Limits of Platelet-Oriented Treatment: "Cilostazol" as Multidisciplinary Approach

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Disclosures

Research Grants/Support

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- Boehringer-Ingelheim
- Otsuka
- Accumetrics
- Multiplate

Honoraria/Consulting

- Otsuka
- Sanofi-Aventis
- Daiichi Sankyo Inc
- Nanosphere

JACC White Paper

J Am Coll Cardiol 2010;56:919-33.

Consensus and Future Directions on the Definition of High On-Treatment Platelet Reactivity to Adenosine Diphosphate

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Marseille, Paris, and Strasbourg, France; Florence, and Milano, Italy; Aachen, Munich, and Bad Krozingen, Germany; Nieuwegein, the Netherlands; Baltimore, Maryland; Jacksonville, Florida; Durham, North Carolina; Boston, Massachusetts; Memphis, Tennessee; Cincinnati, Ohio; La Jolla, California; and Washington, DC

Available methods for testing…

Laboratory-based methods

LTA

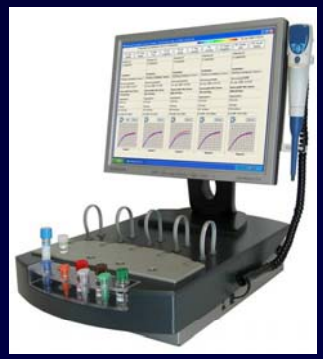
VASP

Platelet-oriented method

Methods allowing near-patient testing

VerifyNow

Whole blood test



Multiplate (MEA)

Most promising for implementation into clinical routine

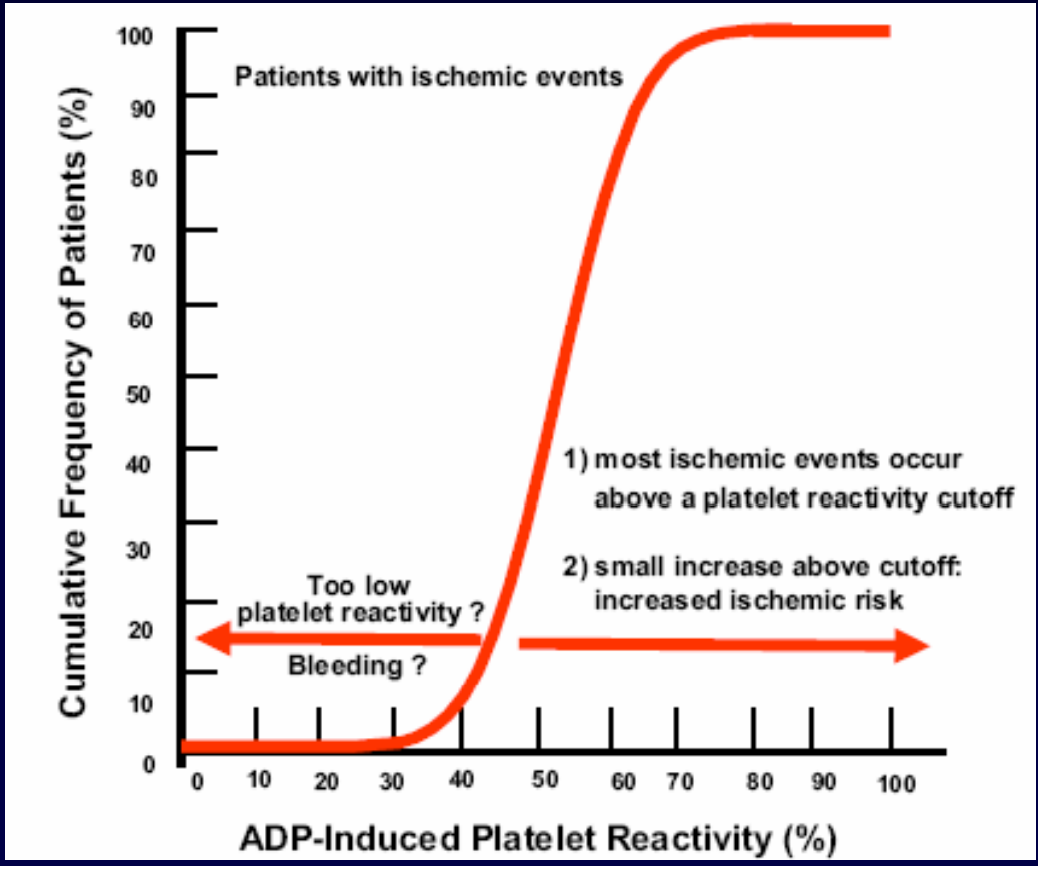
Personalized Antiplatelet Therapy

Recent data suggest that ischemic risk increases rapidly above "a critical level of platelet reactivity"

"High on-treatment platelet reactivity (HPR)"

The criteria of HPR

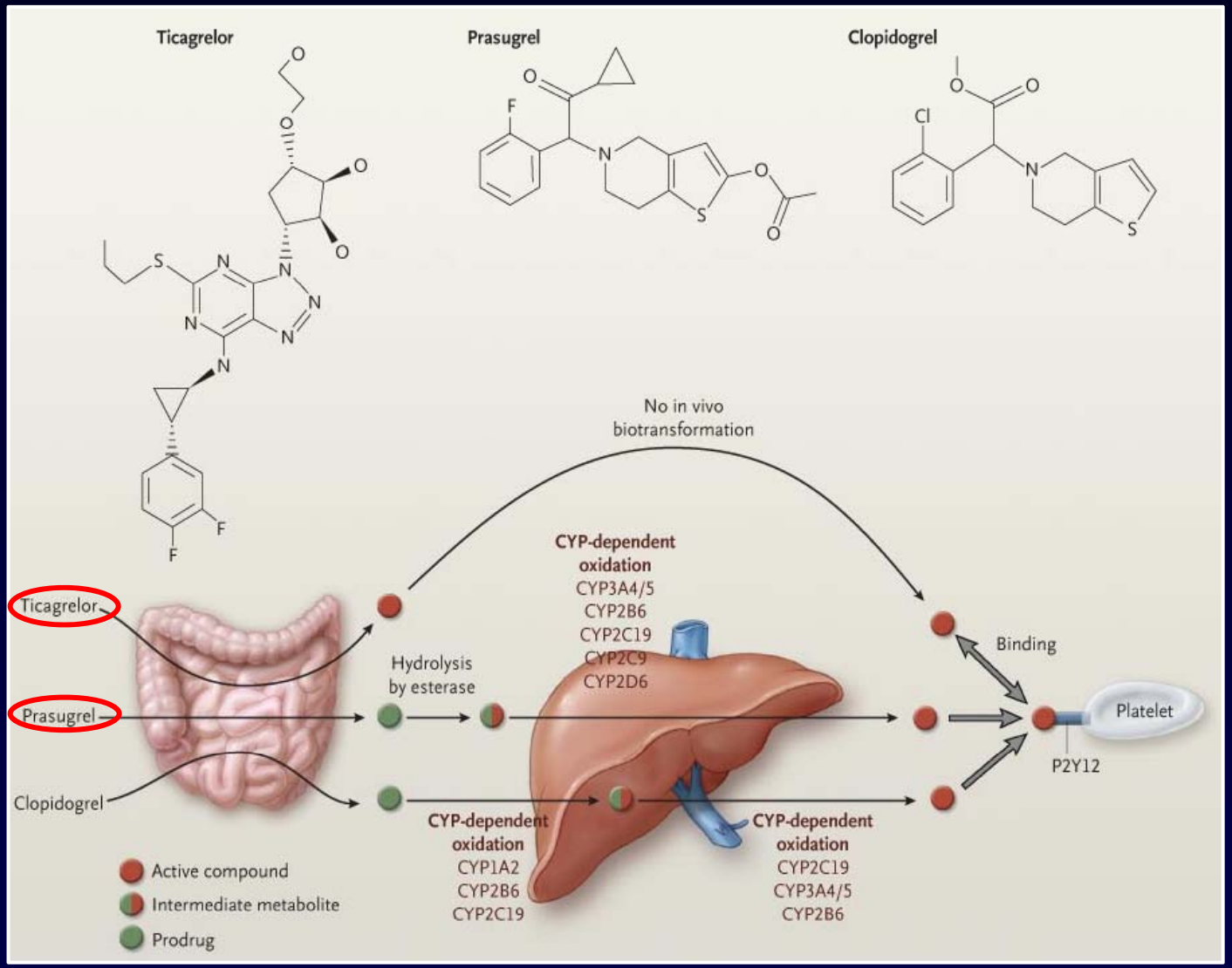
1) 5 µM ADP-PA > 46%
   20 µM ADP-PA > 59%
2) PRU > 235 (VerifyNow)
3) PRI > 50% (VASP)
4) Multiplate > 468 AU



Bonello et al. *J Am Coll Cardiol* 2010;56:919-33

Available Strategies of $P2Y_{12}$ Inhibition

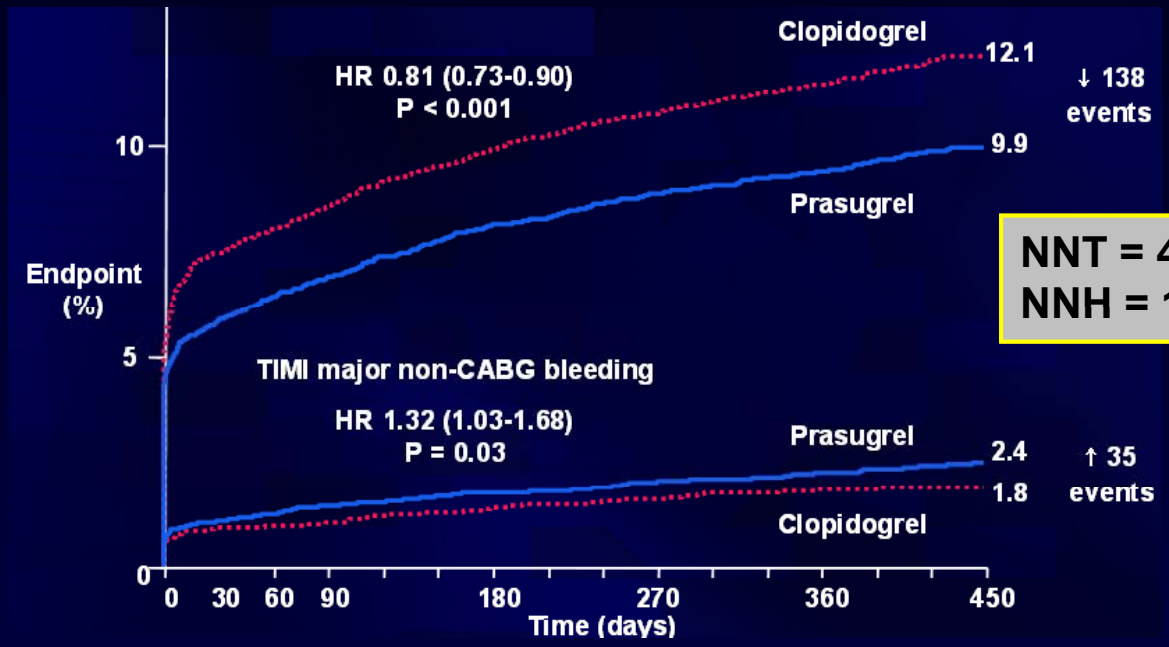
Therapeutic profile not affected by *CYP*, *ABCB1* genetic variation



Schömig A. *N Engl J Med* 2009;361:1108-1111.

TRITON-TIMI 38 Study: Prasugrel vs. Standard Clopidogrel

14.5months CV death, Nonfatal MI and Nonfatal Stroke



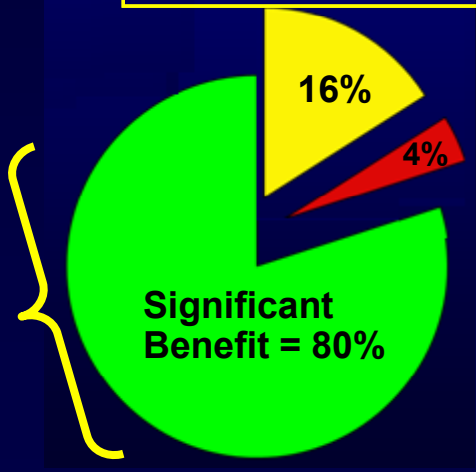
NNT = 46 (1⁰ endpt.)
NNH = 167 (Bleeding)

Reduced MD- 5mg
Guided by PK (n=1159)
Age≥75 yr (n=121) ↑19%
or Wt <60 kg (n=46) ↑40%

TIMI Bleeding

	Prasugrel	Clopidogrel	p-value
Non-CABG	2.4%	1.8%	0.03
Major or Minor	4.0%	3.0%	<0.001
CABG-related	13.4%	3.2%	<0.001

MD 10 mg



Avoid Prior CVA/TIA

Wiviott SD et al. *N Engl J Med* 2007;357:2001-15.

PLATO Trial: Clopidogrel vs. Ticagrelor in ACS Patients

UA / NSTEMI (moderate-high risk), STEMI (if primary PCI, n=8340)
All receiving ASA; clopidogrel-treated or -naïve;
randomized within 24 h of index event

Clopidogrel
300 mg LD+ 75 mg/d;
(additional 300 mg allowed pre PCI)

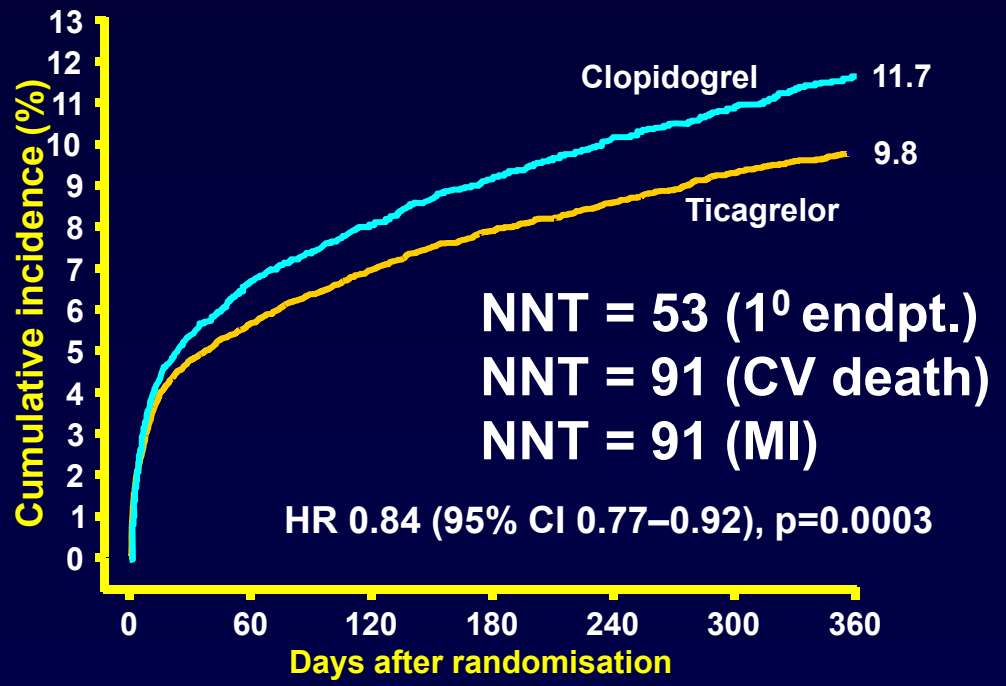
Ticagrelor
180 mg LD+ 90 mg/bd;
(additional 90 mg pre-PCI)

12-month maximum exposure (Minimum 6 months exposure of last included pt)

Clopidogrel Loading Dose
~46% got clopidogrel before randomization
(≥ 600mg = 19.6%)

In 1000 ACS patients, replacing clopidogrel with ticagrelor for 12 months,
- 14 fewer deaths
- 11 fewer MI
- 6-8 fewer cases of ST
- no increase in bleeding requiring ransfusion.

