Ideal patient population for different antiplatelet agents:

Focus on Prasugrel

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What are our options for antiplatelet therapy after PCI?

What are our options?

1. **Aspirin + Plavix (75mg)**
2. **Aspirin + Double dose plavix (150mg): DDAT**
3. **Aspirin + Plavix (75mg) + Cilostazol (200mg): TAT**
4. **Aspirin + Ticagrelor**
5. **Aspirin + Prasugrel**

CURRENT

Study Design

25,087 ACS Patients (UA/NSTEMI 70.8%, STEMI 29.2%)

- ✓ Planned Early (<72 h) Invasive Management with **intended PCI**
- ✓ Ischemic ECG Δ (80.8%) or ↑cardiac biomarker (42%)

Randomized to receive (2 X 2 factorial):

CLOPIDOGREL: Double-dose (600 mg then150 mg/d x 7d then 75 mg/d) **vs Standard dose** (300 mg then 75 mg/d)

ASA: High Dose (300-325 mg/d) **vs Low dose** (75-100 mg/d)

CAG 24,769 (99%)

PCI 17,232 (70%)

No PCI 7,855 (30%)

No Sig. CAD 3,616

CABG 1,809

CAD 2,430

Compliance:

Clop in 1st 7d (median) **7d** **7 d** **2 d** **7d**

Efficacy Outcomes: CV Death, MI or stroke at day 30
Stent Thrombosis at day 30

Safety Outcomes: Bleeding (CURRENT defined Major/Severe and TIMI Major)

