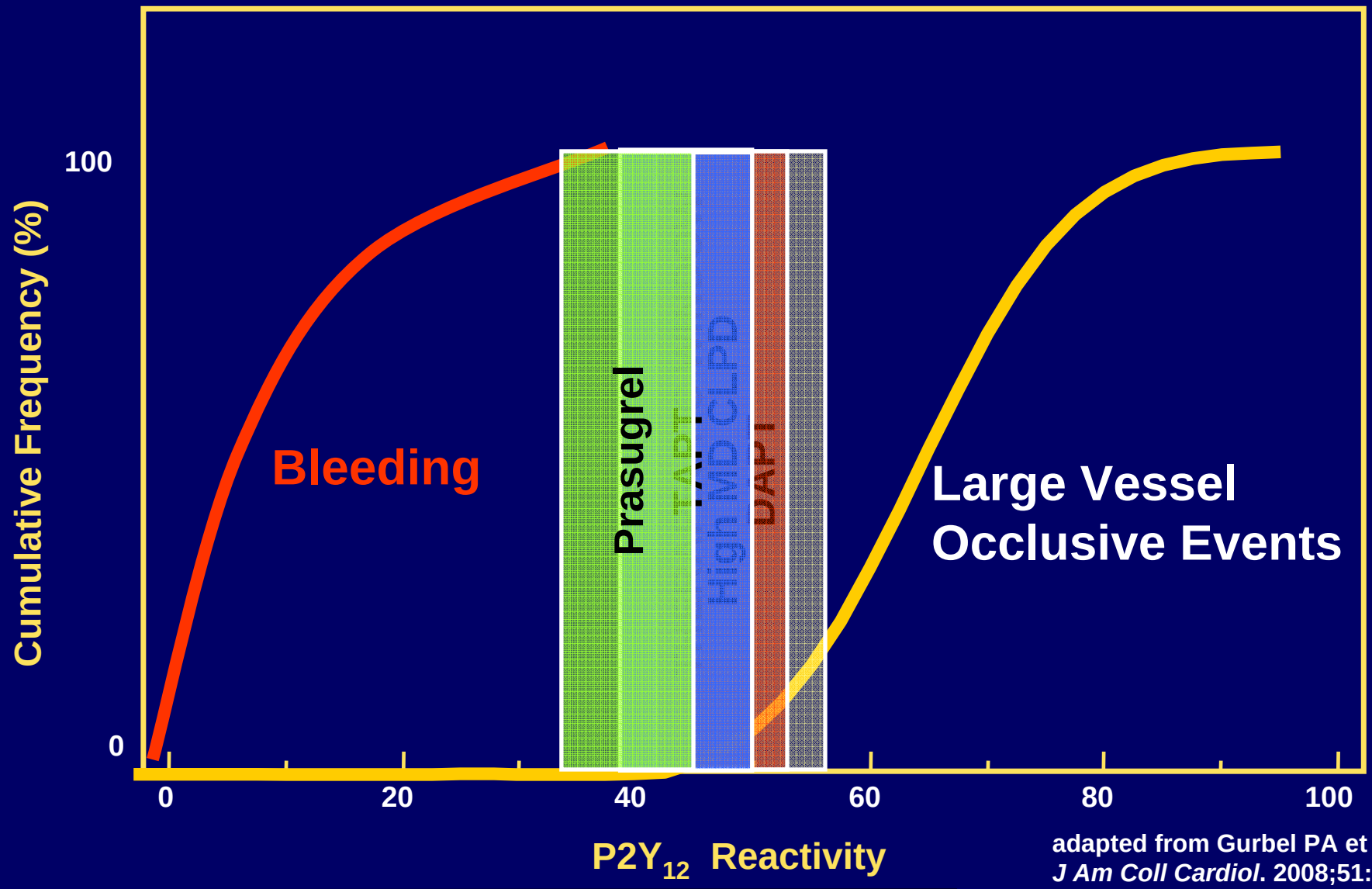
Inhibition of Inflammatory Cascade

Restoration of Endothelial Dysfunction

Reduction of Ischemia-Reperfusion Injury

Inhibition of Neointimal Hyperplasia after Stenting

THE FINAL GOAL of APT:
PREVENT ISCHEMIA-AVOID BLEEDING



adapted from Gurbel PA et al.
J Am Coll Cardiol. 2008;51:B86