Primary Outcome- CV death + MI + stroke

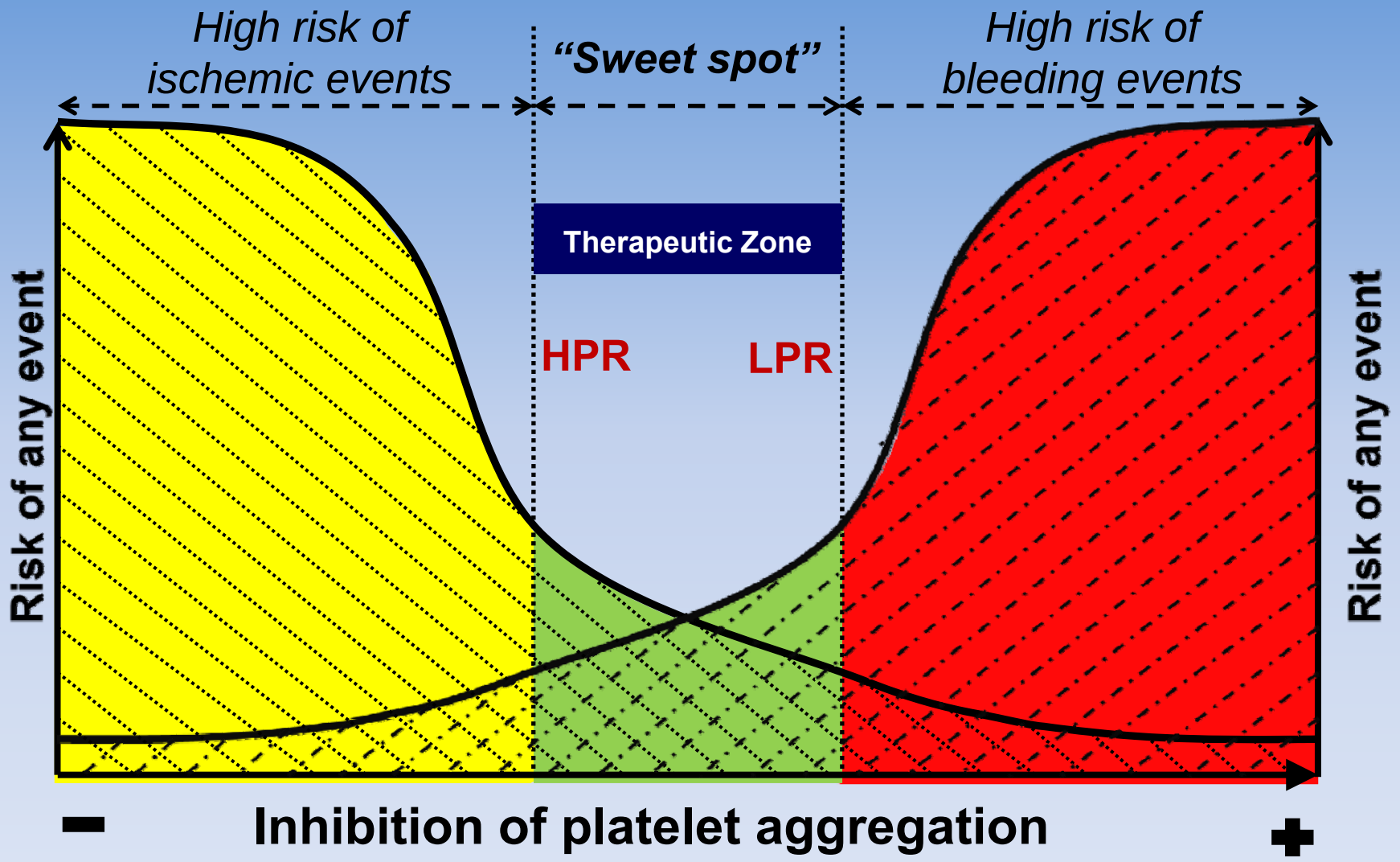


NNT = 53 (1^0 endpt.)
NNT = 91 (CV death)
NNT = 91 (MI)

HR 0.84 (95% CI 0.77–0.92), p=0.0003

Wallentin L et al. *N Engl J Med.* 2009;361:1045-57.

Balancing Safety and Efficacy



Ferreiro & *Angiolillo. Thromb Haemost 2010;103:1128-35.*

How much *enthusiasm* is needed to control platelet activation?

Fortune Cookie

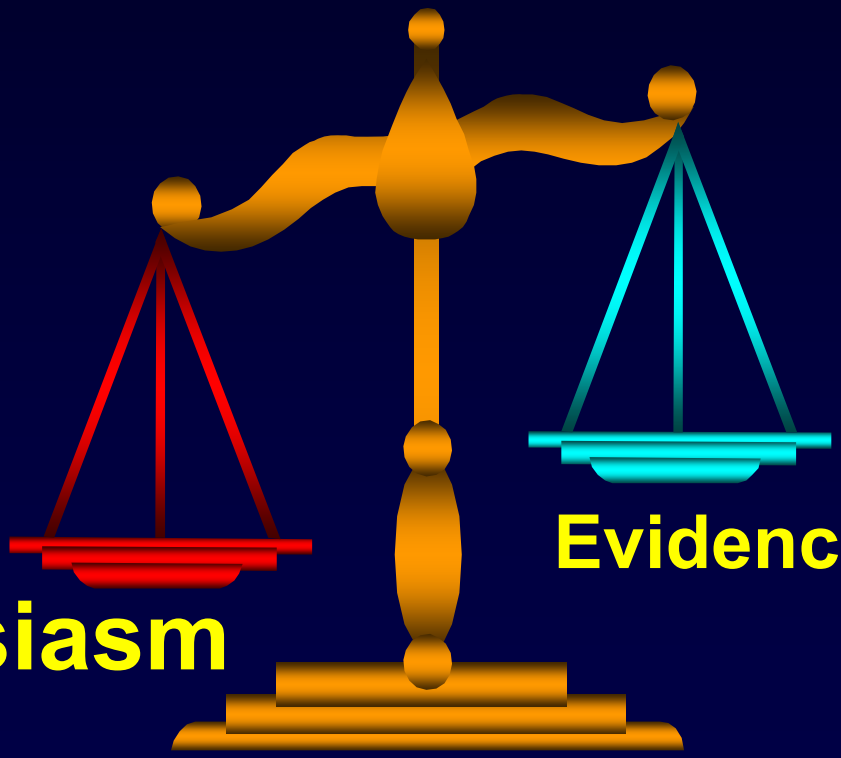
“*Philosophy of Today*” will make Creativity in Tomorrow.

Modern Times = Absence of Philosophy

Leonardo da Vinci
(invention based on philosophy)

“Platelet Research”: Absence of Philosophy

A Case of Enthusiasm Exceeding the Evidence/Philosophy



Evidence/Philosophy

Enthusiasm

Paradox in “Platelet Research”

- “Smoking” paradox
- “Female” paradox
- “Old age” paradox
- “DM” paradox
- “CKD” paradox
- “Asian” paradox
- …

Paradox in “Platelet Research”

- “Smoking” paradox
- “Female” paradox
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- “CKD” paradox
- *“Asian” paradox*
- …

Platelet Reactivity in Korean AMI pts

(First report of ADP-stimulated platelet reactivity in East Asians)

Clopidogrel 600mg LD, followed by 75 mg/d

CYP2C19 SNP	0 *LoF* allele **(n =57)**	1 *LoF* allele **(n=59)**	2 *LoF* alleles **(n = 20)**	*P* value
Rate of HPR	**18 (31.6%)**	**33 (55.9%)**	**12 (65.0%)**	***0.002***
LTA, %				
5 μM ADP-PA	43±14	49±14	52±17	***0.012***
20 μM ADP-PA	54±15	62±12	64±15	***0.002***
VerifyNow				
PRU	226±90	259±74	284±84	***0.018***

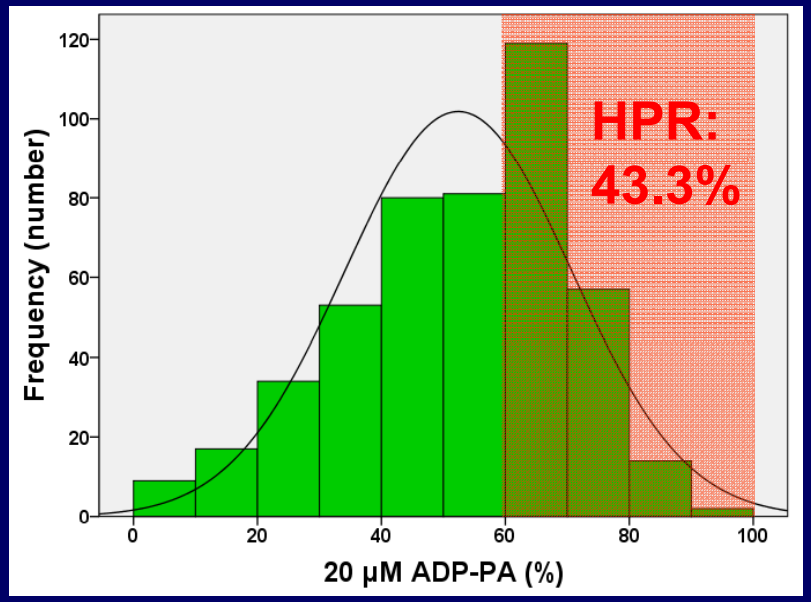
HPR (5 μM ADP-PA > 46%): 47.1%

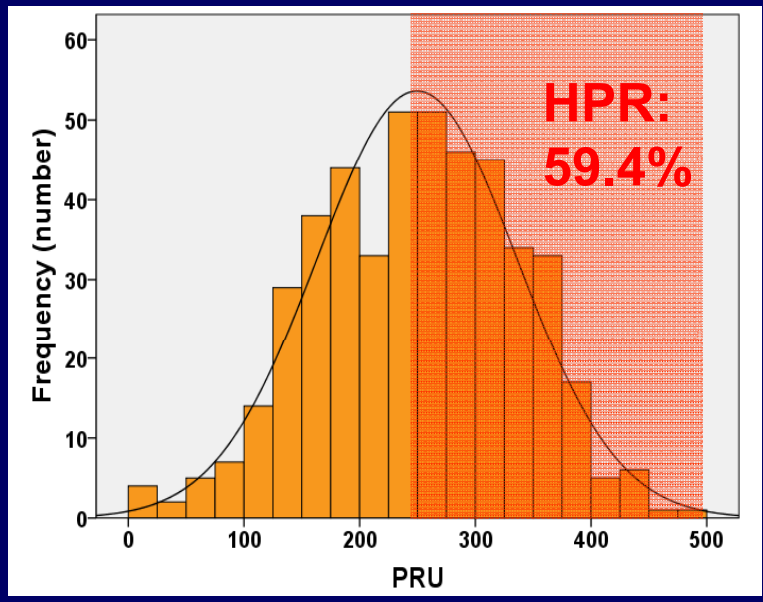
GNUH ACCEL registry

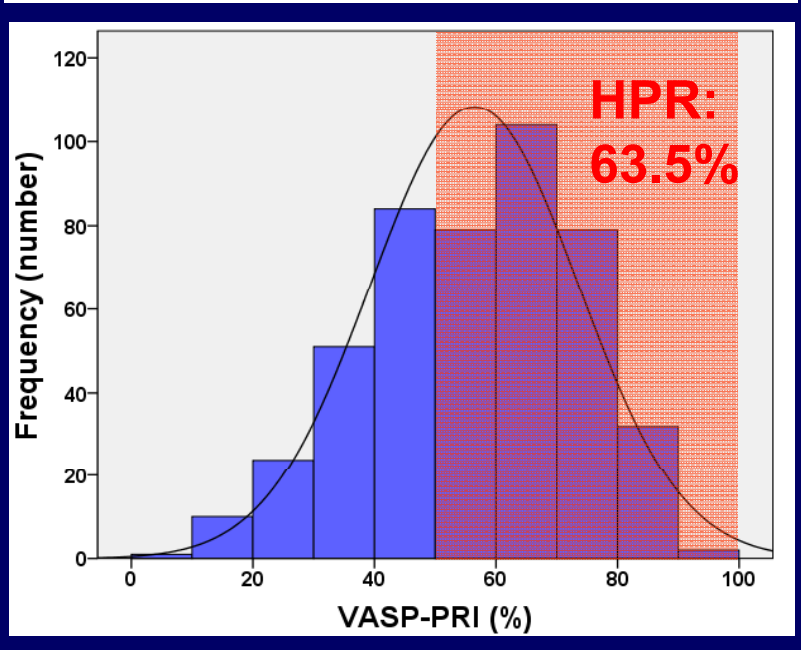
Kim IS, Jeong YH, et al. *J Thromb Haemost* 2009;7:897.

PD profile: Korean patients undergoing elective PCI

(n = 466: at least 12 hours after 600mg clopidogrel LD)



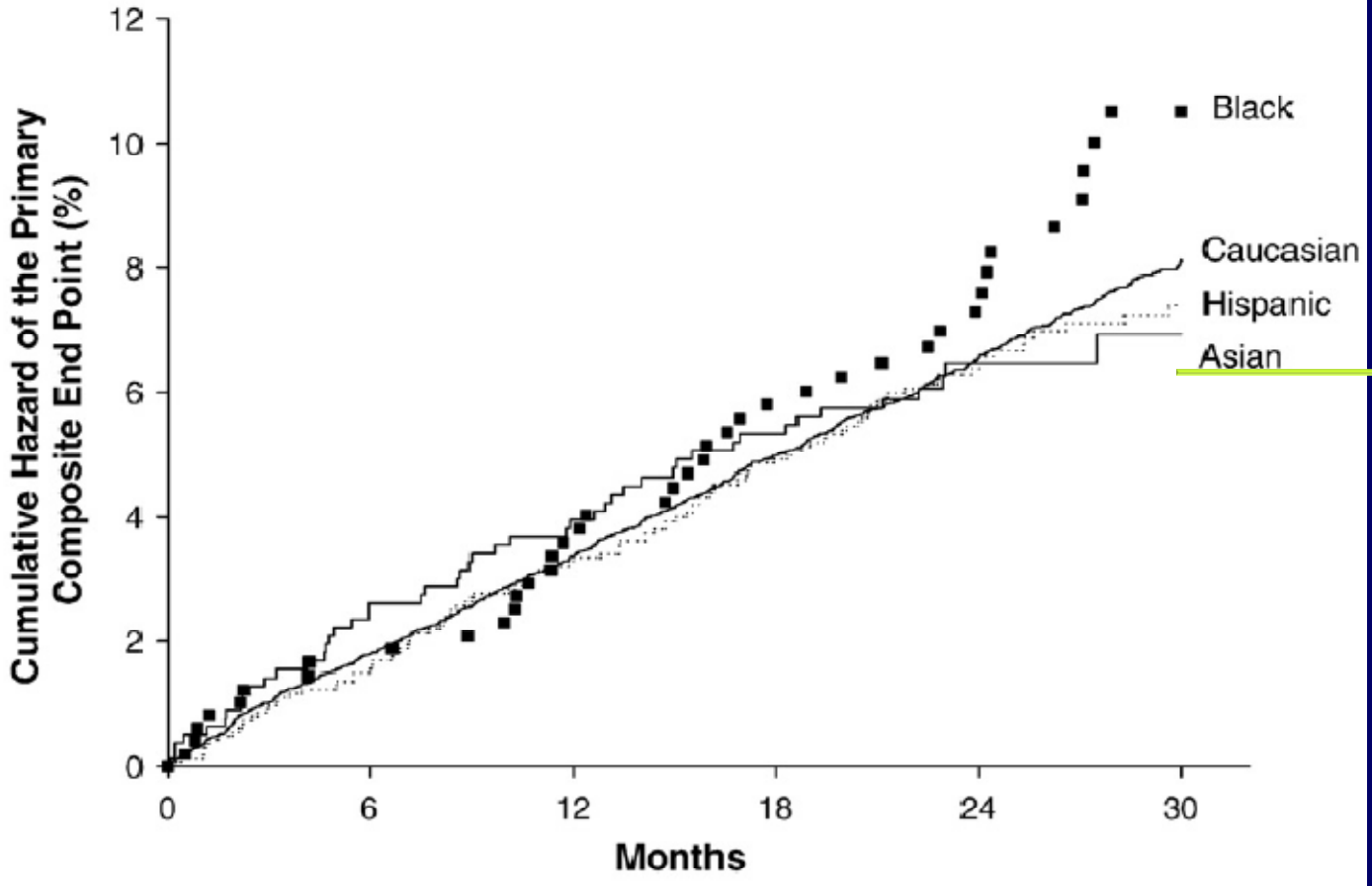




High prevalence of HPR:
High frequency of *CYP2C19 LoF* allele
(East Asians: Caucasian = 60-70%: 25-30%)

Jeong et al. Presented in ESC 2011.