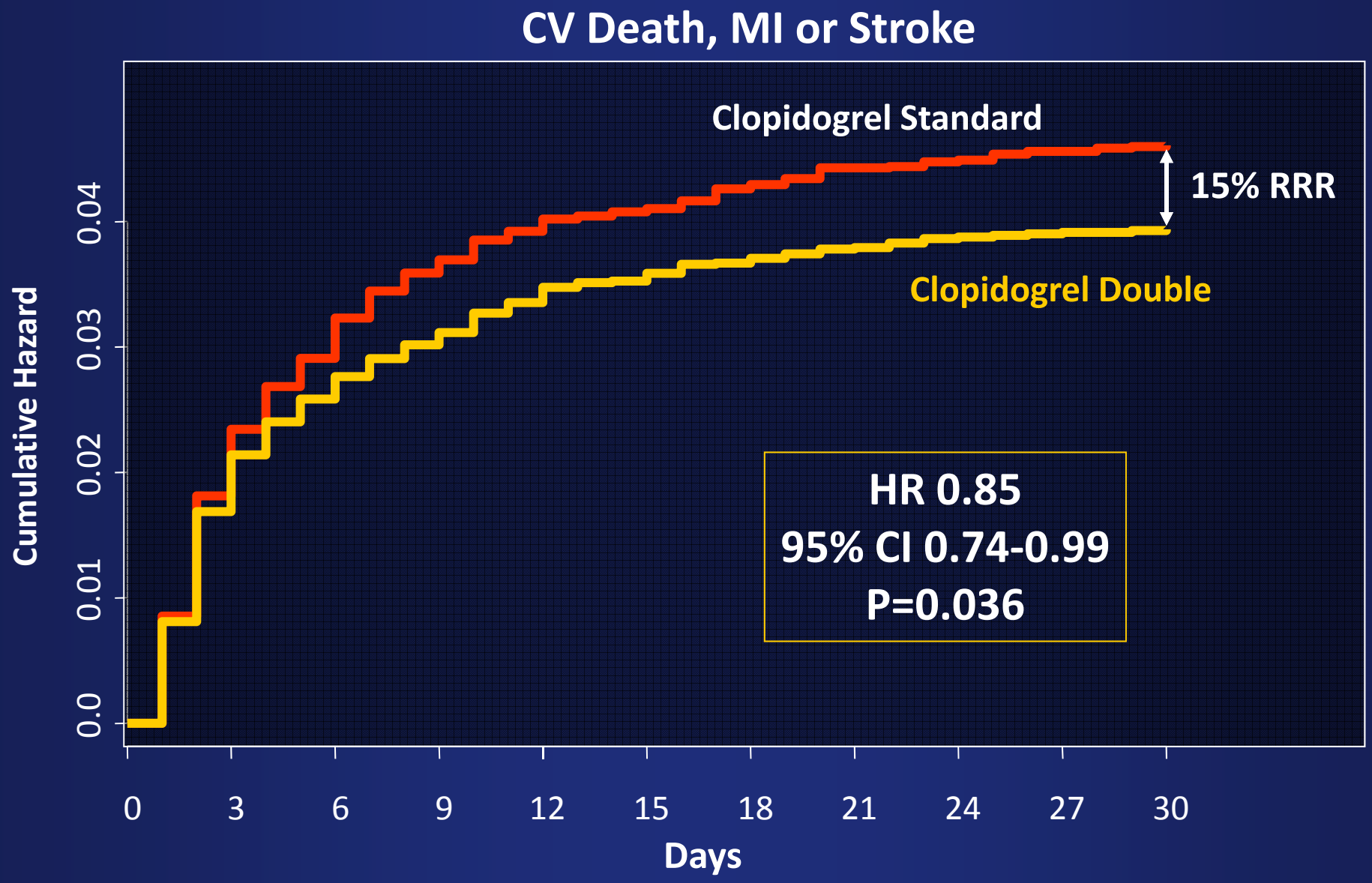
Key Subgroup: PCI v No PCI

Complete Followup 99.8%

CURRENT

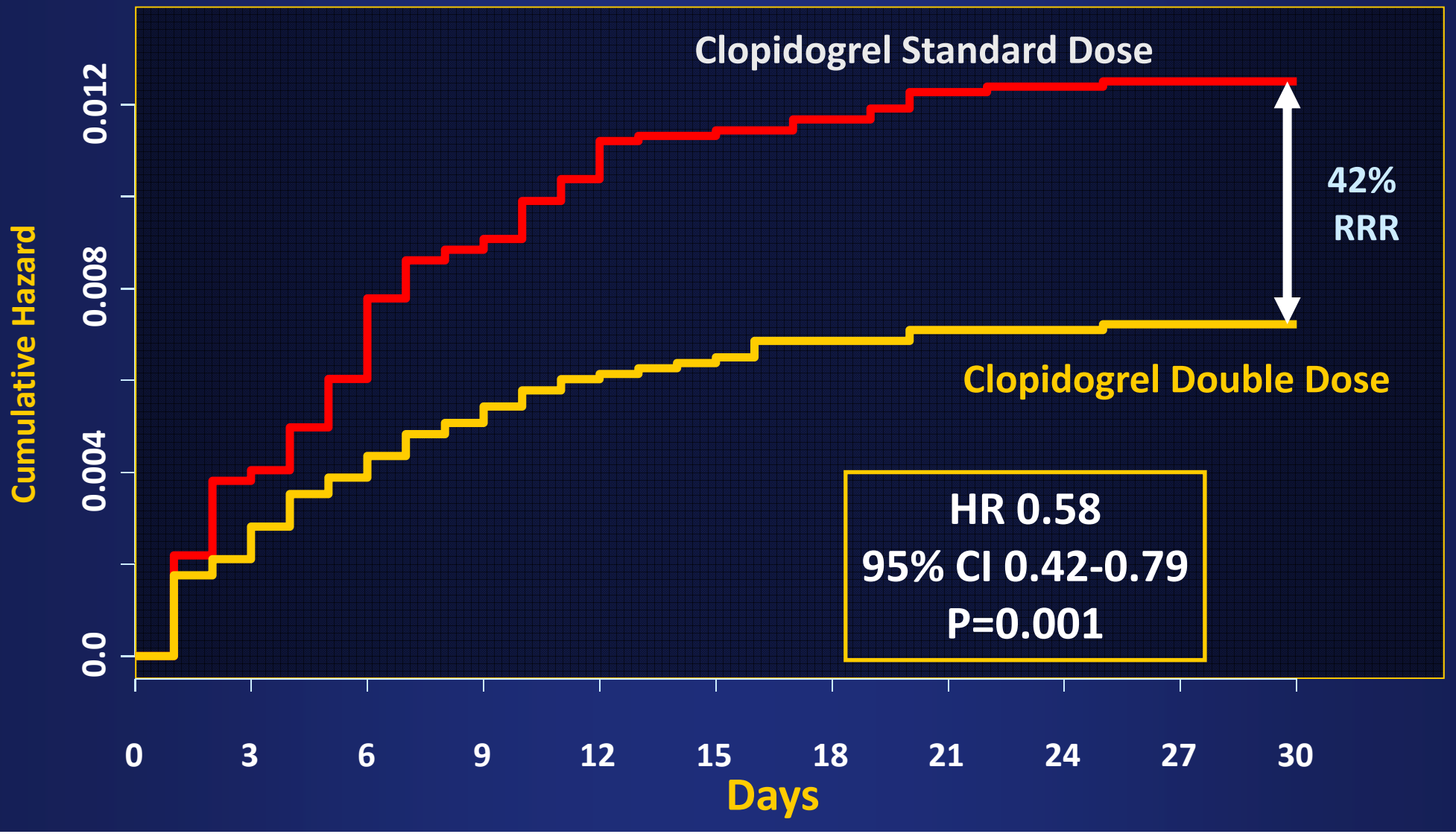
Clopidogrel: Double vs Standard Dose

Primary Outcome: PCI Patients



CURRENT

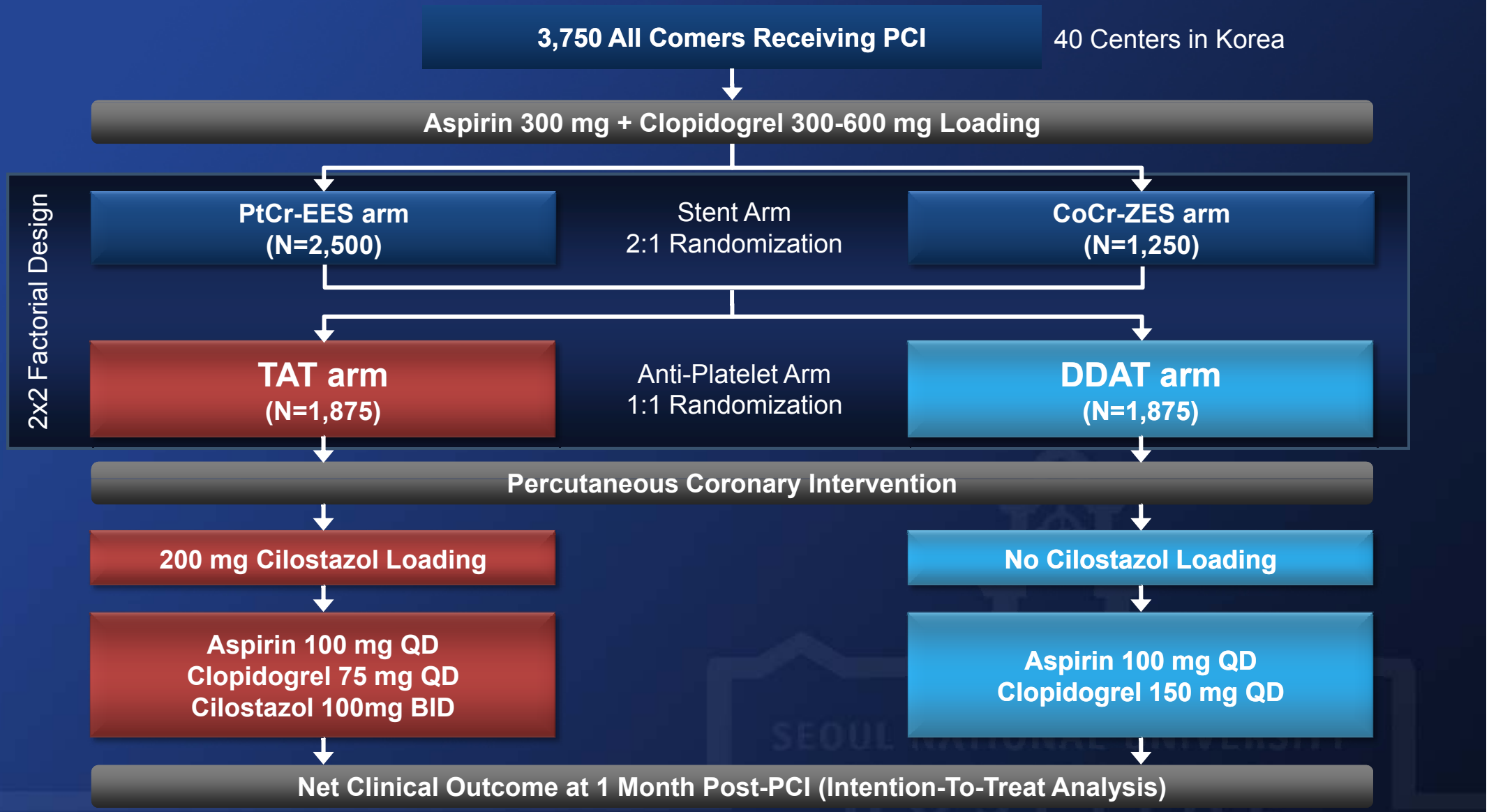
Clopidogrel: Double vs Standard Dose
Definite Stent Thrombosis (Angio confirmed)



Study Design

Prospective, single-blinded, randomized multi-center trial

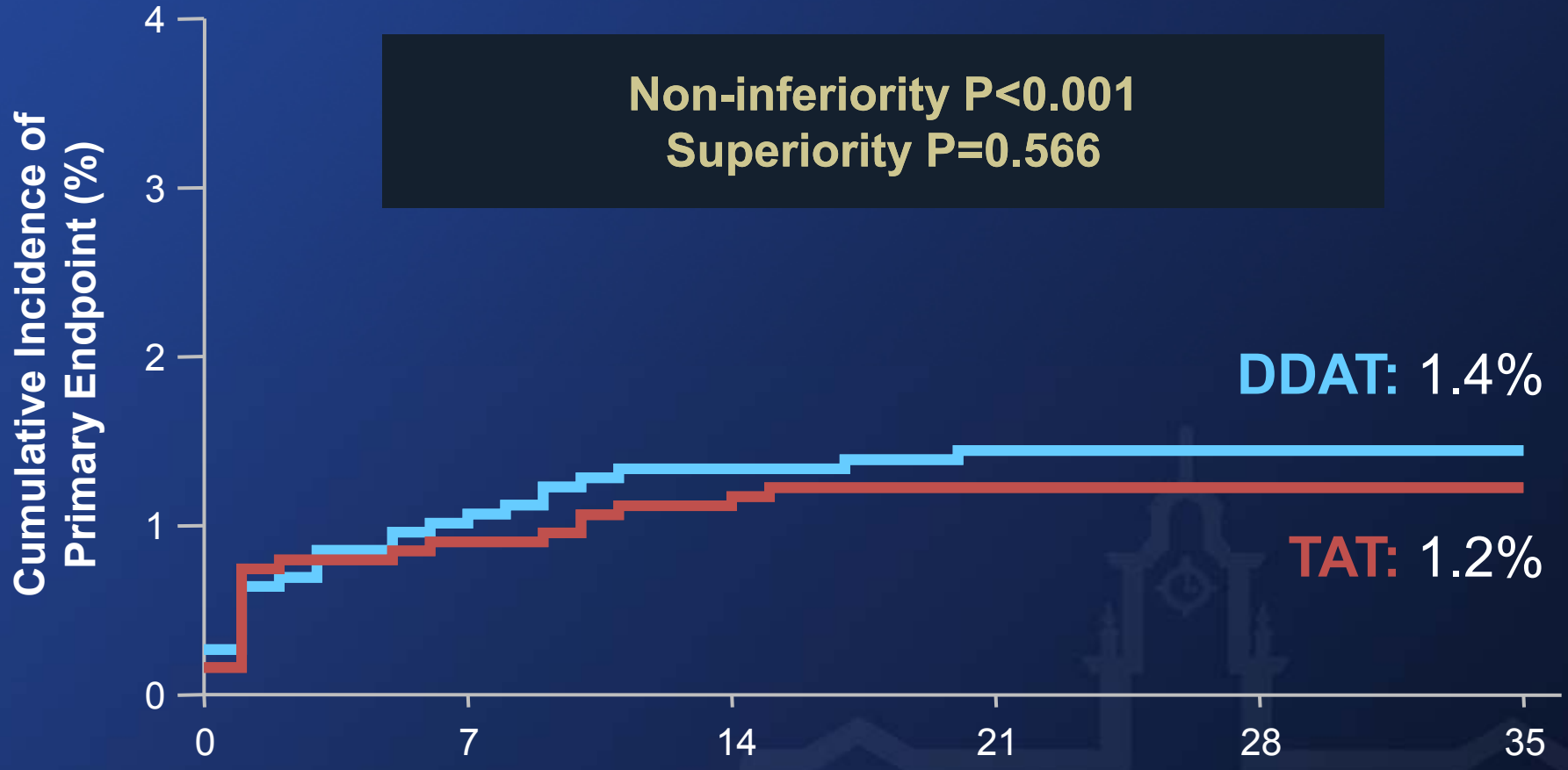
HOST ASSURE



Primary Endpoint

HOST ASSURE

Composite of Cardiac death, nonfatal MI, stroke, definite/probable ST, and PLATO major bleeding

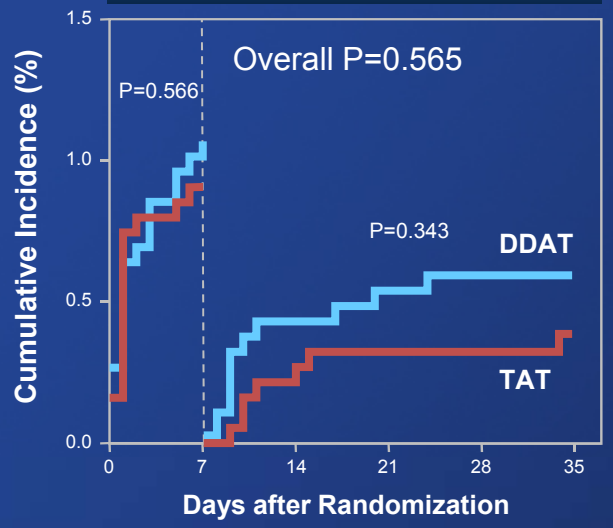


No. at Risk						
TAT	1,879	1,855	1,845	1,832	1,763	1,538
DDAT	1,876	1,848	1,836	1,820	1,764	1,525