Racial Difference in CV death/MI/stroke among Pts on Antiplatelet Therapy



No. at Risk						
Asian	775	753	738	725	373	149
Black	486	474	461	448	330	143
Caucasian	12502	12263	12026	11781	8569	4620
Hispanic	1613	1583	1550	1517	1065	540

GUSTO Mod bleed HR

3.78 (1.35-1.60)

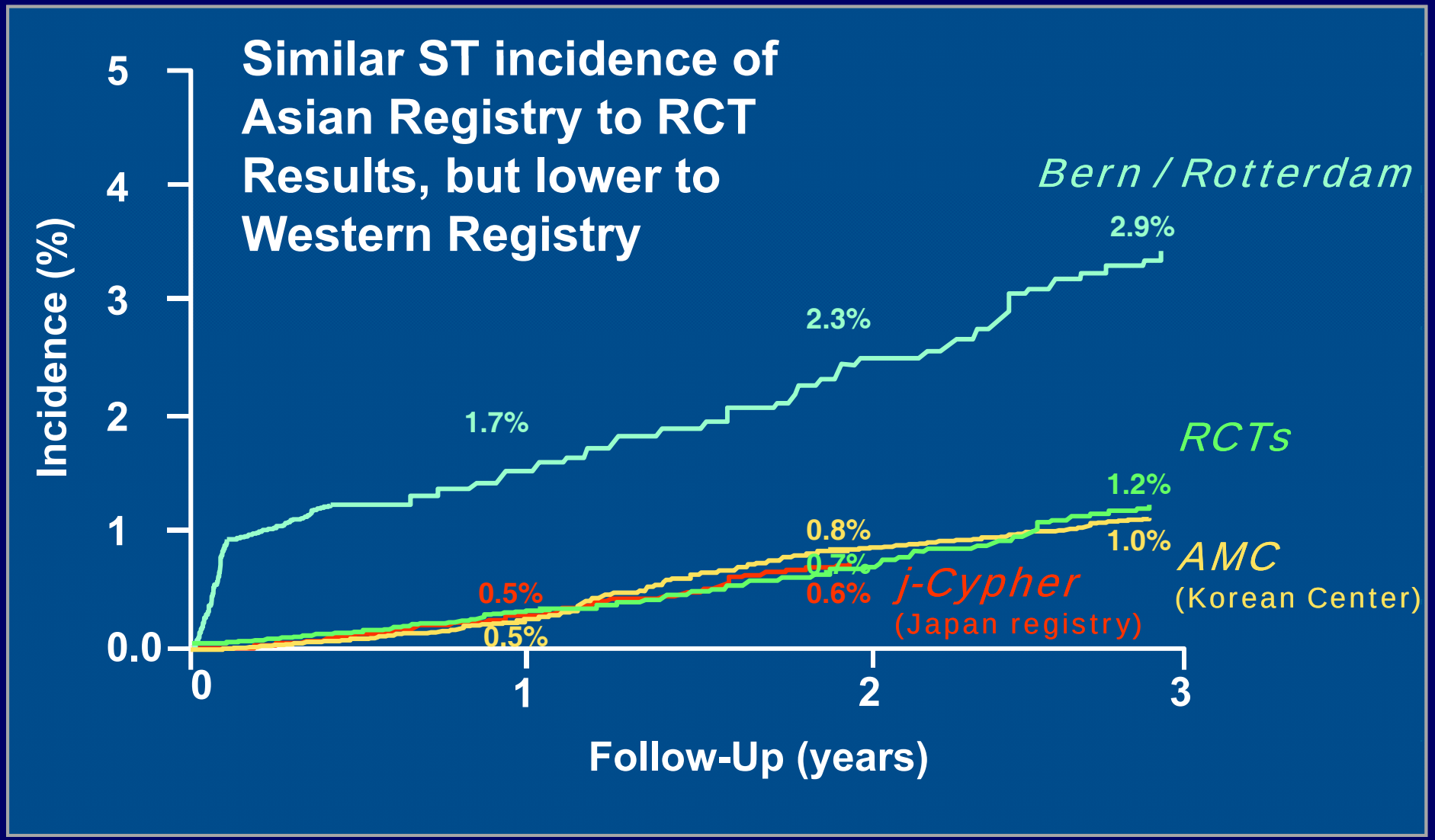
1.46 (0.63-3.36)

1.00 (Reference)

3.15 (1.09-9.11)

Mak KH et al. CHARISMA study. *Am Heart J* 2009;157:658.

Racial difference of Stent Thrombosis: Asian vs. Western Population



What's the magic in Asians?

VS.

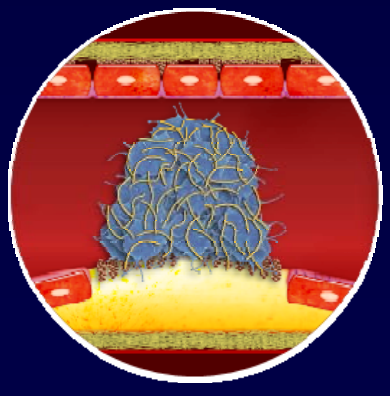
Development of Arterial Thrombi

Platelet-activating factor
Endothelin 1
Thromboxane A_2
Tissue factor
Tissue-factor-bearing microparticles
Clotting factors
Von Willebrand factor
Plasminogen activator inhibitor 1
α2-plasmin inhibitor
Carboxypeptidase B2
Others…

Procoagulant forces

Prostacyclin
Nitric oxide
Carbon monoxide
Antithrombin
Protein C/protein S/thrombomodulin system
Tissue factor pathway inhibitor
Tissue-type plasminogen activator
Urokinase-type plasminogen activator
Others…

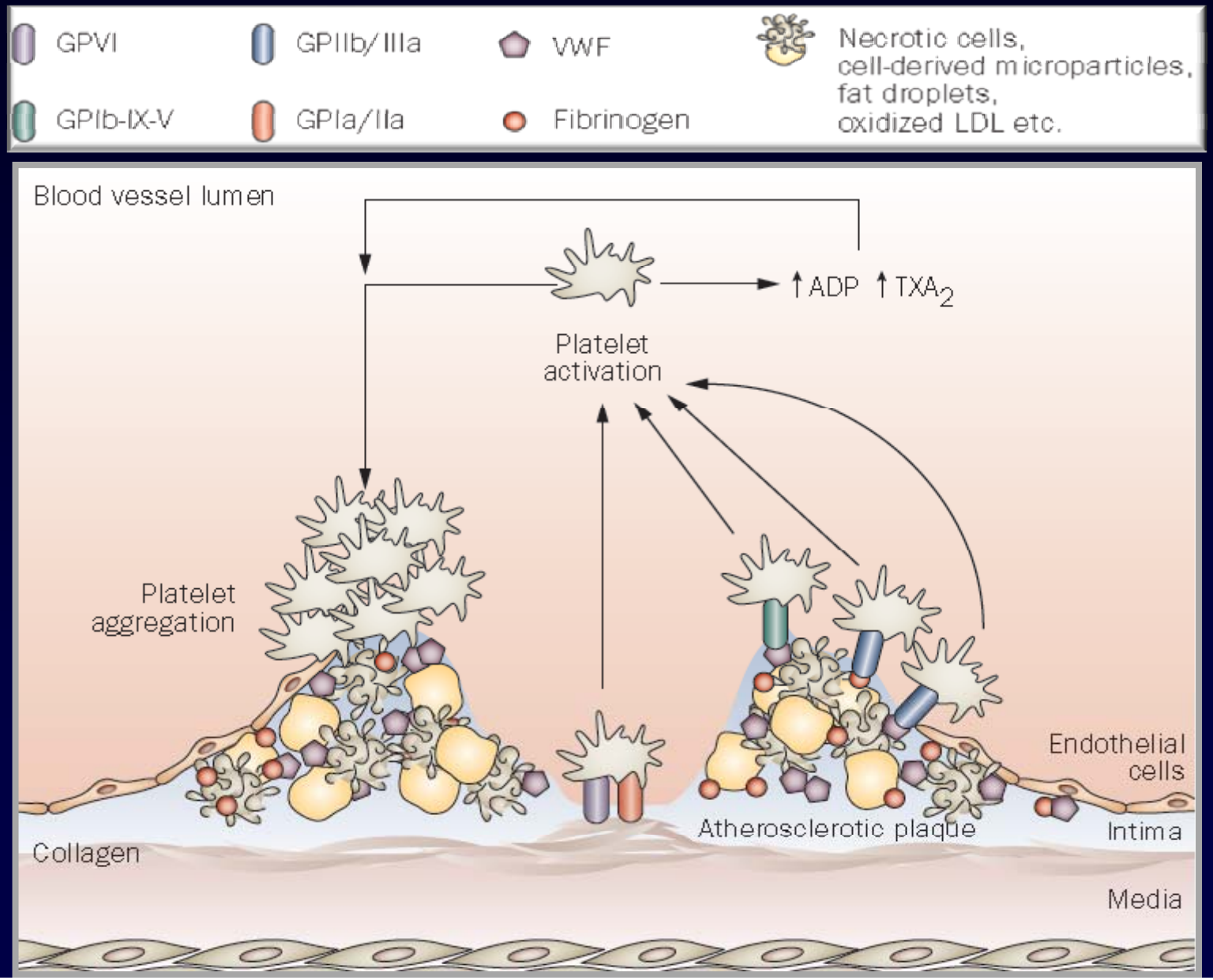
Anticoagulant forces



Lippi et al. *Nat Rev Cardiol*. 2011;8:502–512.

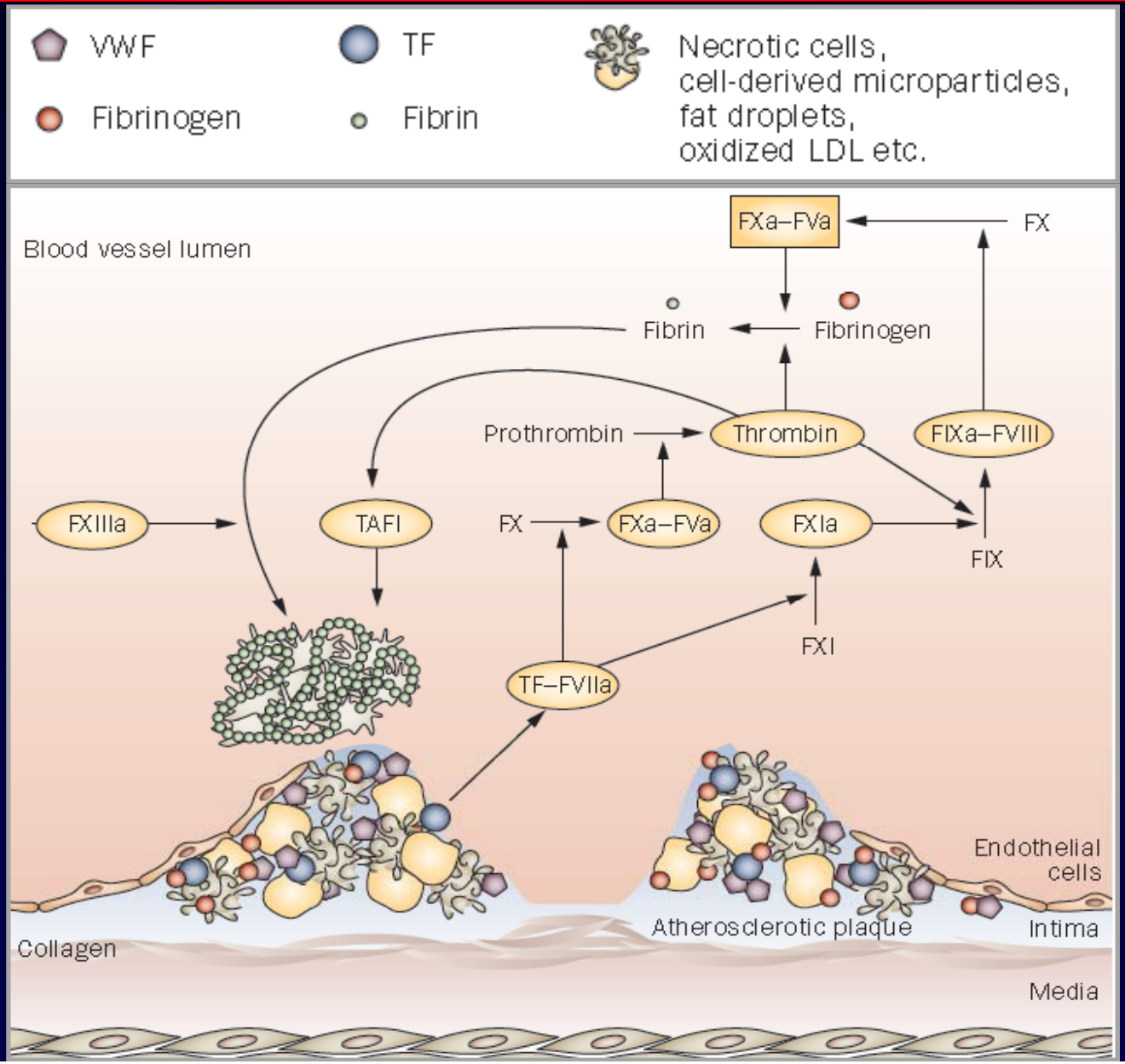
Platelet Activation and Aggregation

Lippi et al. *Nat Rev Cardiol*. 2011;8:502–512.



Activation of Blood Coagulation

Lippi et al. *Nat Rev Cardiol*. 2011;8:502–512.



Plausible Mechanism of Atherothrombosis

Progenitor cell

Endothelial dysfunction
(e.g. adhesion melecule: vWF)

Obesity

Oxidative stress

Platelet activation

Inflammation
(e.g. monocyte, CRP)

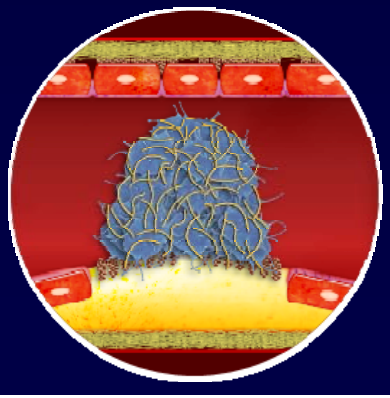
Procoagulant activity
(e.g. TF-Thrombin-Fibrin)

Gene-environment interaction (RACE)

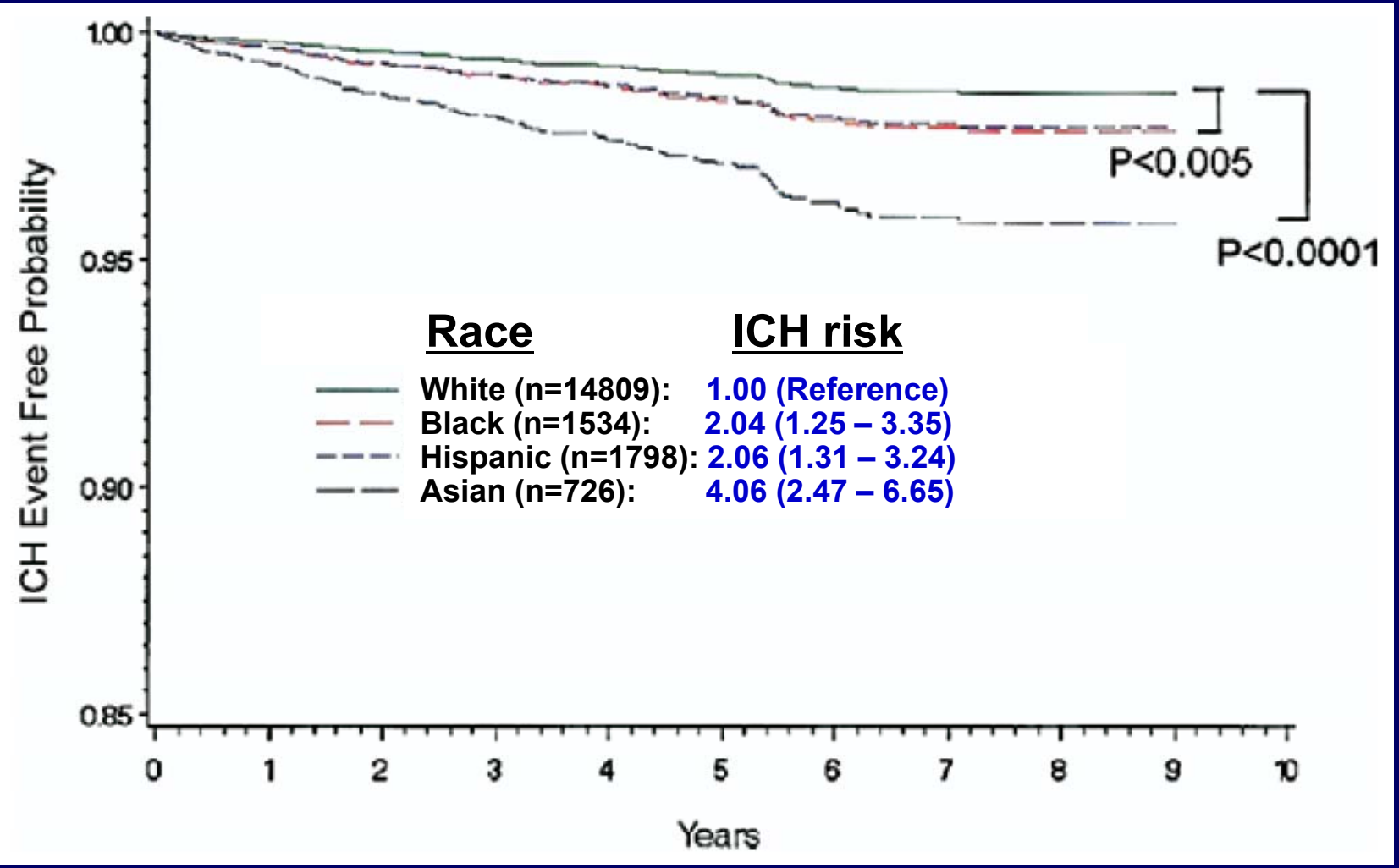
Shearing force

Lipid particle
(e.g. oxidized LDL, HDL)

Fibrinolytic activity

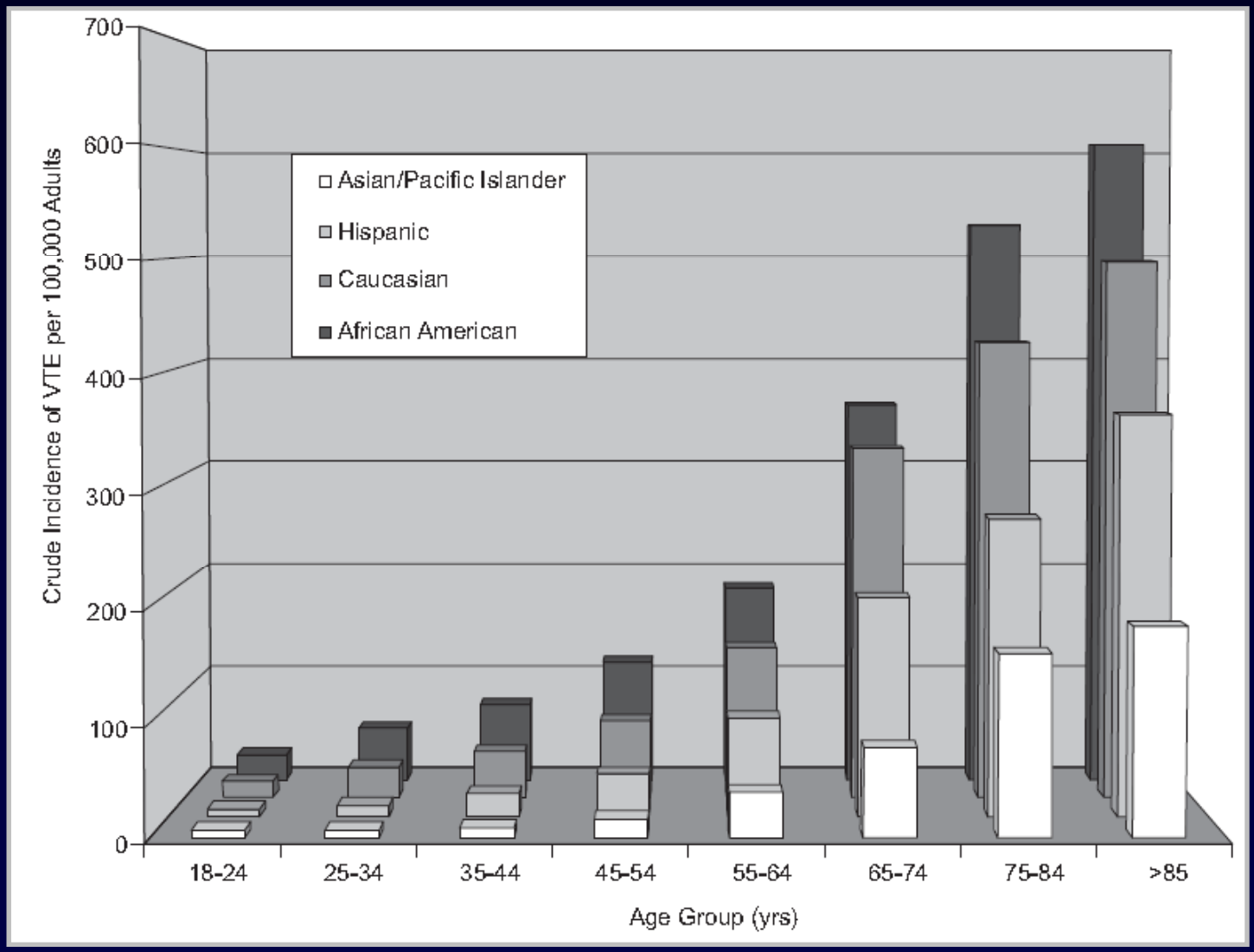


Racial Difference in ICH Risk among AF Pts on Warfarin (18867 pts admitted to Kaiser Permanente Southern California)



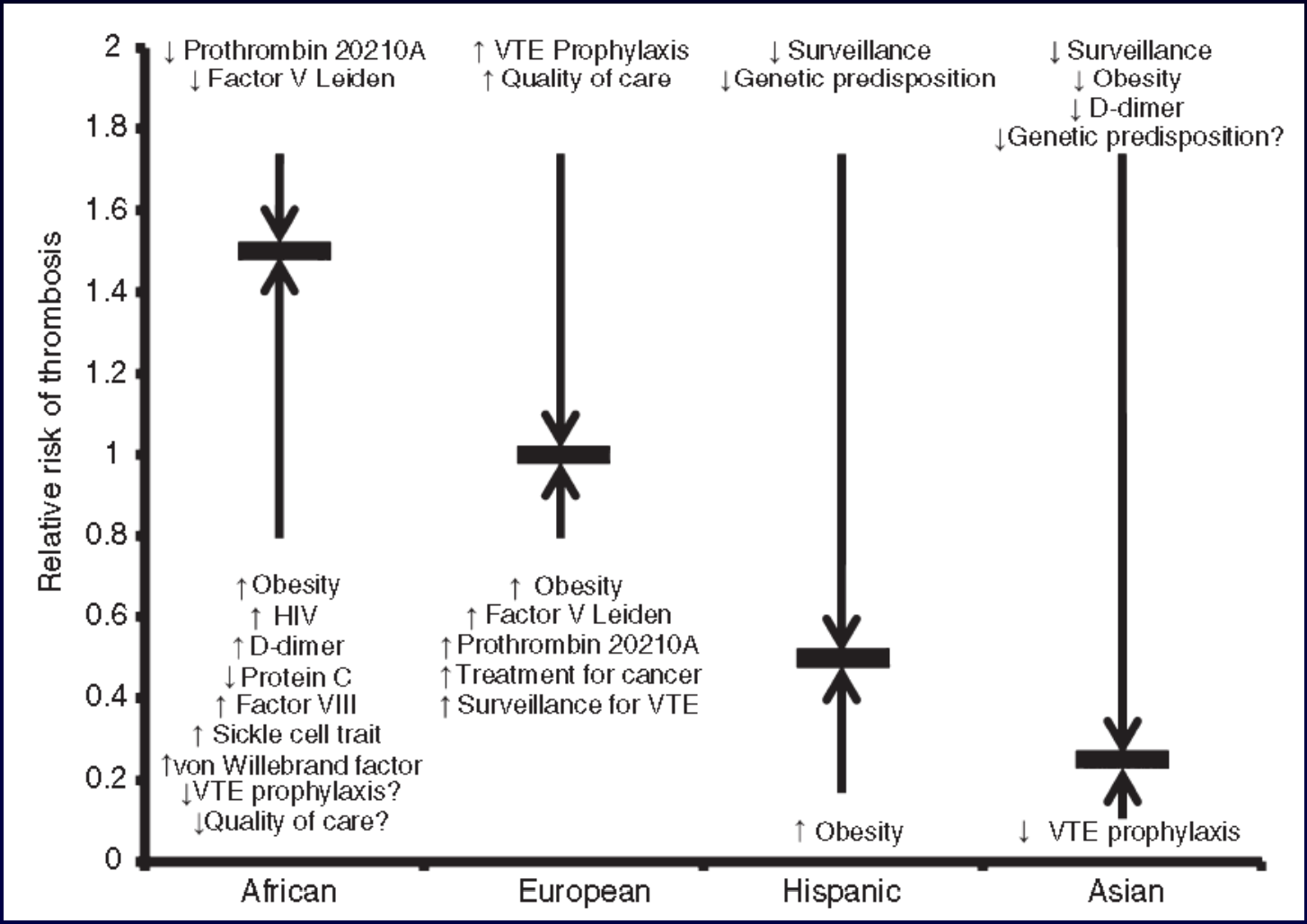
Shen AY, et al. *J Am Coll Cardiol* 2007;50:309.

Effect of age on the incidence of VTE among different racial/ethnic groups



White RH et al. *Thromb Res* 2009;123:S11–S17.

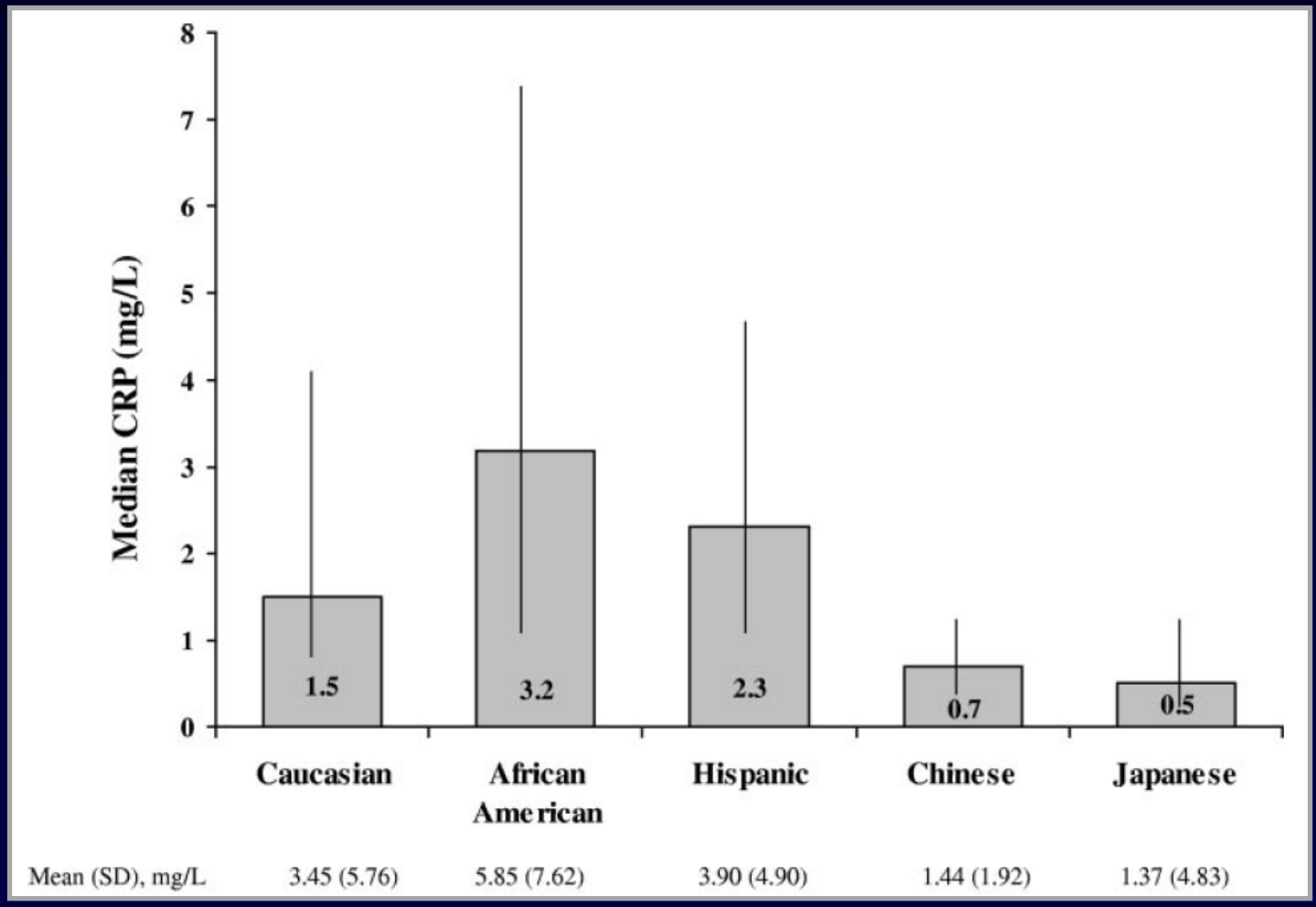
Theoretical Reason for Racial Difference in VTE



Zakai NA et al. *J Thromb Haemost* 2011; 9: 1877–82.

Ethnic Difference in CRP level

A cross-sectional analysis of 3154 women, without known CVD and hormone therapy (SWAN study)



Kelley-Hedgepeth et al. *Clin Chem*. 2008;54:1027-37.

ACCEL-LOADING-ACS

Multicenter Randomized Trial Evaluating *Efficacy of Cilostazol* on Platelet reactivity, Inflammation, and Myonecrosis in ACS Patients

Young-Hoon Jeong, MD, PhD

On behalf of the ACCEL-LOADING-ACS Investigators

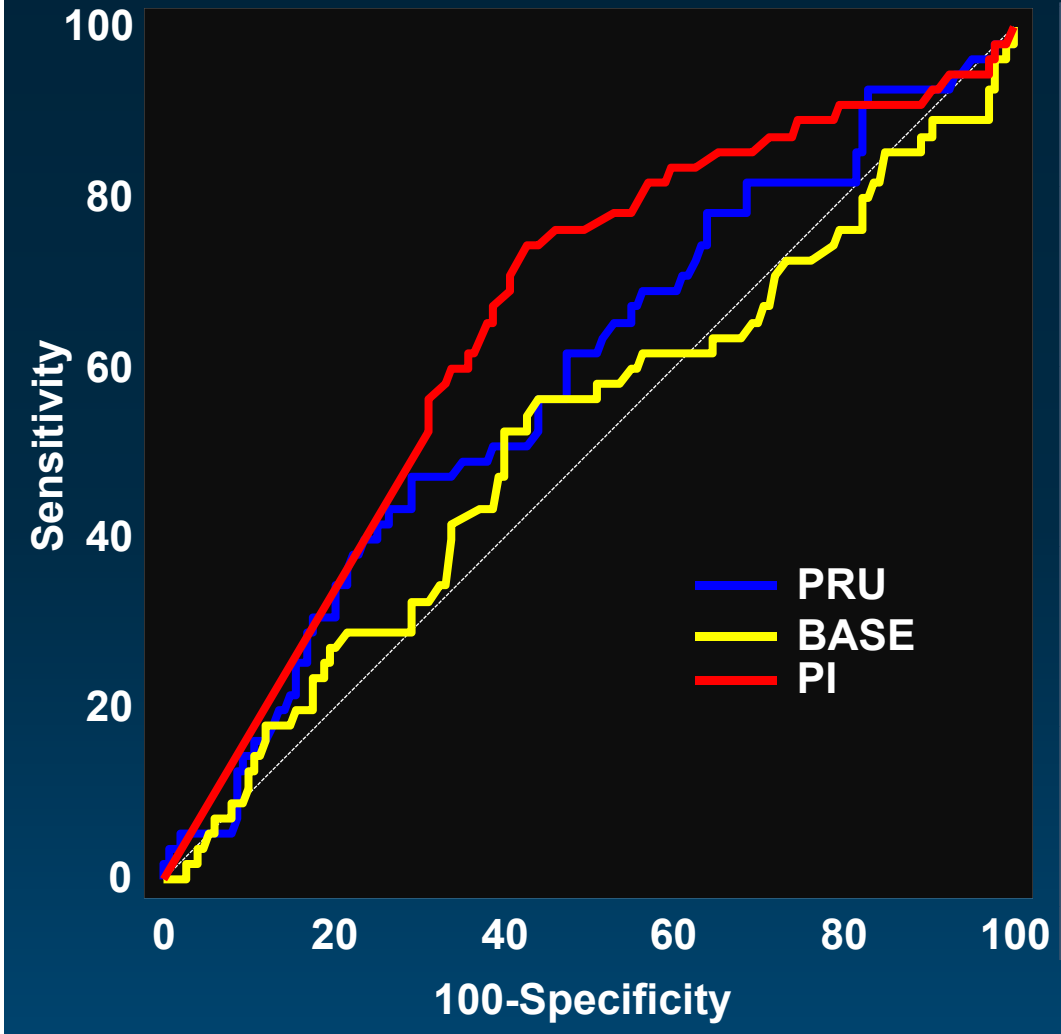
Gyeongsang National University Hospital, Jinju, Korea;
Sinai Center for Thrombosis Research, Baltimore, MD, USA.