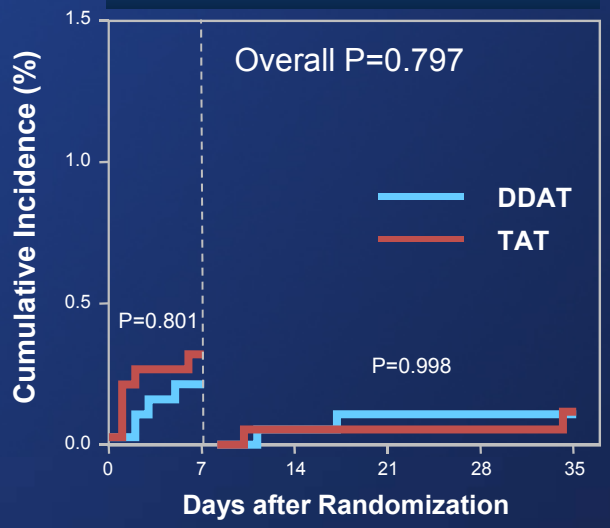
Landmark Analysis

HOST ASSURE

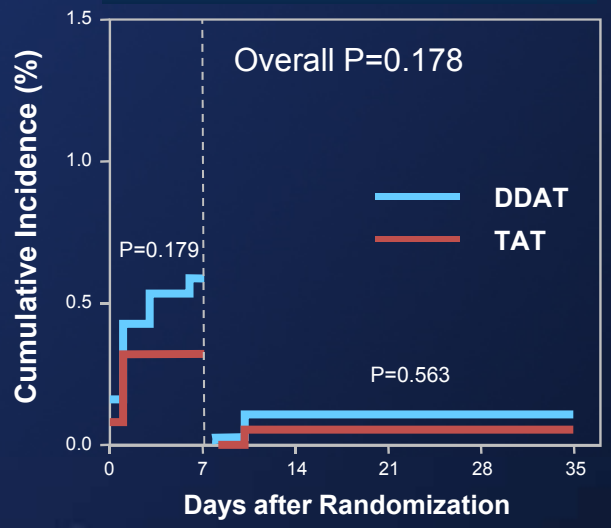
Primary Endpoint



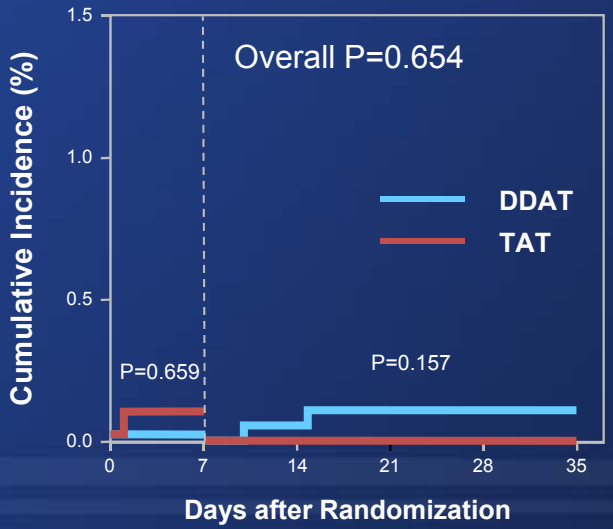
Cardiac Death



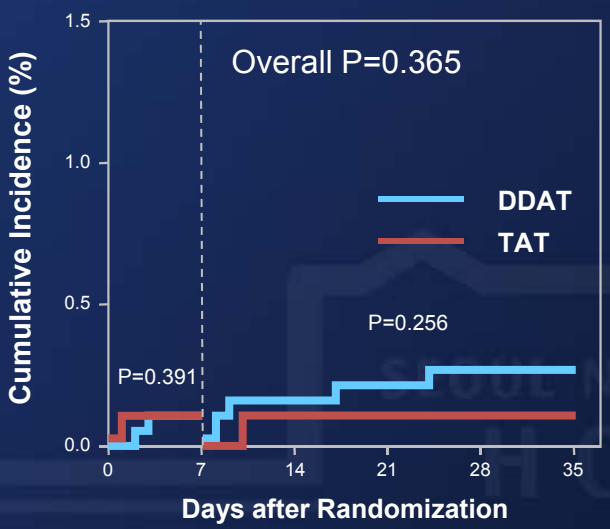
Nonfatal MI



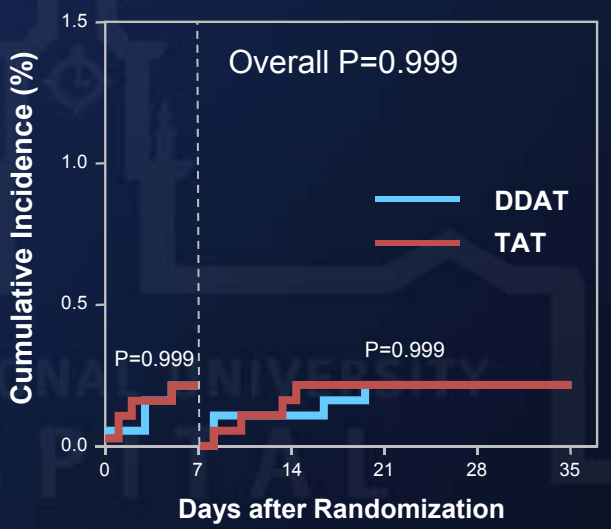
Stroke



Definite/Probable ST



PLATO Major Bleeding



Why do we need newer agents?

1. Unmet needs in thrombosis : higher efficacy needed in adverse clinical situations.

2. Wide variability in Clopidogrel response

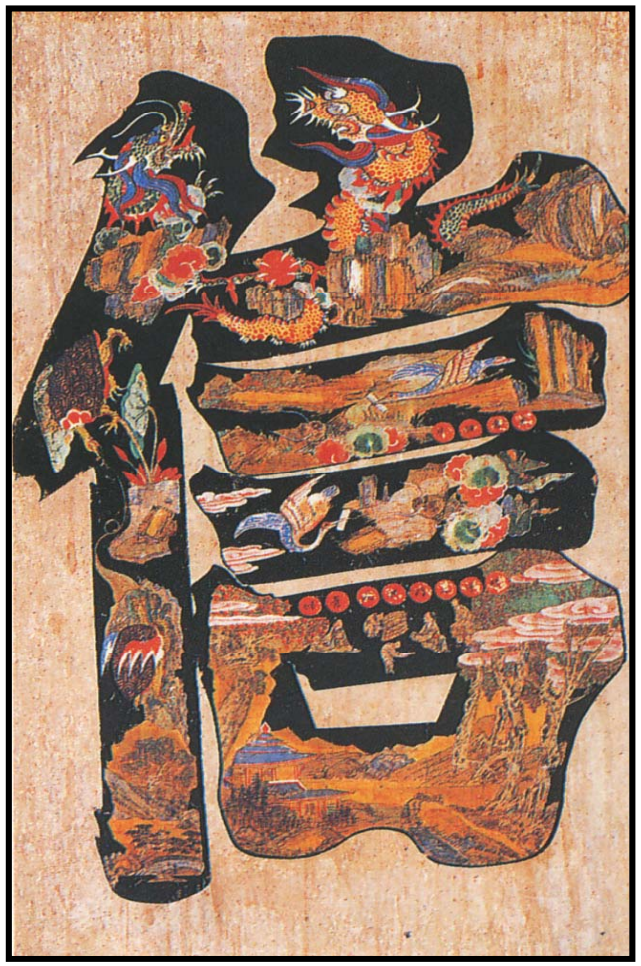
a. genetic variation

b. possible drug interactions (Cytochrome enzymes): PPIs, lipophilic statins, CCBs etc

→ We need a more reliable antiplatelet agent!

Reliability:

ability of a person or system to perform and maintain its functions in routine circumstances, as well as hostile or unexpected circumstances.



Why do we need newer agents?

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2. Wide variability in Clopidogrel response

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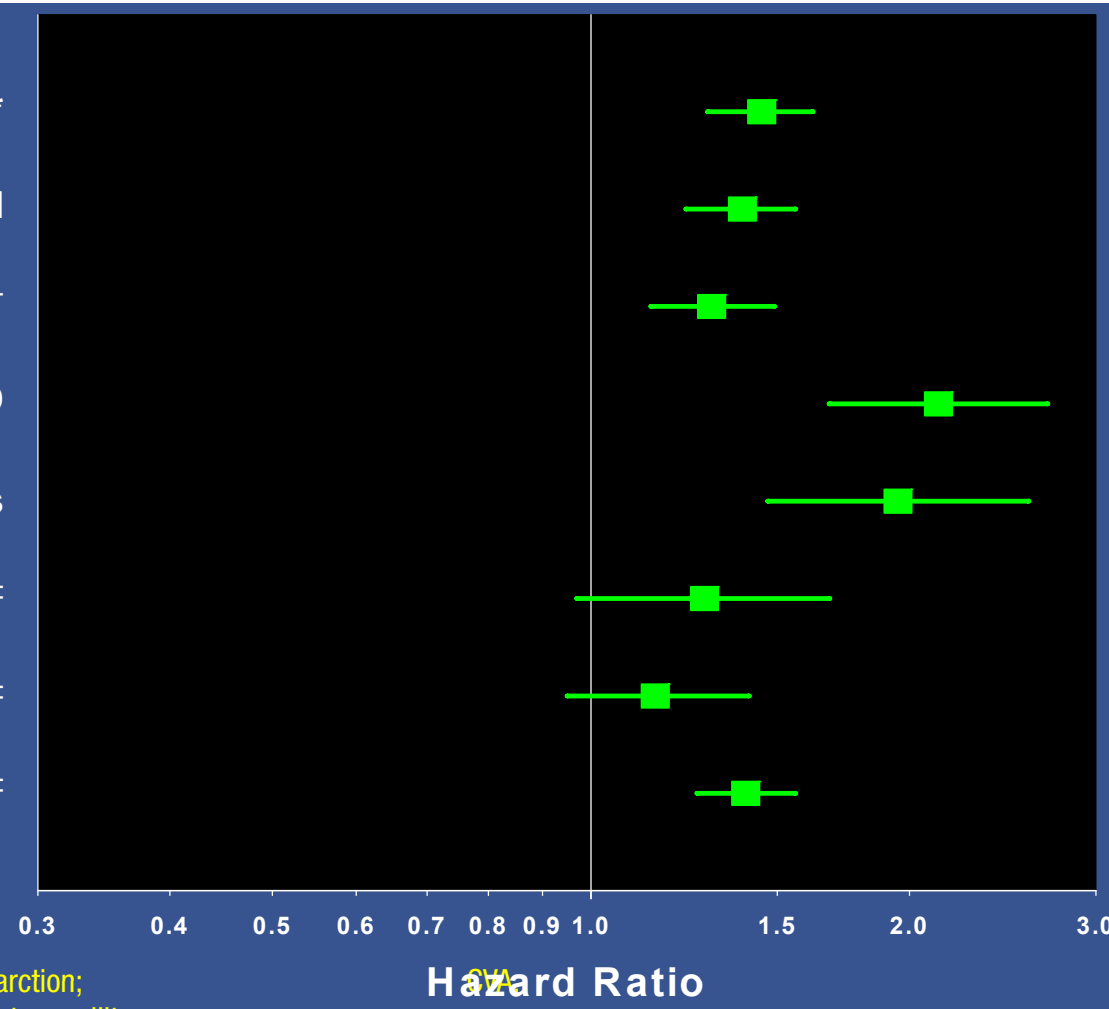
Results – Clinical Events by DM Status (DM vs. No DM)



	DM (%)	No DM (%)
CVD/MI/CVA*	14.6	9.9
CVD/MI	13.1	9.2
MI†	10.7	8.0
CVD	3.8	1.8
Stent thrombosis	2.8	1.4
Major bleed‡	2.6	2.0
Major or minor bleed‡	4.8	4.2
D/MI/CVA*/Major bleed‡	16.9	11.9

CVD,cardiovascular death; MI, myocardial infarction; CVA, cerebrovascular accident; D, death; DM, diabetes mellitus