ANGIOPLASTY SUMMIT TCTAP 2012

ClinicalTrials.gov Identifier: NCT01354808

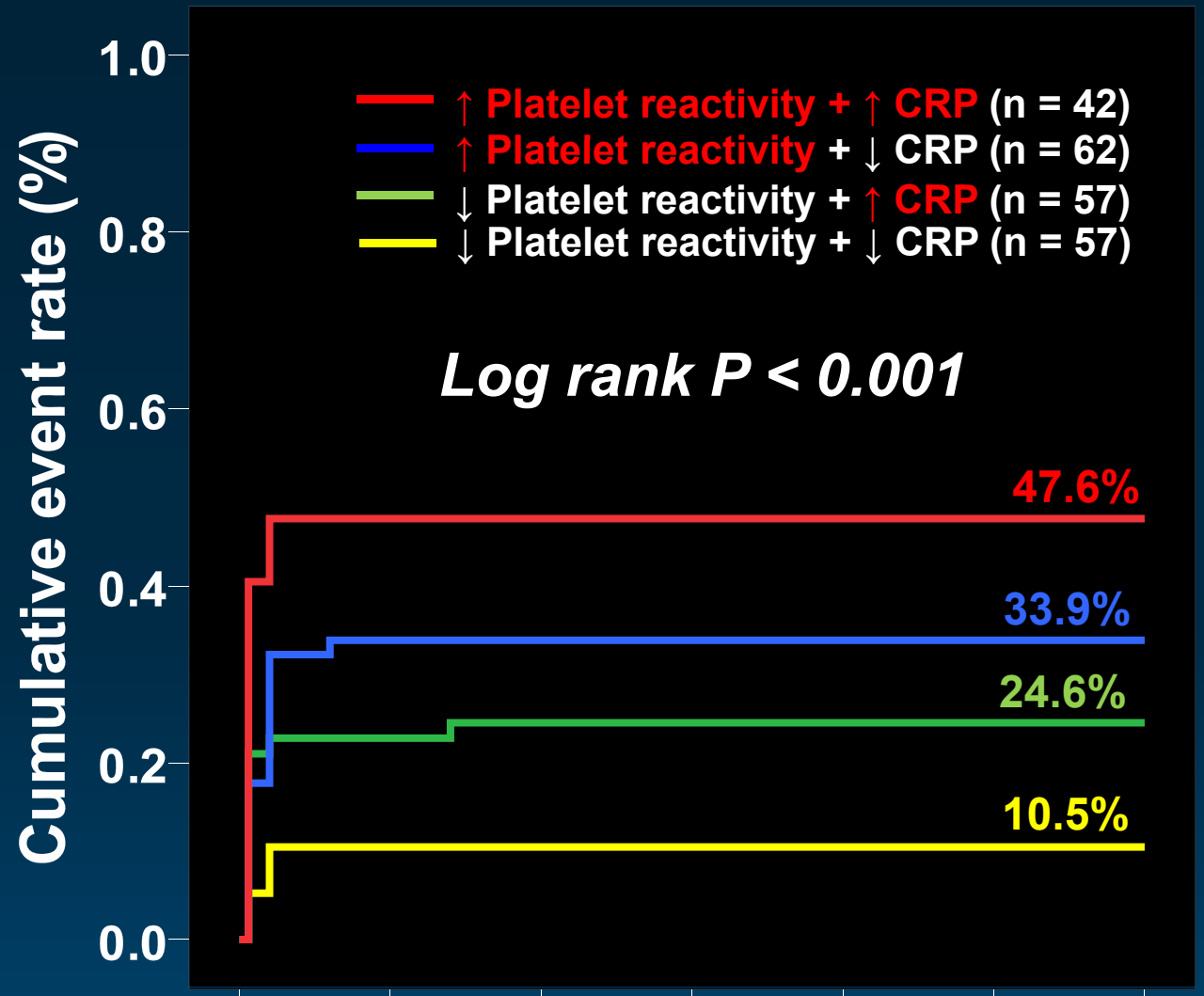
Relationship between VerifyNow and 30-day MACE

ROC curve analysis



	PRU	BASE	PI
AUC	0.583	0.516	0.649
Cutoff	>288	≤ 293	≤ 12%
Sensitivity	47.3%	52.7%	74.6%
Specificity	70.8%	59.9%	57.1%
PPV	37.7%	33.0%	39.4%
NPV	78.2%	77.2%	85.7%
+LR	1.62	1.62	1.74
-LR	0.75	0.75	0.45
Accuracy	64.2%	57.9%	62.0%

30-day MACE in PCI-treated ACS patients according to Combined VerifyNow and CRP



ACCEL-LOADING-ACS.
Jeong YH, et al.
TCTAP 2012.

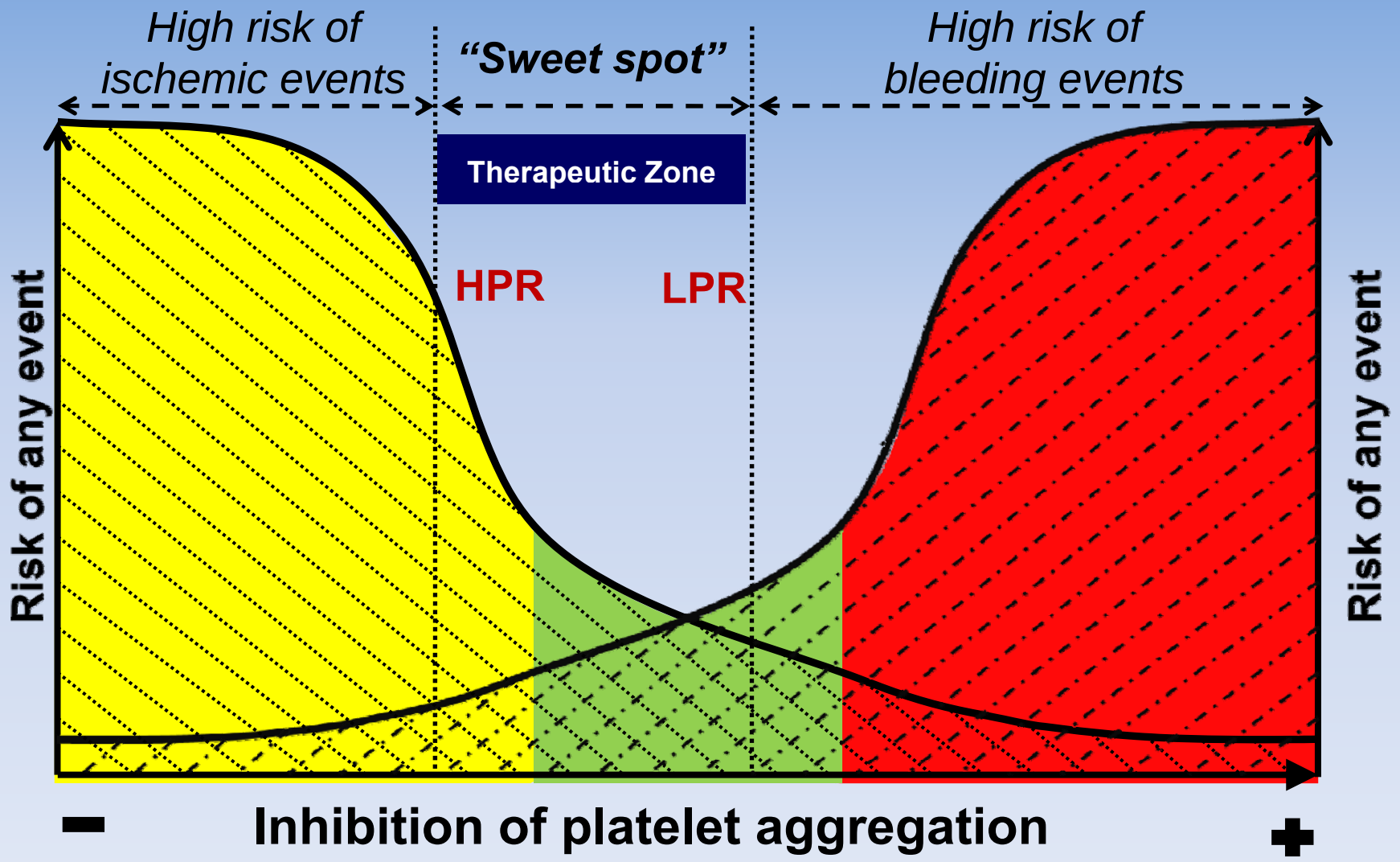
Asians may have low “thrombogenicity”

VS.

Balancing Safety and Efficacy in East Asians

← Shift to left side

Platelet activation may be protected from other mechanisms.



“Cilostazol” as Multidisciplinary Approach

Role of Phosphodiesterases (PDEs) and Inhibitors

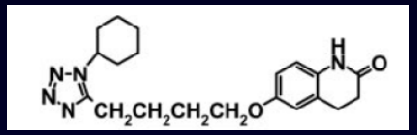
↑ cAMP and cGMP → ↑ protein kinase → phosphorylation of specific substrates

Family	Substrate	Tissue expression	Inhibitors	Disease targets
PDE1	cGMP > cAMP	Heart, vascular smooth muscle and brain	Vinpocetine, IC86340	Cerebrovascular disorders and age-related memory impairment, cardiac hypertrophy
PDE2	cGMP = cAMP	**Platelets**, heart and endothelial cells	EHNA, EHNA analogues: BAY 60-7550, PDP	Memory impairment , endothelial permeability in inflammatory conditions
PDE3	cAMP > cGMP	**Platelets**, vascular smooth muscle, corpus cavernosum and heart	**Cilostazol, milrinone**, vesnarinone, lixazinone, anagrelide	Peripheral vascular disease, congestive heart failure, airways disease, fertility, ischaemic cardiovascular disease
PDE4	cAMP	Lung, heart, vascular smooth muscle, brain, inflammatory and immune cells	Rolipram, etazolate, zardaverine	Chronic obstructive pulmonary disease, asthma, allergic disease
PDE5	cGMP	**Platelets**, vascular smooth muscle and corpus cavernosum	**Sildenafil**, vardenafil, tadalafil, zaprinast, **dypiridamole**	Erectile dysfunction, ischaemic cardiovascular disease
PDE6	cGMP > cAMP	Retinal rods and cones	Sildenafil, zaprinast, dypiridamole	None
PDE7	cAMP > cGMP	T cell, B cell, skeletal muscle and heart	BRL 50481, IC242, dypiridamole	Inflammation, osteoporosis
PDE8	cAMP	Testis, eye, liver, kidney, skeletal muscle, embryo, ovary and brain	Zaprinast	None
PDE9	cGMP	Brain, small intestinal smooth muscle, liver, kidney, lung, testis, skeletal muscle and heart	BAY 73-6691	Alzheimer's disease
PDE10	cAMP > cGMP	Testis and brain	None	None
PDE11	cAMP = cGMP	Skeletal muscle, prostate, kidney, liver, pituitary, salivary glands and testis	None	None

Gresele et al. *Br J Clin Pharmacol* 2011;72:634-646.

Pharmacokinetics and Pharmacodynamics of Cilostazol

6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydro-2(1H)-quinolinone



- **Mechanism:**
  - Inhibition of PDE3 (platelets, VSMC, heart, and adipocytes) → ↑ cAMP
  - Inhibition of adenosine uptake (erythrocytes, platelets, muscle cells, and endothelial cells) → ↑ adenosine

- **Metabolism:** Extensively metabolized by liver
  excreted by urine (74%) and feces (20%)
  - pathway: OPC-13015 (CYP3A4)
    OPC-13213 (CYP3A5 and 2C19)

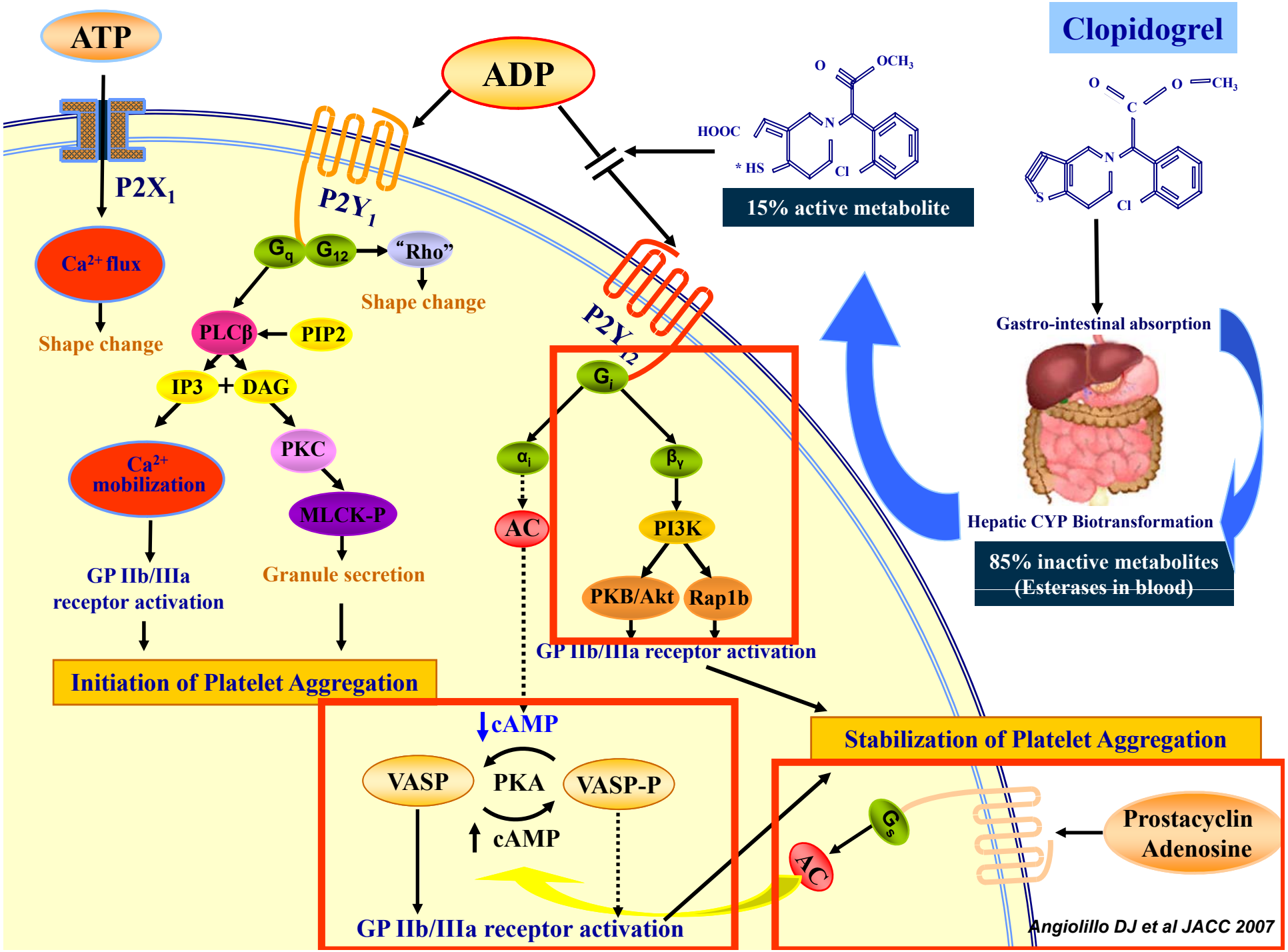
- **Max. concentration:** 3~3.65 hours
- **Max. platelet inhibition:** ~6 hours

Jeong YH et al. *Circ J.* 2011;75:2534-6.

Cilostazol: old drug, but new mechanism

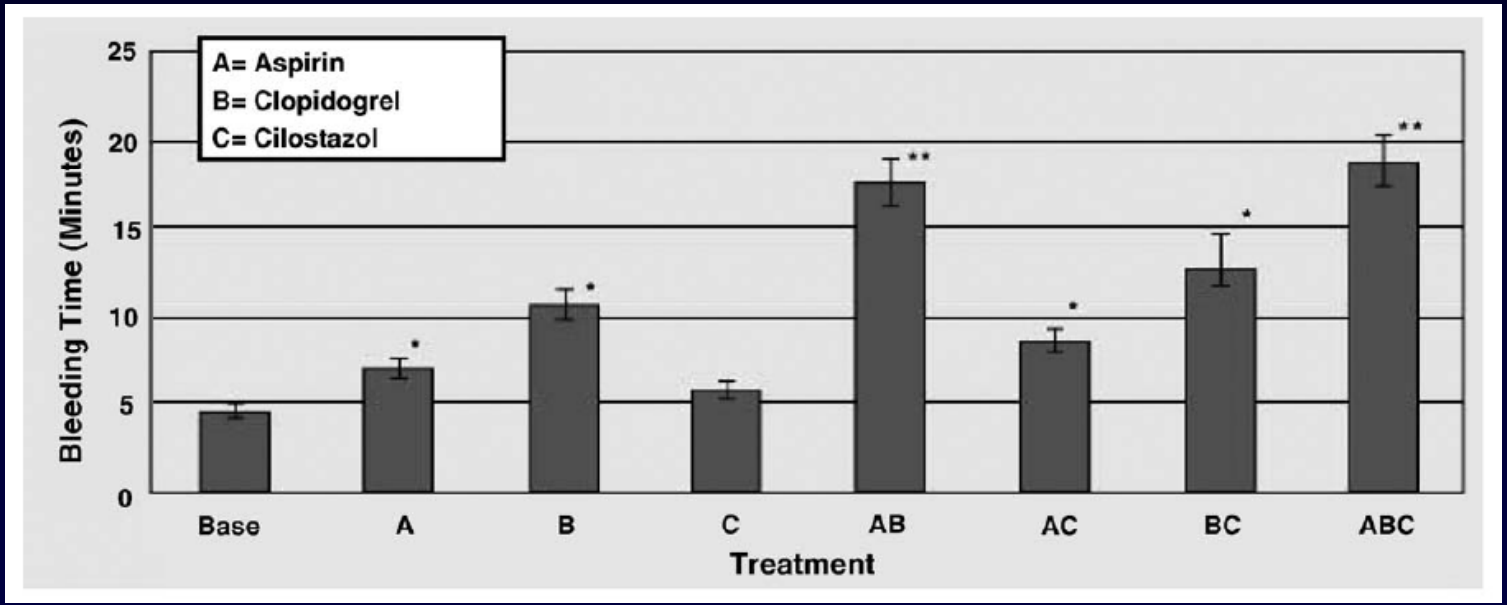
	PDE3-dependent (cAMP)	PDE3-independent
Antiplatelet effect	O	O (adenosine)
Vasodilatory effect (VSMC relaxation)	O	O (adenosine)
Antiproliferative effect (control of VSMC proliferation and migration)	O	O (adenosine)
Effect on endothelial dysfunction (NO release)	Δ	Δ (PGE_1, PGI_2, Sirt 1)
Antiatherogenic effect (↓ adhesion molecule, ↓ inflammatory cells and cytokines)	Δ	-
Control of dyslipidemia (↓ triglyceride, ↑ HDL-cholesterol and apolipoprotein A_1)	Δ (lipoprotein lipase)	-
Protection against ischemia/reperfusion injury (PI3/Akt pathway)	-	Δ (adenosine)
Positive chronotropic effect	O	-
Negative chronotropic effect	-	Δ (adenosine)

Jeong YH et al. *Circ J.* 2011;75:2534-6.