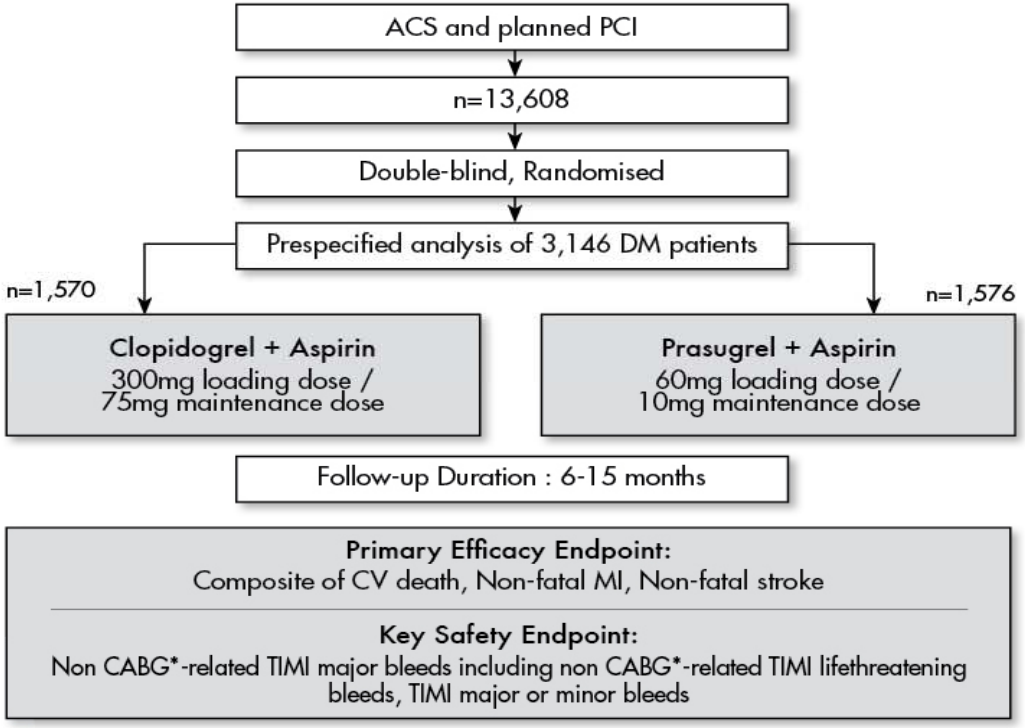
*The composite of cardiovascular death, nonfatal MI, or nonfatal stroke

†Any MI (fatal or nonfatal)

‡Not related to CABG

Data from Wiviott SD, et al. *Circulation*. 2008;118(16):1626-1636

Prespecified Analysis of DM in TRITON TIMI 38



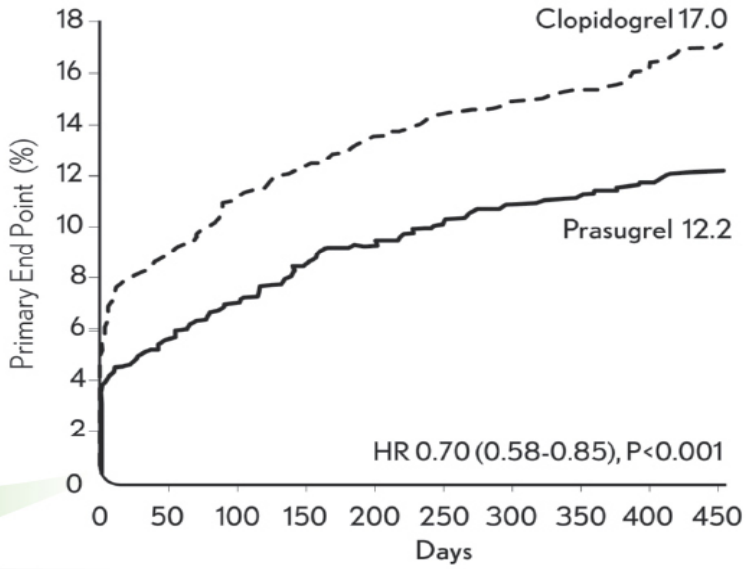
*CABG: coronary-artery bypass grafting

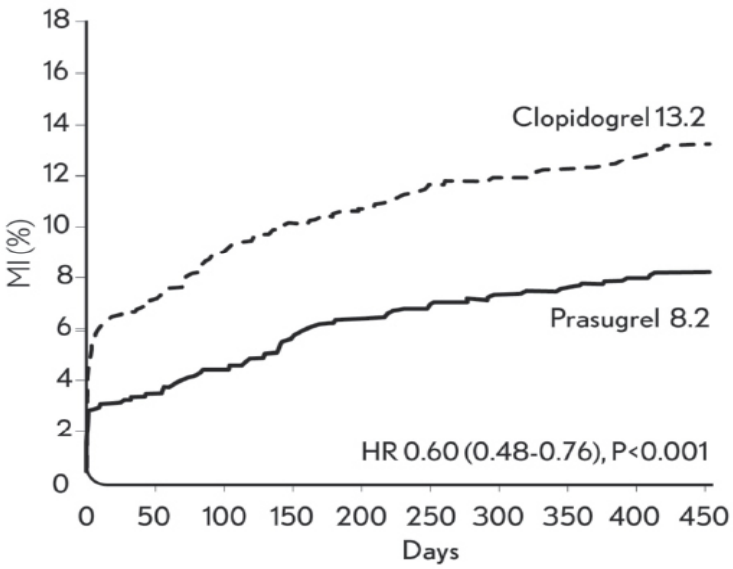
- Classified 13,608 subjects on the basis of preexisting history of DM and further according to insulin use. Prespecified analyses of the primary and key secondary end points, including net clinical benefit were compared by use of the log-rank test. [20]
- 3,146 subjects had a preexisting history of DM, including 776 receiving insulin[20]
  - Clopidogrel + Aspirin : 1,570 subjects - Prasugrel + Aspirin : 1,576 subjects

Data from Ref 20. Wiviott SD et al. Circulation. 2008;118:1626-1636

Efficacy Endpoints

- 30% relative risk reduction of primary efficacy endpoints (CV death, non-fatal MI or stroke) in diabetic patient group vs. 19% relative risk reduction in whole population compared with clopidogrel [10, 20]
- 40% relative risk reduction of myocardial infarction in diabetic patient group vs. 24% relative risk reduction in whole population compared with clopidogrel [10, 20]