ATP
ADP
P2X1
P2Y1
P2Y12
Ca2+ flux
Shape change
Gq
G12
"Rho"
Shape change
PLCβ
PIP2
IP3
DAG
PKC
Ca2+ mobilization
MLCK-P
GP IIb/IIIa receptor activation
Granule secretion
Initiation of Platelet Aggregation
Gi
αi
βγ
AC
PI3K
PKB/Akt
Rap1b
GP IIb/IIIa receptor activation
cAMP
VASP
PKA
VASP-P
cAMP
GP IIb/IIIa receptor activation
Stabilization of Platelet Aggregation
Gs
AC
Prostacyclin
Adenosine
Angiolillo DJ et al JACC 2007
HOOC
* HS
Cl
15% active metabolite
Clopidogrel
Gastro-intestinal absorption
Hepatic CYP Biotransformation
85% inactive metabolites
(Esterases in blood)

Less Bleeding Tendency of Cilostazol

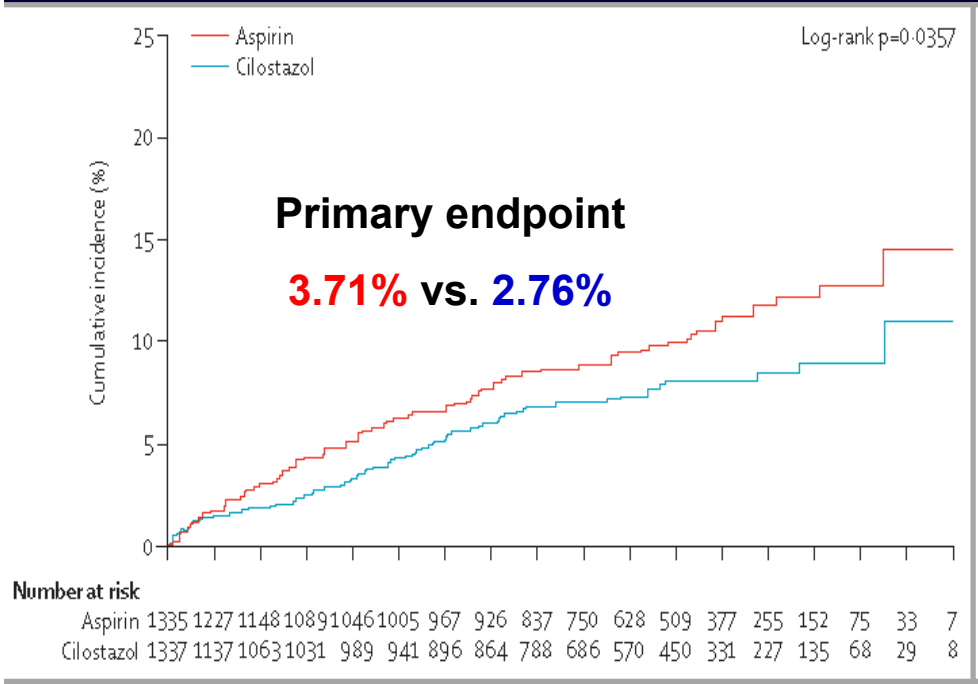
- **Bleeding time of APT** Wilhite et al. *J Vasc Surg* 2003;38:710-3.

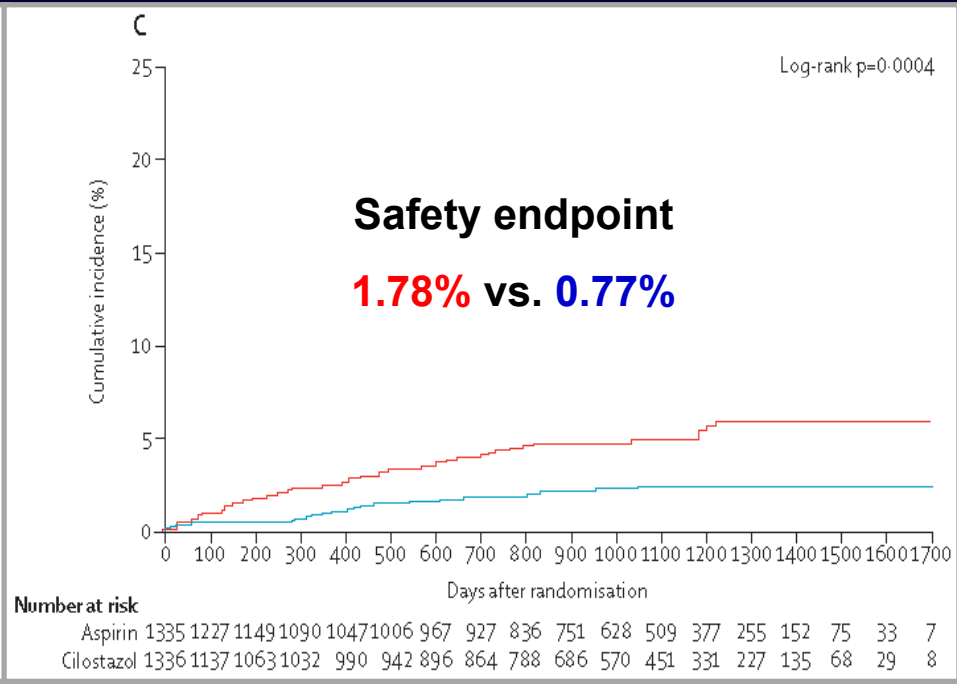


- **Endothelium-targeted antithrombotic therapy**
- **Relatively short recovery time of platelet function**

Antiplatelet and Vasodilation of Cilostazol

- Peripheral artery disease: FDA approved
- Secondary prevention of Cerebral infarction: more benefit than aspirin





CSPS 2. Shinohara et al. *Lancet Neurol* 2010; 9: 959–68.

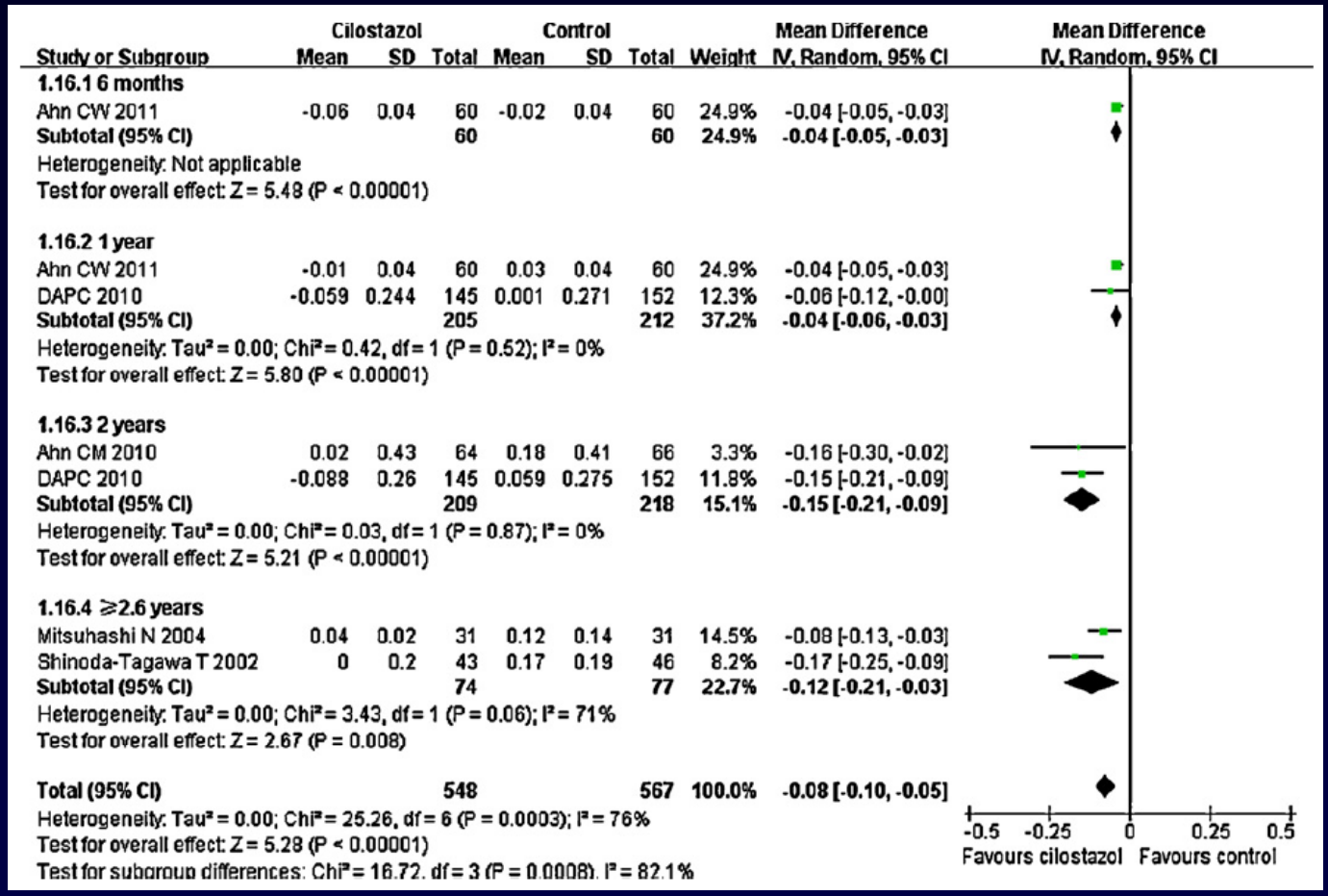
Effect of Cilostazol on Dyslipidemia

Authors	Year	No of patients	Dose mg (daily)	Duration (weeks)	Effect (%)	p
Triglycerides						
Dawson *et al.* [7]	1998	52	200	2	-24	NS
		50		4	-31	NS
		47		8	-28	NS
		44		12	-25	NS
Elam *et al.* [8]	1998	95	200	12	-15	< 0.001
Lee *et al.* [12]	2001	16	200	8	-29	< 0.05
Nakamura *et al.* [9]	2003	17	200	24	-34	< 0.01
Wang *et al.* [10]	2003	56	200	24	-23	< 0.01
Samra *et al.* [13]	2003	123	100/200	12	-30	NS
O'Donnell *et al.* [11]	2009	39	200	6	-19	< 0.01
				24	-27	< 0.05
HDL-C						
Money *et al.* [14]	1998	120	200	16	+11	NS
Dawson *et al.* [7]	1998	52	200	2	+8	NS
		50		4	+18	NS
		47		8	+18	NS
		44		12	+18	NS
Elam *et al.* [8]	1998	95	200	12	+10	< 0.001
Lee *et al.* [12]	2001	16	200	8	+12	< 0.05
Nakamura *et al.* [9]	2003	17	200	24	+4	NS
Wang *et al.* [10]	2003	56	200	24	+17	< 0.001
Samra *et al.* [13]	2003	123	100/200	12	+20	< 0.05
O'Donnell *et al.* [11]	2009	39	200	6	+7	< 0.001
				24	+14	< 0.001

Rizzo M, et al. *Expert Opin Pharmacother.* 2011;12:647-55.

Antiatherogenic Effect of Cilostazol

Progression of maximal carotid intima-media thickness (mm) (Metaanalysis: n = 698)



Study or Subgroup	Cilostazol Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.16.1 6 months								
Ahn CW 2011	-0.06	0.04	60	-0.02	0.04	60	24.9%	-0.04 [-0.05, -0.03]
Subtotal (95% CI)			**60**			**60**	**24.9%**	**-0.04 [-0.05, -0.03]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.48 (P < 0.00001)								
1.16.2 1 year								
Ahn CW 2011	-0.01	0.04	60	0.03	0.04	60	24.9%	-0.04 [-0.05, -0.03]
DAPC 2010	-0.059	0.244	145	0.001	0.271	152	12.3%	-0.06 [-0.12, -0.00]
Subtotal (95% CI)			**205**			**212**	**37.2%**	**-0.04 [-0.06, -0.03]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.42$, df = 1 (P = 0.52); $I^2 = 0\%$								
Test for overall effect: Z = 5.80 (P < 0.00001)								
1.16.3 2 years								
Ahn CM 2010	0.02	0.43	64	0.18	0.41	66	3.3%	-0.16 [-0.30, -0.02]
DAPC 2010	-0.088	0.26	145	0.059	0.275	152	11.8%	-0.15 [-0.21, -0.09]
Subtotal (95% CI)			**209**			**218**	**15.1%**	**-0.15 [-0.21, -0.09]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.03$, df = 1 (P = 0.87); $I^2 = 0\%$								
Test for overall effect: Z = 5.21 (P < 0.00001)								
1.16.4 ≥2.6 years								
Mitsuhashi N 2004	0.04	0.02	31	0.12	0.14	31	14.5%	-0.08 [-0.13, -0.03]
Shinoda-Tagawa T 2002	0	0.2	43	0.17	0.19	46	8.2%	-0.17 [-0.25, -0.09]
Subtotal (95% CI)			**74**			**77**	**22.7%**	**-0.12 [-0.21, -0.03]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.43$, df = 1 (P = 0.06); $I^2 = 71\%$								
Test for overall effect: Z = 2.67 (P = 0.008)								
Total (95% CI)			**548**			**567**	**100.0%**	**-0.08 [-0.10, -0.05]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 25.26$, df = 6 (P = 0.0003); $I^2 = 76\%$								
Test for overall effect: Z = 5.28 (P < 0.00001)								
Test for subgroup differences: $Chi^2 = 16.72$, df = 3 (P = 0.0008), $I^2 = 82.1\%$								

Mean Difference IV, Random, 95% CI

-0.5 -0.25 0 0.25 0.5

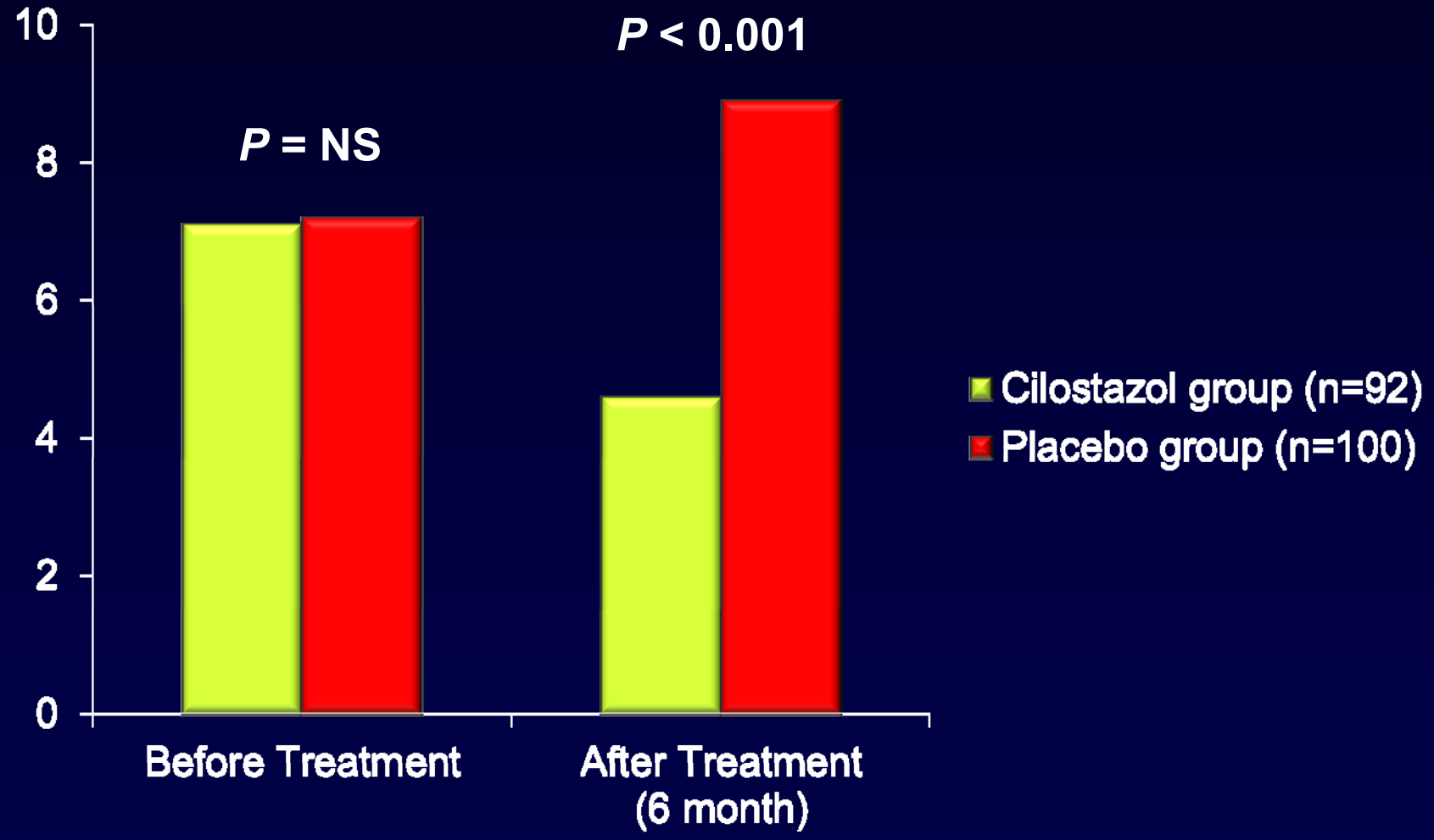
Favours cilostazol Favours control

Unproven effect of cilostazol on CAD plaque progression

Geng DF et al. *Atherosclerosis.* 2012;220:177-83.