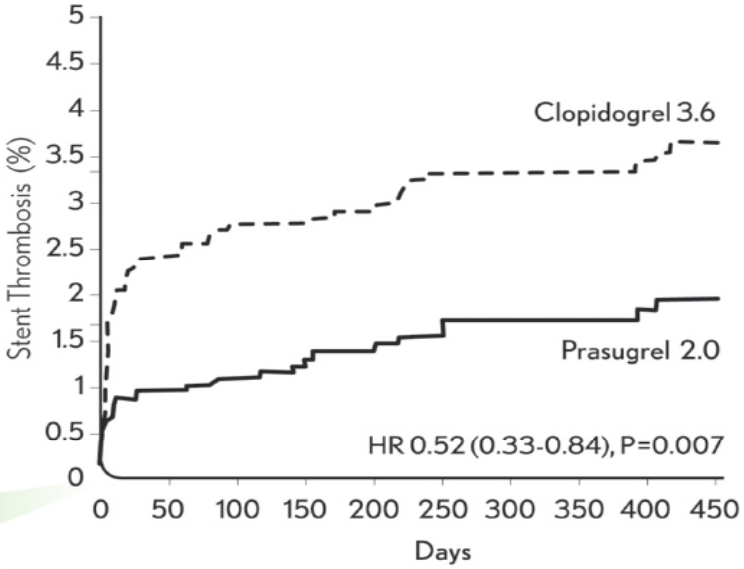


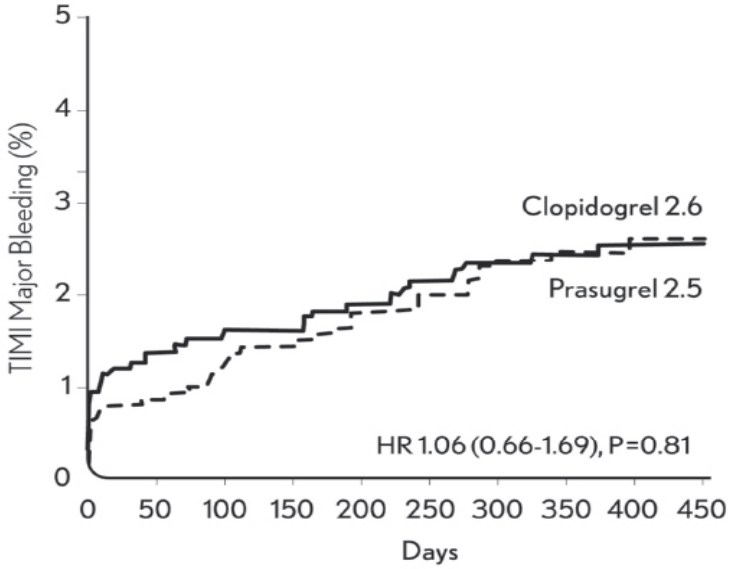


Data from Ref 20. Wiviott SD et al. Circulation. 2008;118(16):1626-1636

Efficacy and Safety Endpoints

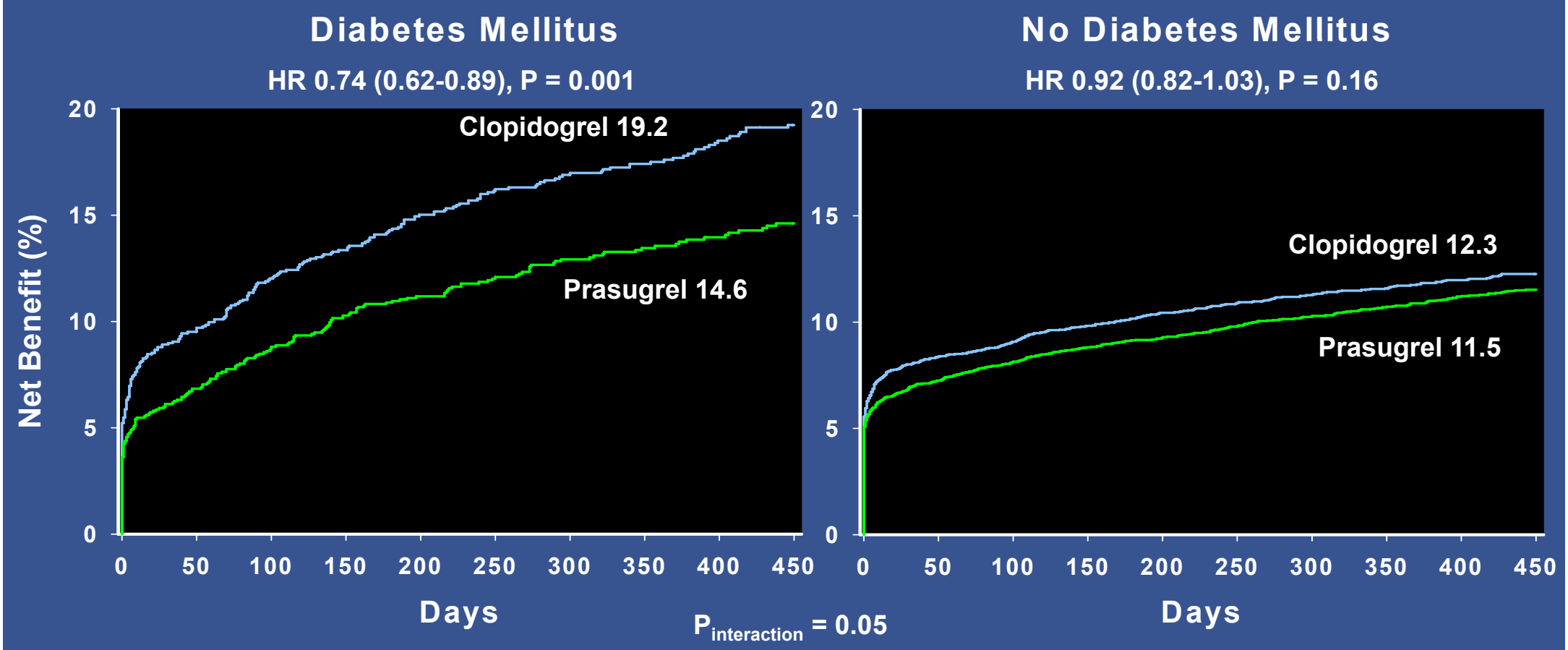
- 48% relative risk reduction of stent thrombosis in diabetic patient group vs. 52% relative risk reduction in whole population compared with clopidogrel [10, 20]
- No increase of major bleeding in diabetic population, leading to a greater net clinical benefit of prasugrel in diabetic patients [20]





Data from Ref 20. Wiviott SD et al. Circulation. 2008;118(16):1626-1636

Prasugrel vs. Clopidogrel by DM Status: Net clinical benefit*

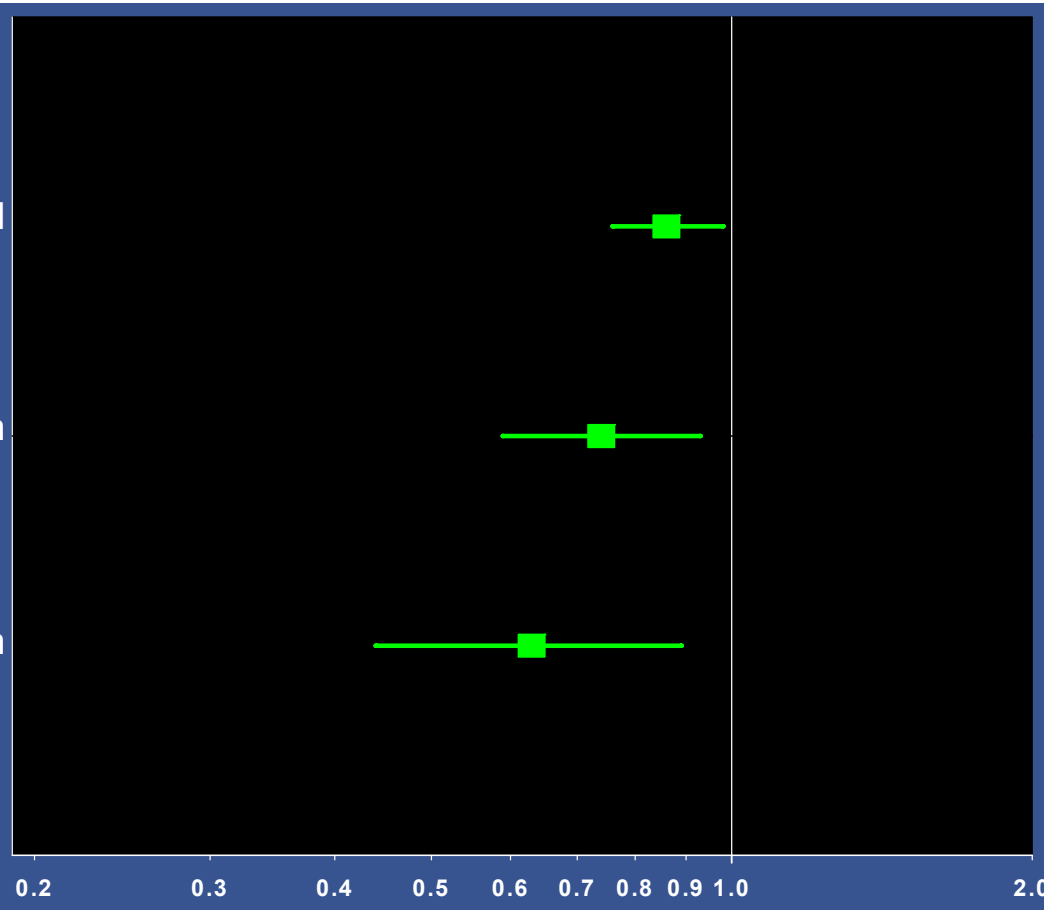


¥Death, nonfatal MI, nonfatal cerebrovascular accident, nonfatal TIMI major bleed not related to CABG

HR, hazard ratio; MI, myocardial infarction; DM, diabetes mellitus CABG, coronary artery bypass graft

Data from Wiviott SD, et al. *Circulation*. 2008;118(16):1626-1636

Results – Reduction in Primary End Point* by DM Status and Treatment Group



	Clopidogrel (%)	Prasugrel (%)	Reduction In Risk (%)
No DM	10.6	9.2	14
DM no insulin	15.3	11.5	26
DM on insulin	22.2	14.3	37

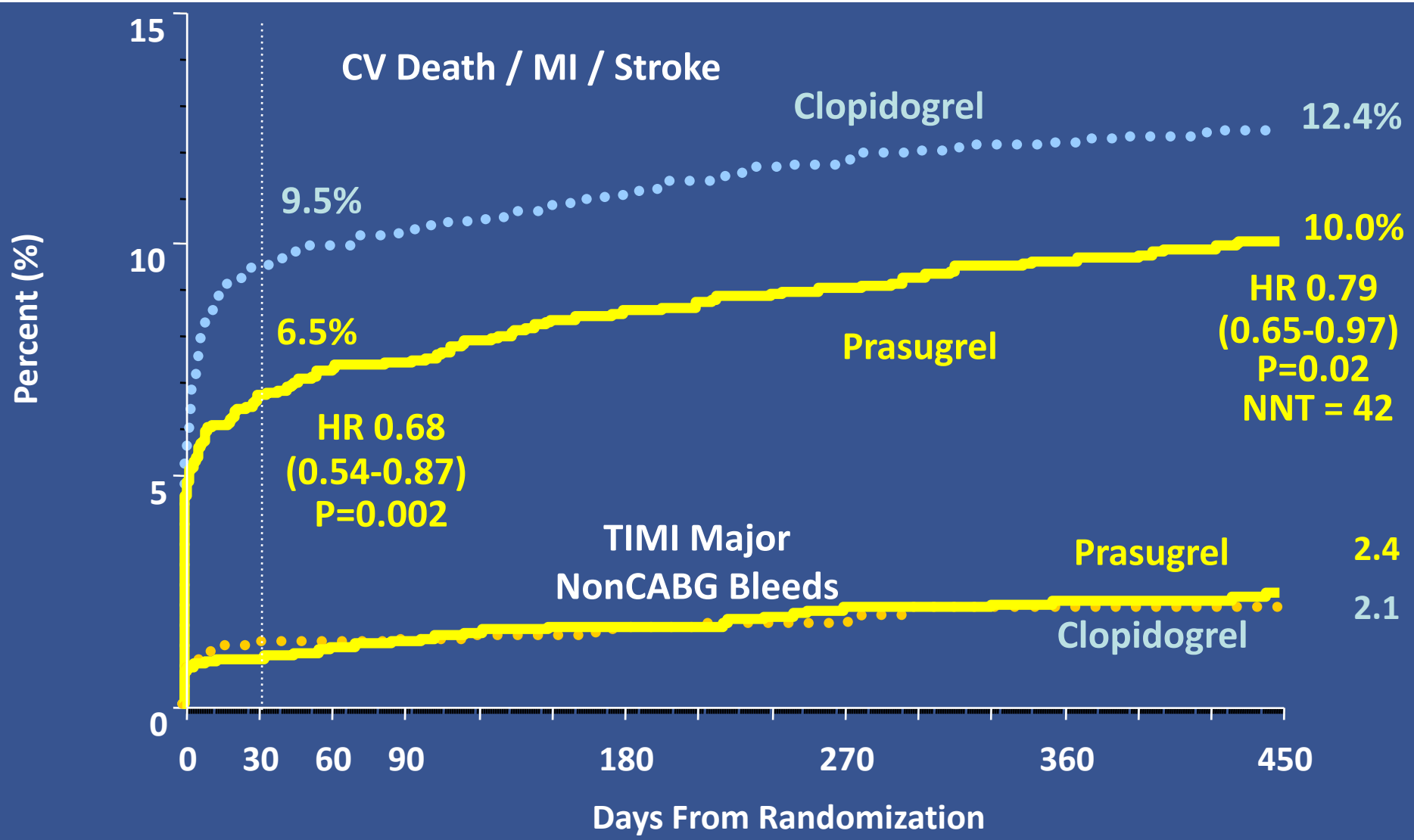
*The composite of cardiovascular death, nonfatal MI, or nonfatal stroke

DM, diabetes mellitus

Data from Wiviott SD, et al. *Circulation*. 2008;118(16):1626-1636

TRÎTON TIMI-38

STEMI Cohort N=3534

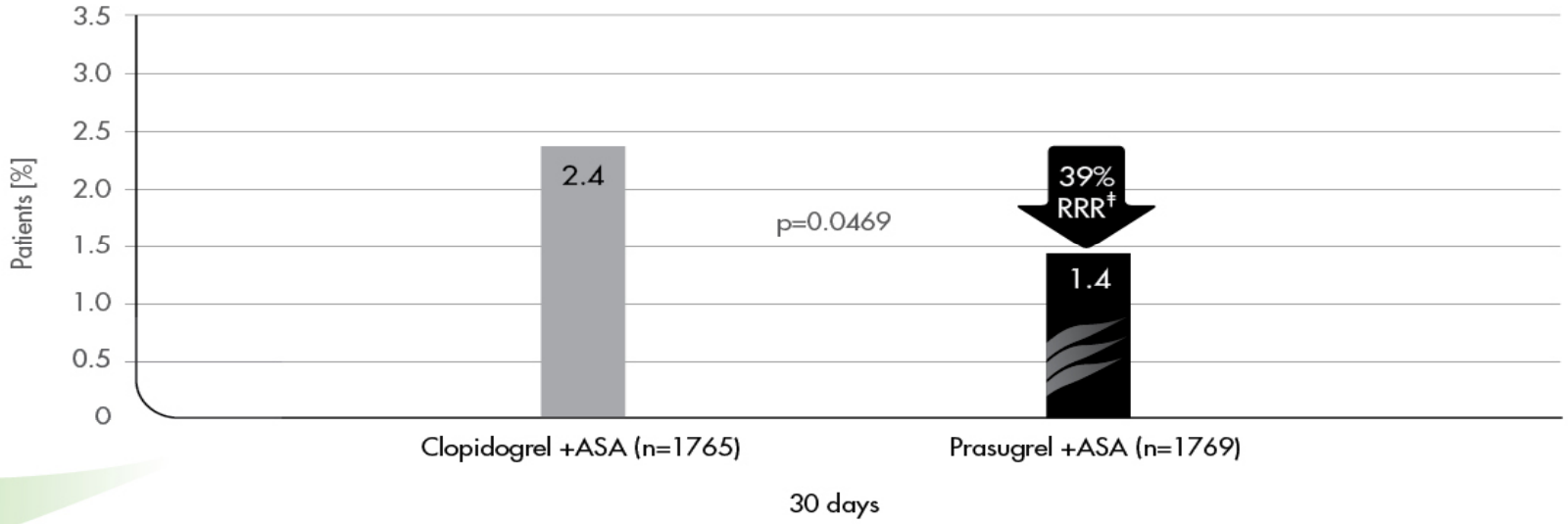


Montalescot et al Lancet 2008

Mortality Benefit

- Prasugrel showed a 39% relative risk reduction in cardiovascular death at 30days vs clopidogrel in STEMI patients [18]

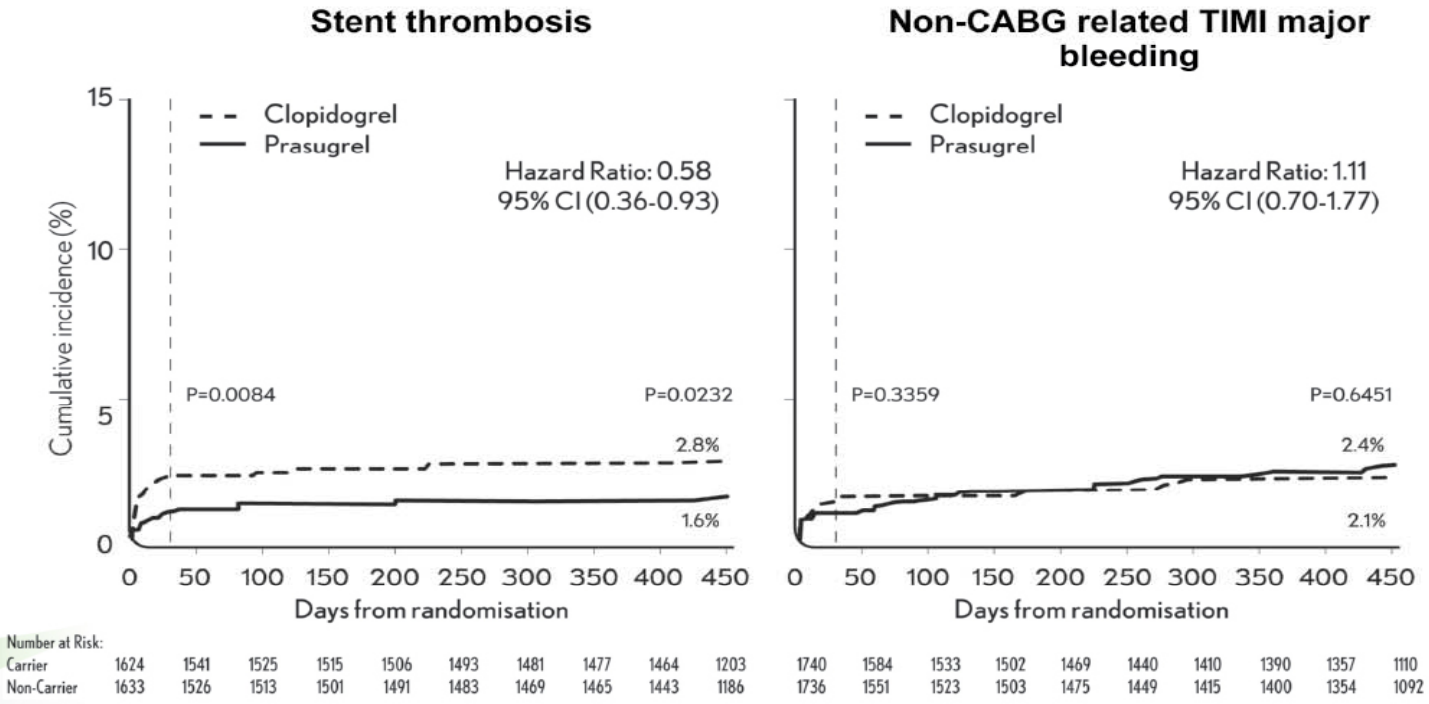
Figure. STEMI Cohort CV Death at 30 Days [18]



Data from Ref 18. Montalescot G. et al. Lancet 2009;373:723-731

2012-1088-03 Jan 2014

Efficacy and Safety Endpoints



Kaplan-Meier curves for selected endpoints. (Dotted line represents 30days)

Data from Ref 18. Montalescot G et al. Lancet 2009;373(9665):723-731

2012-1088-03 Jan 2014

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What is the scope of the problem in Korea

1. What genetic variants determine clopidogrel OPR?
2. Are there differences in the frequency of the CYP2C19 LOF allele between Koreans and Westerners.
3. Is genetic risk related with outcome in Koreans?
4. What is the distribution of OPR in Koreans and is HOPR related with outcome?

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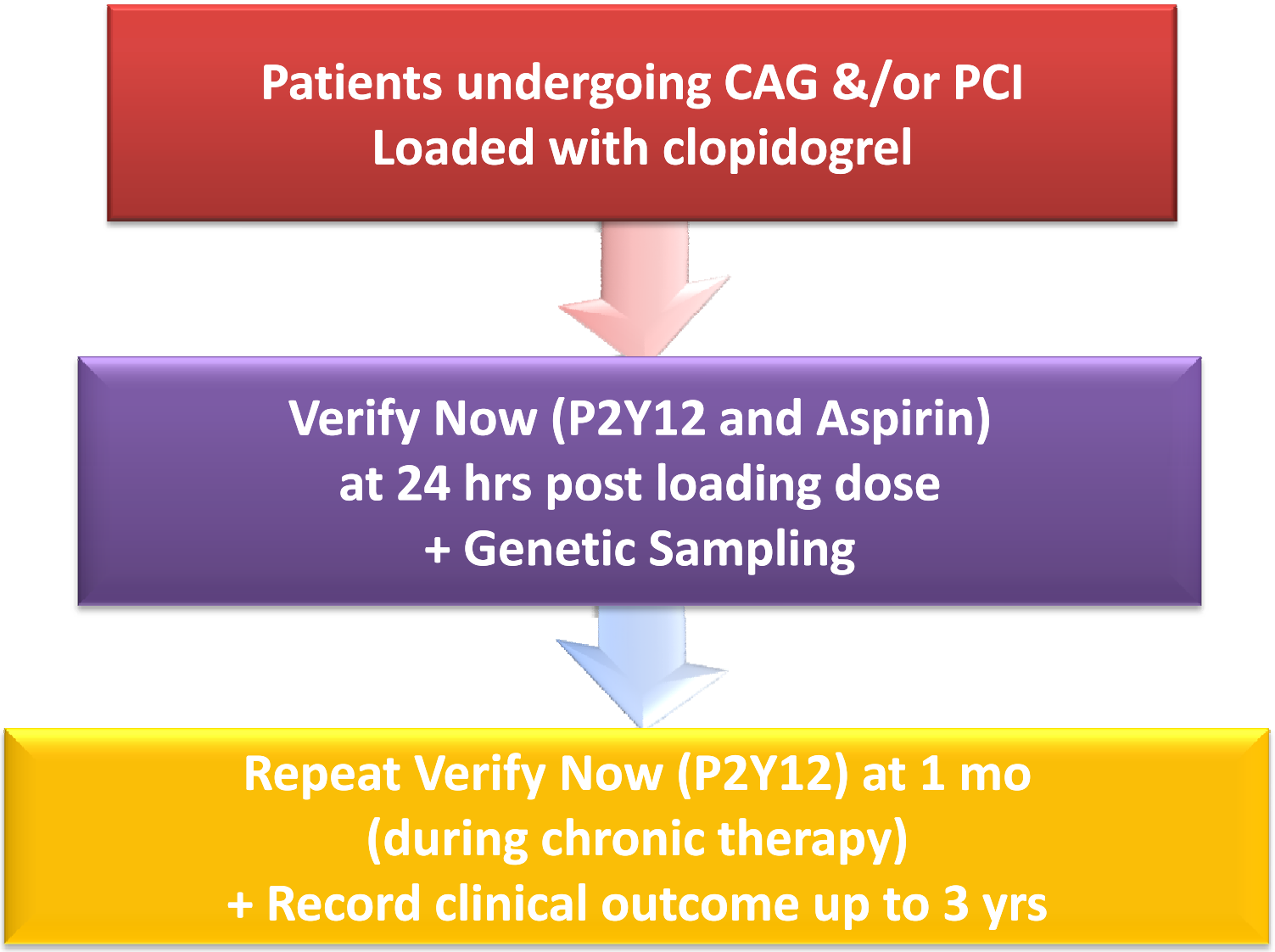
The SNUH CROSS-VERIFY cohort : Scheme