Effect of Cilostazol on Inflammation

High-sensitivity CRP (mg/L) in Type 2 DM patients with PAOD (n = 192)



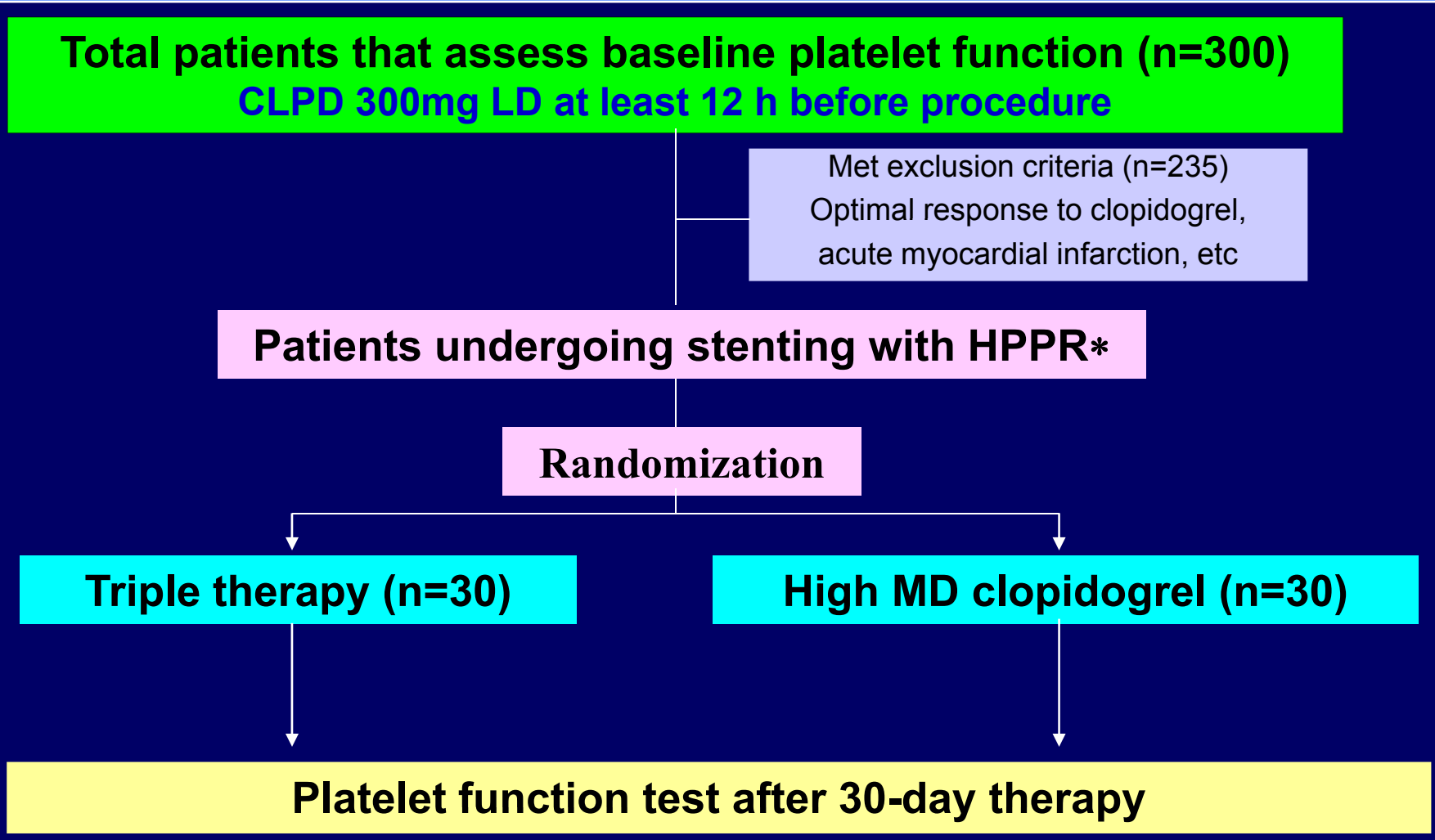
Hsieh, et al. *Circ J* 2009;73:948–954.

“ACCEL” series: searching for cilostazol’s secret

- ACCEL-RESISTANCE (J Am Coll Cardiol)
- ACCEL-AMI (Circ Cardiovasc Interv)
- ACCEL-COMPLEX (Thromb Haemost)
- ACCEL-DM (Diabetes Care)
- ACCEL-POLYMORPHISM (Circ Cardiovasc Interv)
- ACCEL-AMI2C19 (JACC Cardiovsc Interv)
- ACCEL-DOUBLE (JACC Cardiovasc Interv)
- ACCEL-TRIPLE (Br J Clin Pharmacol)
- ACCEL-SWITCH (J Thromb Haemost)
- ACCEL-DOUBLE-2N3 (Eur Heart J: in submission)
- ACCEL-PPI (ACC 2012)
- ACCEL-LOADING-ACS (TCTAP 2012 LBCT session)
- ACCEL-HPR (on writing)
- ACCEL-PARAZOL (on writing)
- ACCEL-EPISODE (on going)

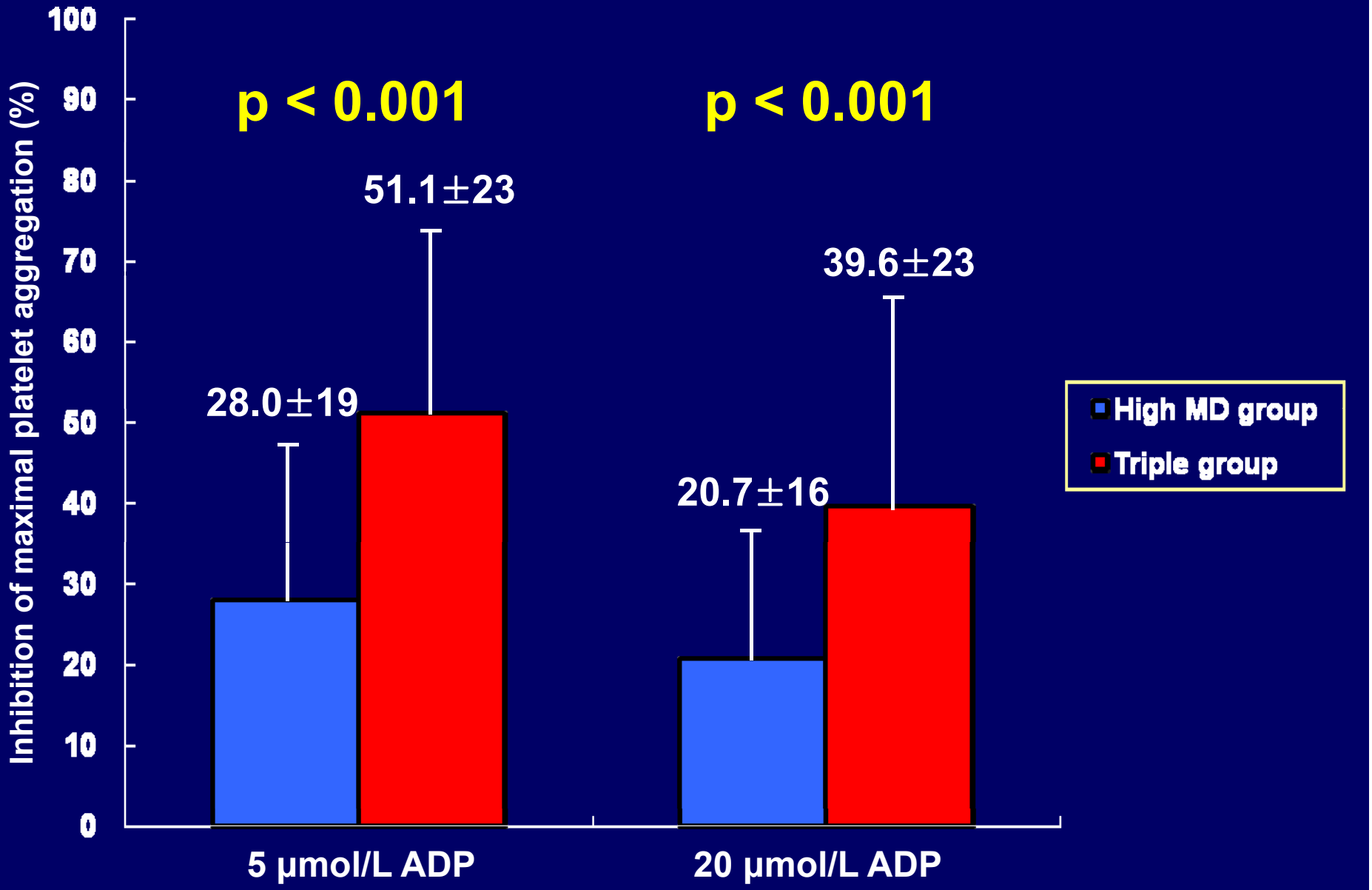
*A*djunctive *C*ilostazol vs. high-MD *C*lopidogr*EL* in HPR (ACCEL-RESISTANCE study)

*High On-Tx Platelet Reactivity (HPR) : 5 μM ADP-induced PA > 50%



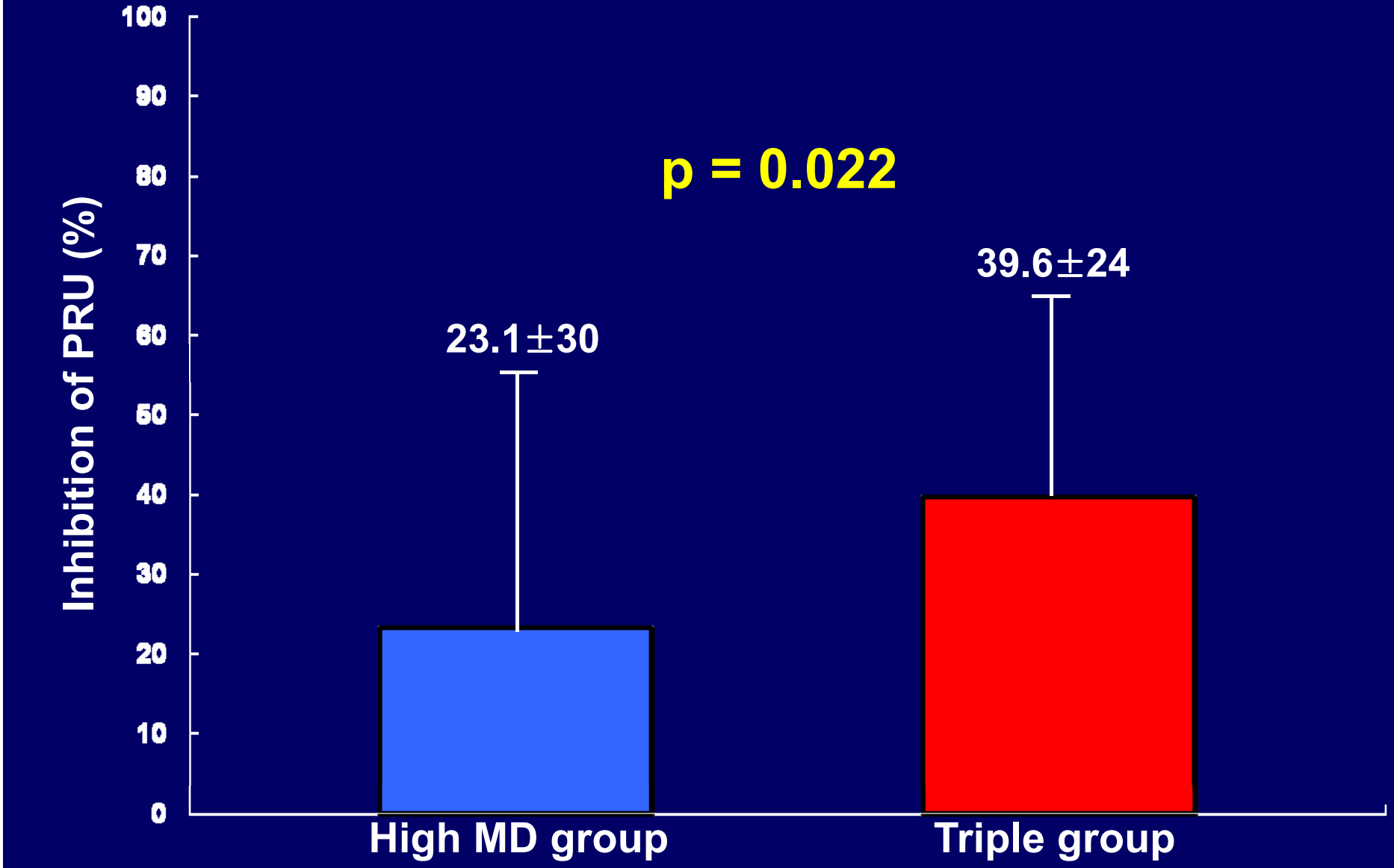
Jeong YH, et al. *JACC* 2009;53:1101.

Inhibition of Maximal Platelet Aggregation



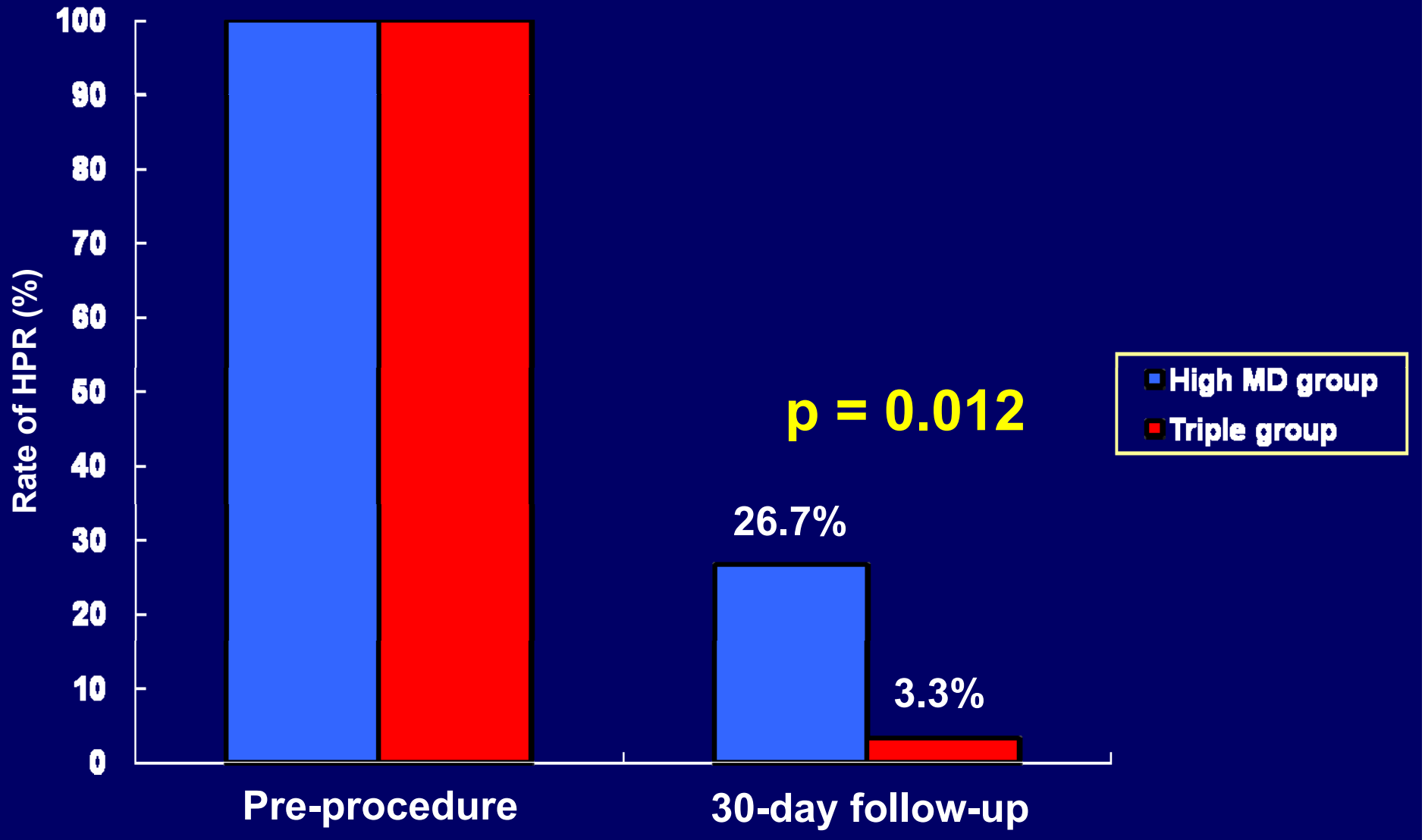
Jeong YH, et al. *JACC* 2009;53:1101.