Study Overview

1676 patients received PCI initially enrolled in CROSS-VERIFY during study period

→ 38 patients: non-DES implantation
2 patients: non-Korean ethnicity
229 patients: refused genetic sampling
143 patients : usage of cilostazol

1264 patients available for genotyping

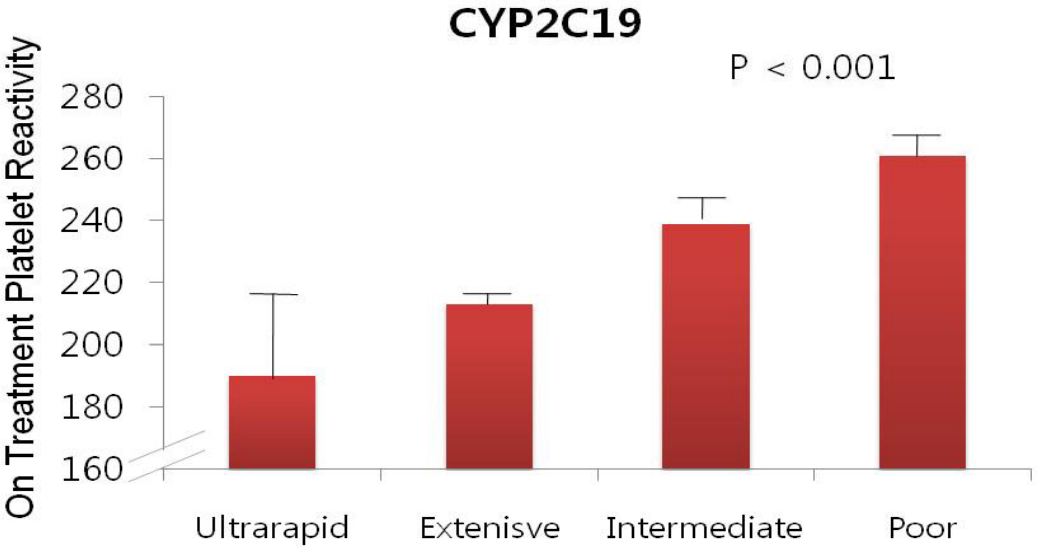
TaqMan™ Assay	SNaPshot™ Multiplex Analysis
• CYP1A2*1F (-163C>A, rs762551)	• CYP2B6*6 (K262R, rs2279343)
• CYP2C19*2 (P227P, rs4244285)	• CYP2C19*17 (-806C/T, rs12248560)
• CYP2C19*3 (W212X, rs4986893)	
• CYP3A4 (IVS10+12G/A, rs2242480)	
• CYP3A5 (CYP3A5*3, rs776746),	
• ABCB1 (C3435T, rs1045642)	
• PON-1 (Q192R, rs662)	

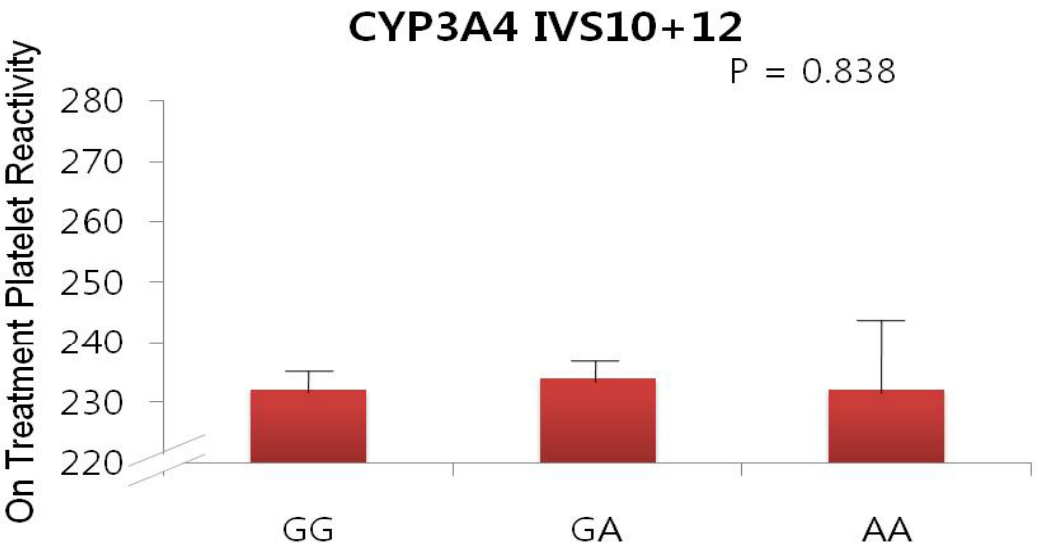
Park KW, Kim HS et al. in Submission to Heart

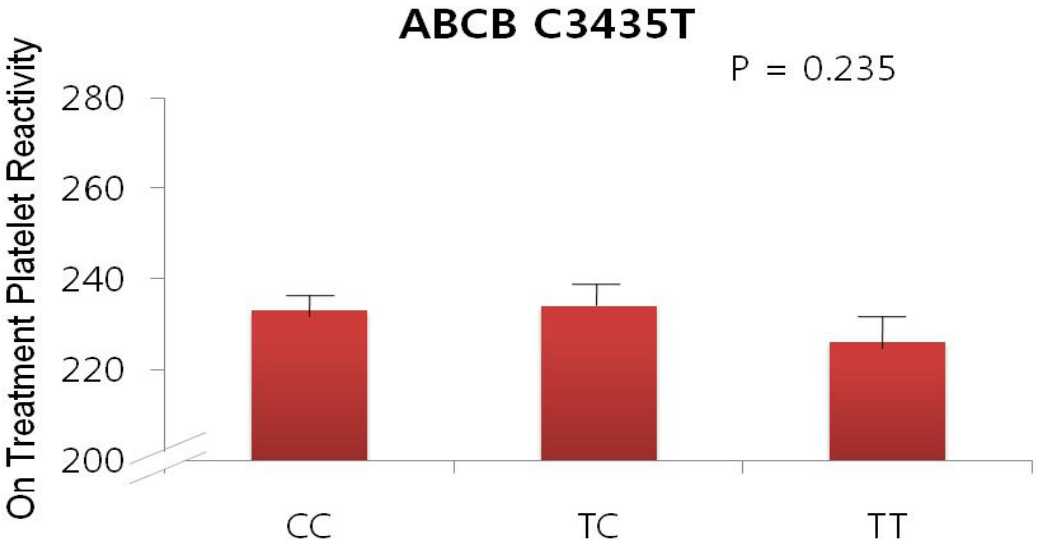
Seoul National University Hospital Cardiovascular Center

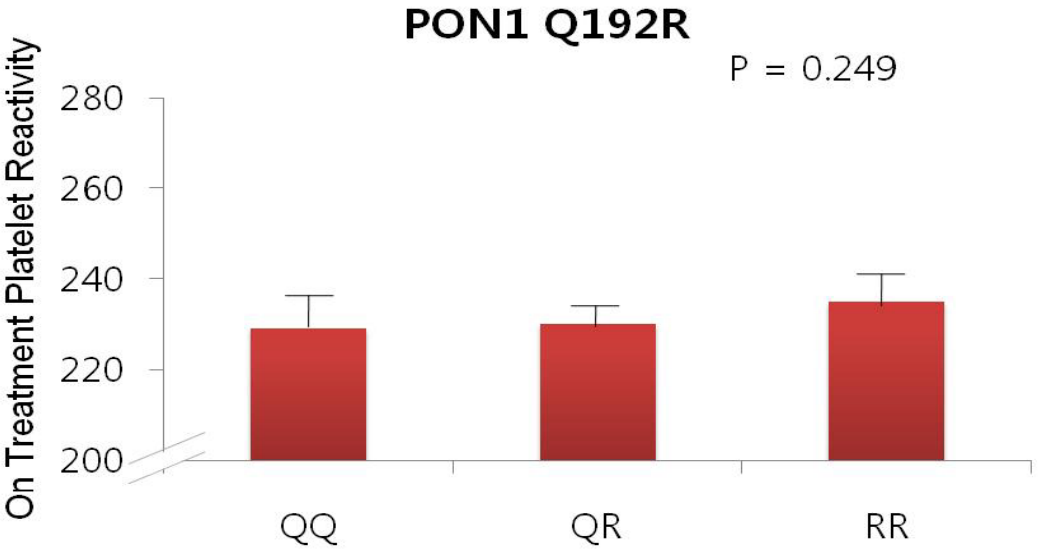
Genetic Determinants of HOPR

CROSS-VERIFY cohort: N=1264









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Does ethnicity matter?