Percent change of PRU



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

Rate of HPR
(5 μM ADP-induced PA > 50%)



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

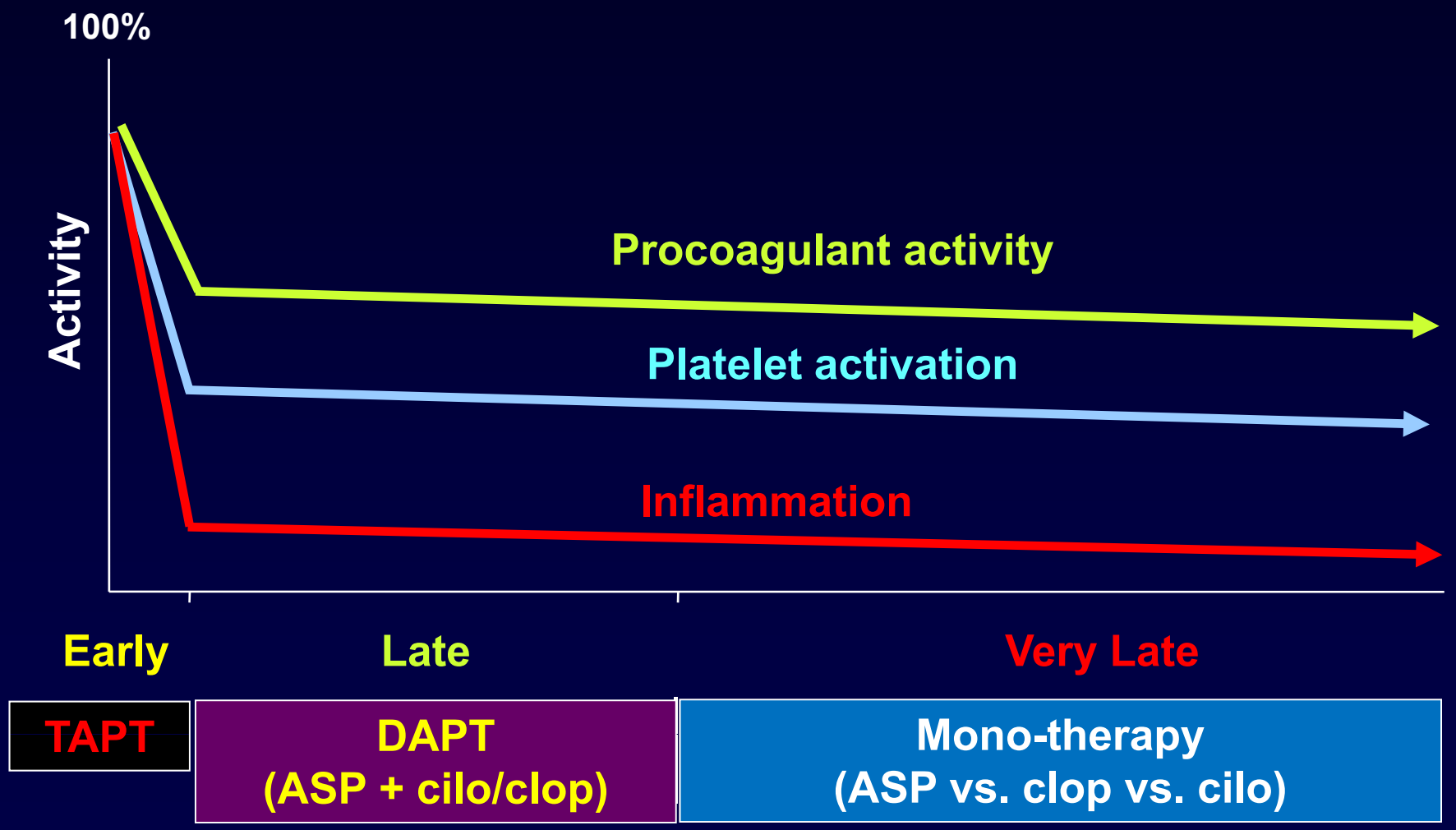
"ACCEL" series: searching for cilostazol's secret

- ACCEL-RESISTANCE: Clopidogrel nonresponsiveness
- ACCEL-AMI: AMI patients
- ACCEL-COMPLEX: Complex PCI
- ACCEL-DM: Diabetes patients
- ACCEL-POLYMORPHISM: CYP2C19 polymorphism
- ACCEL-AMI2C19: CYP2C19 polymorphism
- ACCEL-PPI: proton pump inhibitor

Proven efficacy of adjunctive cilostazol to DAPT

- HPR
- AMI
- DM
- Complex PCI
- *CYP2C19* polymorphism
- Proton pump inhibitor

Postulated Disease Activity in East Asians



CIDES Trial

(Cilostazol for Diabetic Patients in DES)

280 DM patients undergoing elective PCI:

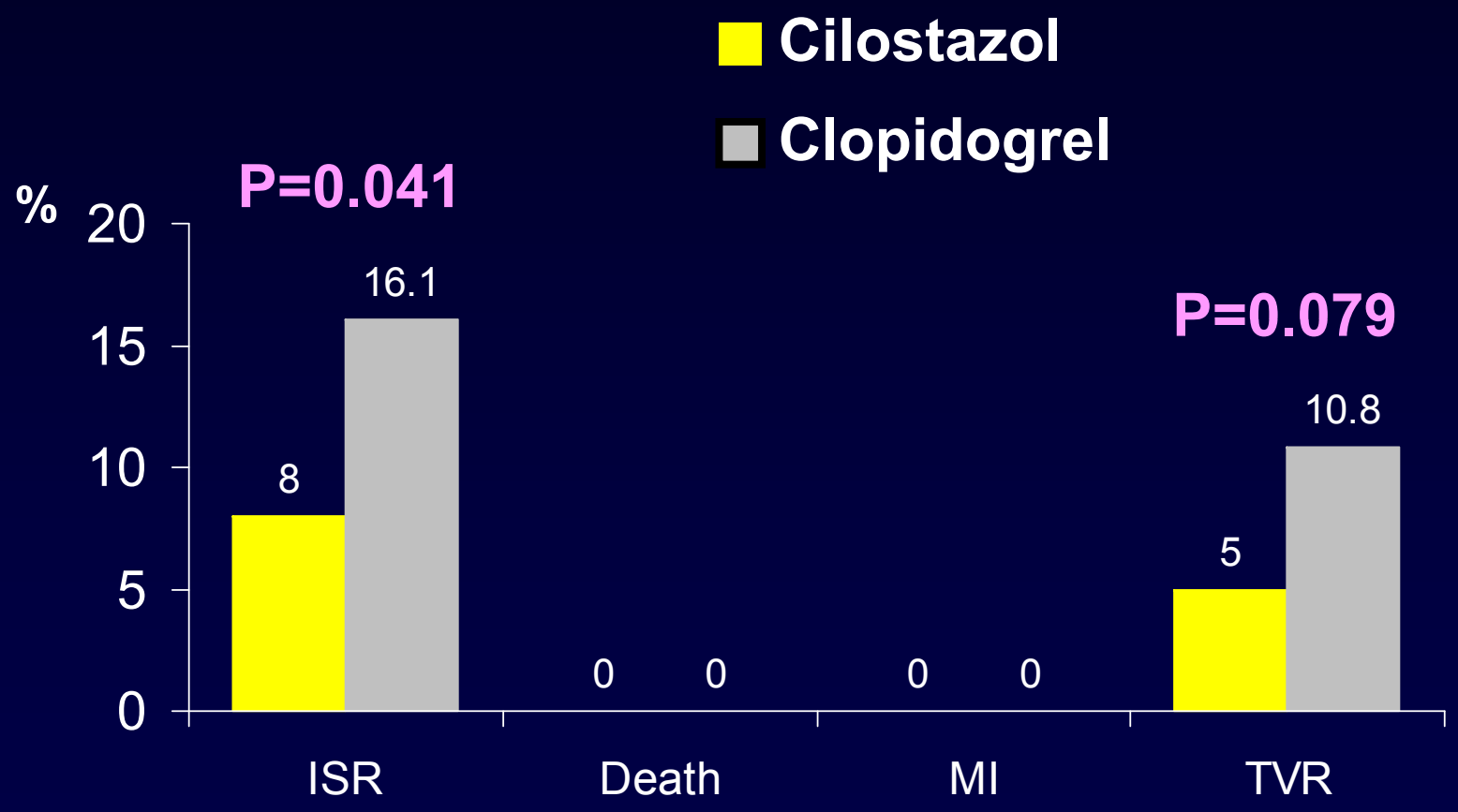
Aspirin+ Clopidogrel + Cilostazol for 1 mo.

Clopidogrel 75 mg/d for 5 mo. (n = 139)	Cilostazol 100 mg bid for 5 mo. (n = 141)

- Primary end point: MLD at 6 mo.
- Secondary end point: mean %DS, ISR, MACE

Ahn YK, et al. *Circ J* 2008;72:35.

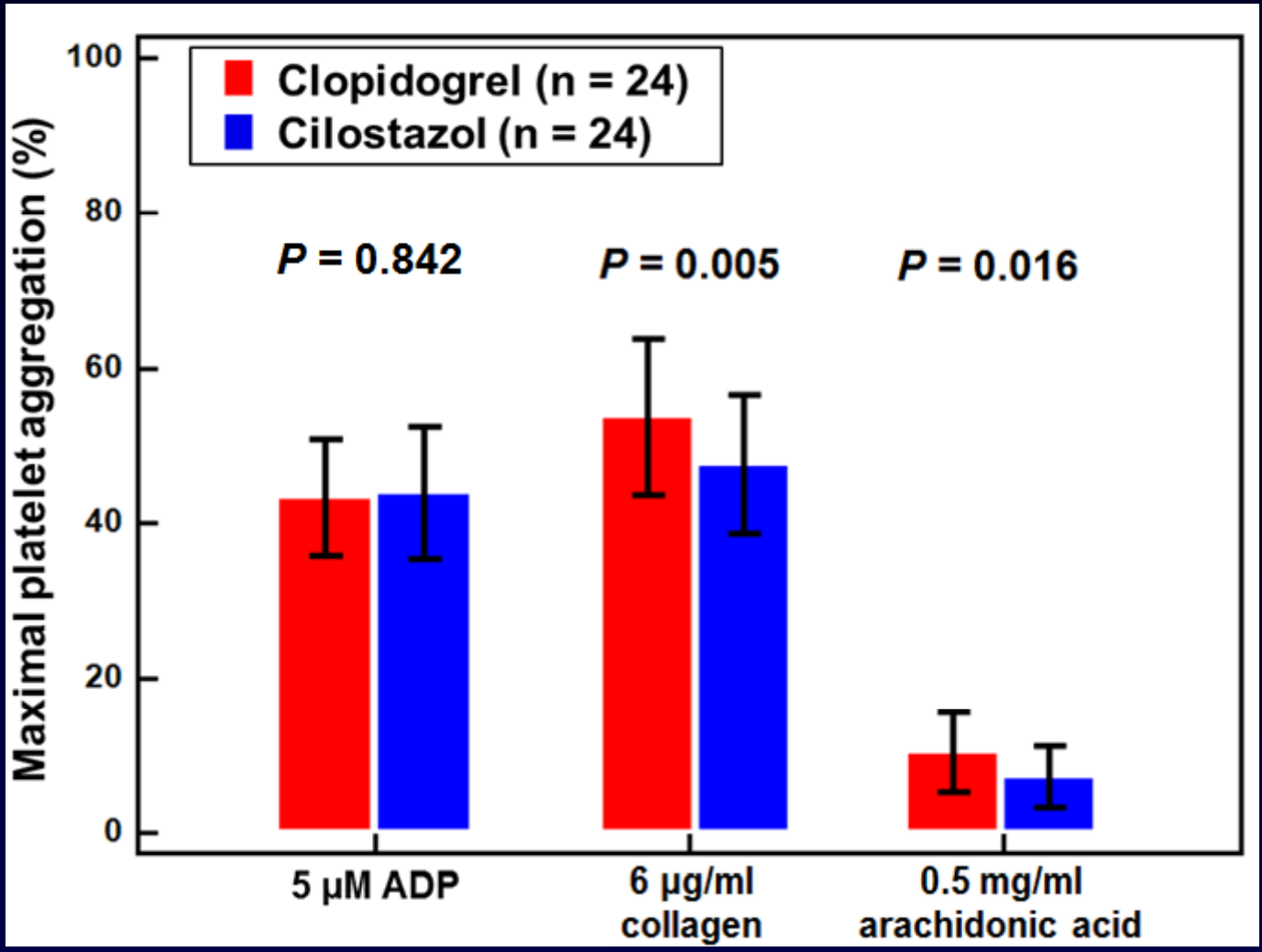
Clinical events at 6 months



Ahn YK, et al. *Circ J* 2008;72:35.

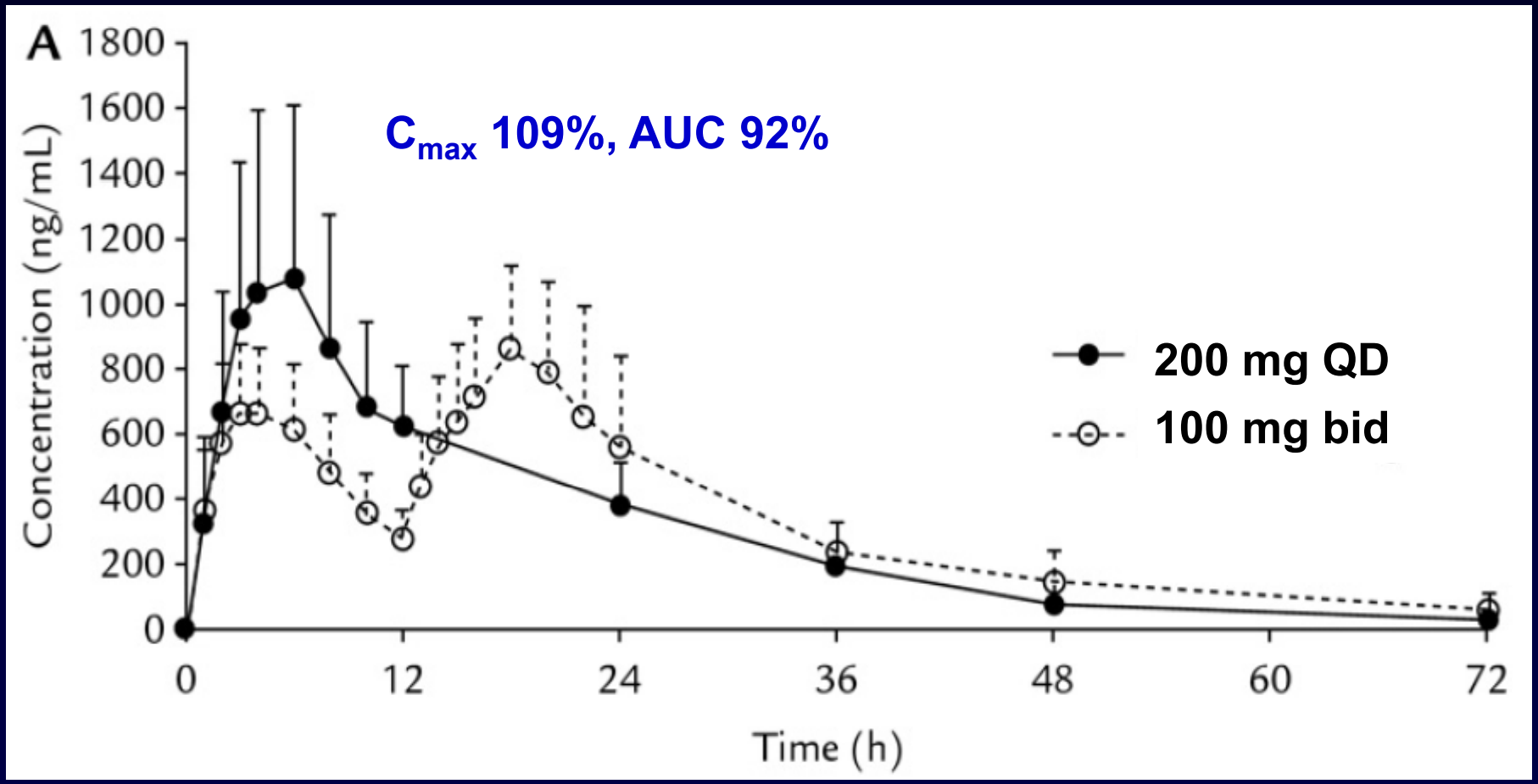
PD Effect of Clopidogrel vs. Cilostazol in DES-treated patients

CYP2C19 LoF allele carriers



Jeong YH, et al. *J Thromb Haemost*; in revision.

PK of Shorting-acting vs. Slow-release Cilostazol



Lee DH, et al. *Clin Ther.* 2011;33:2038-53

God did not want to use “the same language”

God might want “multidisciplinary approach” and “race-based antithrombotic treatment”