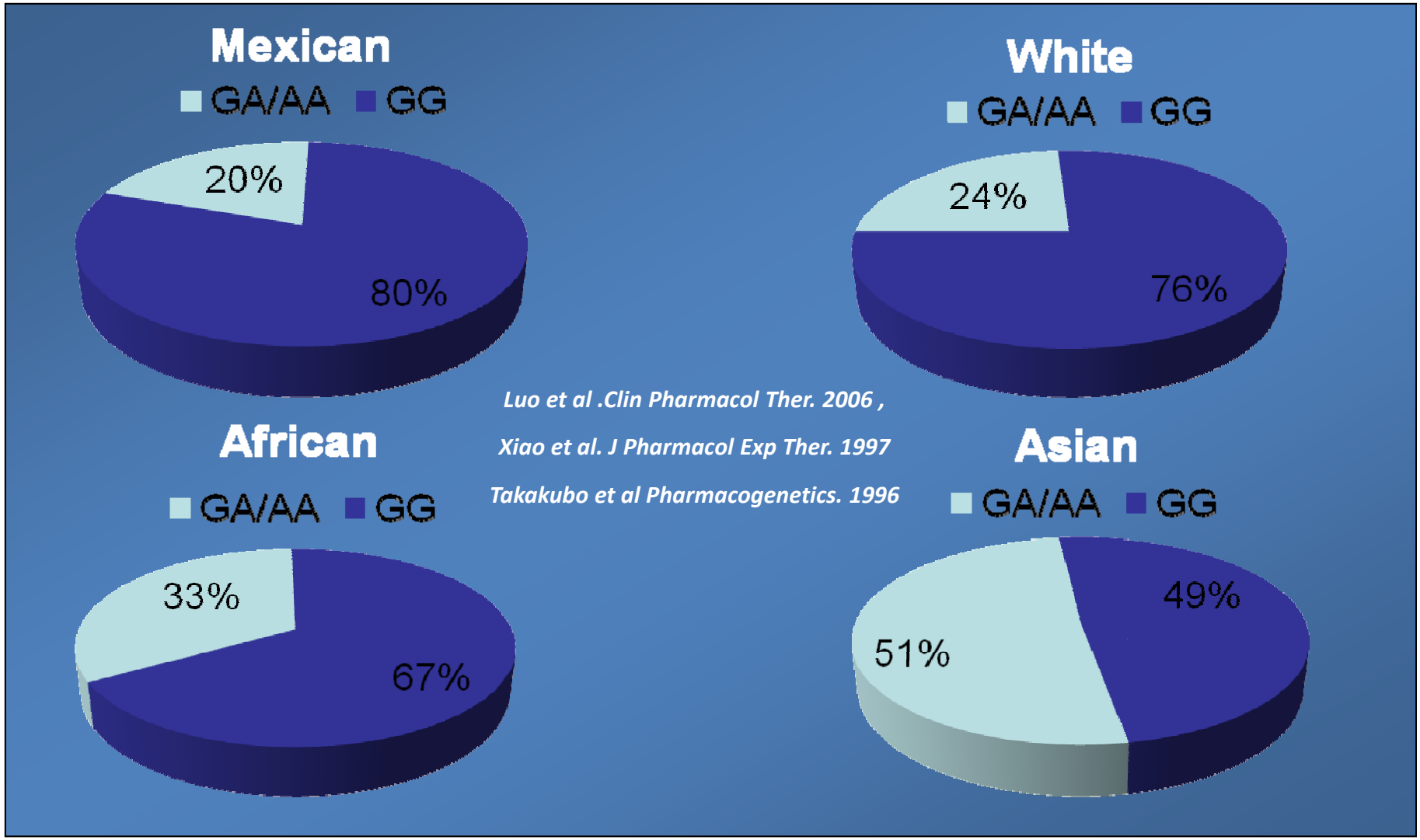
Characteristic	Mean Residual Platelet Reactivity (PRU)		P Value
	Characteristic present	Characteristic absent	
Age > 75 yrs	214 ±77	201±79	0.161
Men	200±77	220±82	0.041
Non-Caucasian ethnicity	229±79	202±78	0.047
Diabetes mellitus	220±73	196±80	0.005
⋮	⋮	⋮	⋮

Price MJ et al, Circulation 2009

- **Non-Caucasian ethnicity :**
  1. **has higher residual platelet activity**
  2. **an independent predictor of high on-treatment plt reactivity**

     (OR: 3.05, 95% CI: 1.49 to 6.28, p=0.002)

*Different CYP2C19 *2 Allele Frequency*



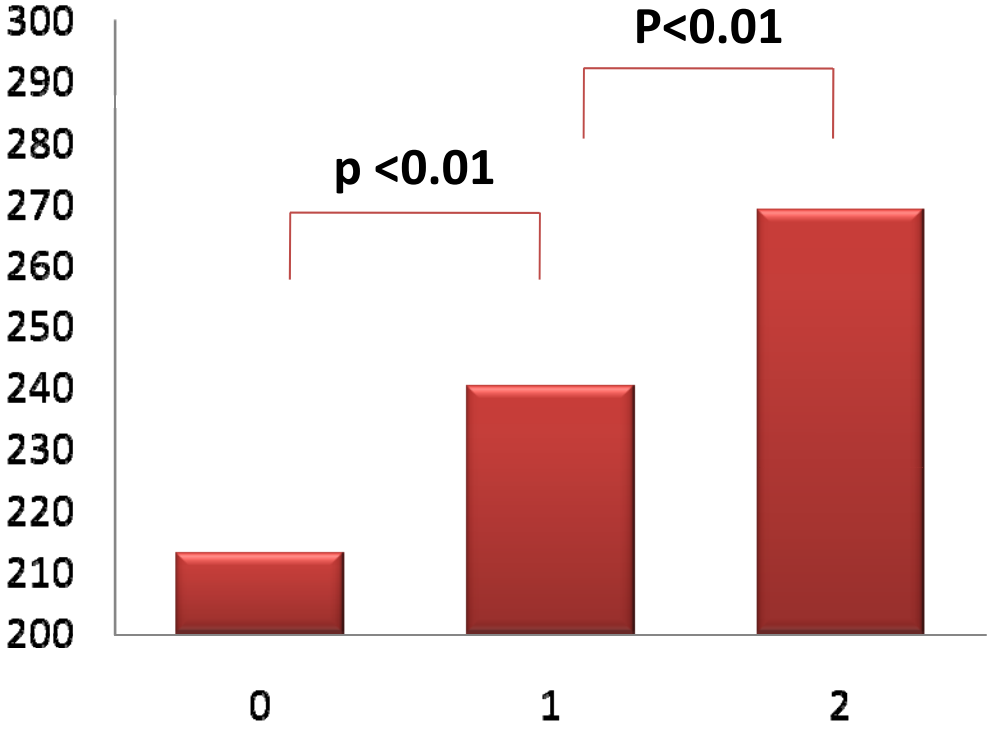
Luo et al .Clin Pharmacol Ther. 2006 ,

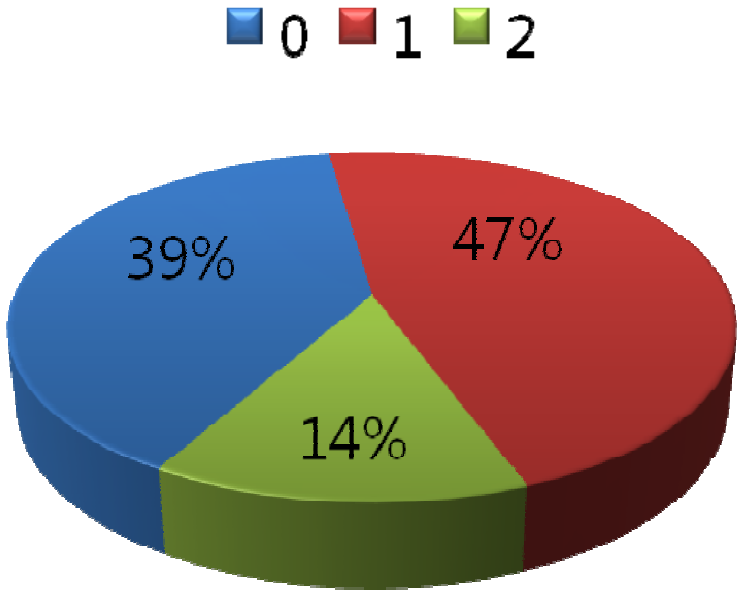
Xiao et al. J Pharmacol Exp Ther. 1997

Takakubo et al Pharmacogenetics. 1996

CYP2C19 LOF alleles : CROSS VERIFY cohort

Number of LOF alleles





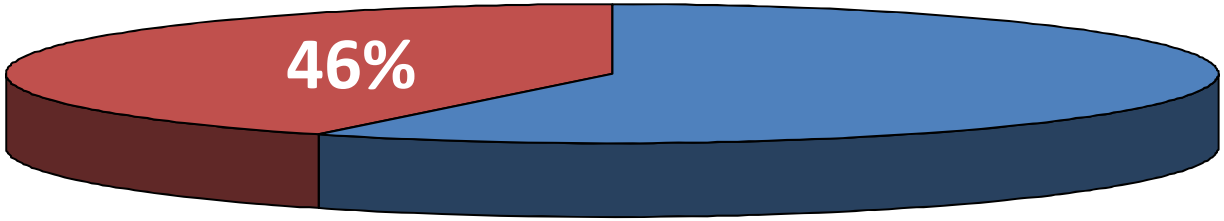
	Zero (*1/*1)	One (*1/*2, *1/*3)	Two (*2/*2, *2/*3, *3/*3)	p-value
Freq	523	622	134	
PRU	213.4±81.1	240.2±83.3	269.2±76.0	<0.001

Unpublished data from the CROSS VERIFY cohort
Park KW, Kim HS et al. in submission to Heart

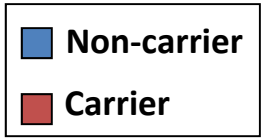
Different CYP2C19 LOF Frequency

: according to Asian Ethnicity

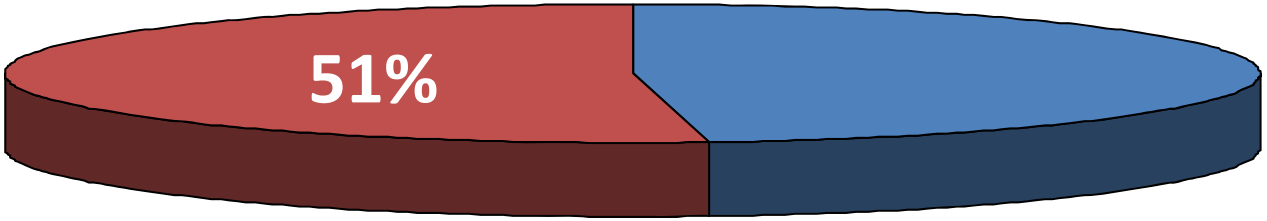
Japanese Population



Sawada T et al. Circulation J 2011.



Chinese Population



Zhou Q et al. Pharmacogenomics J 2009

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Association of cytochrome P450 2C19*2 polymorphism with clopidogrel response variability and cardiovascular events in Koreans treated with drug-eluting stents

Il-Young Oh,[1,2] Kyung Woo Park,[1] Si-Hyuk Kang,[1] Jin Joo Park,[1] Sang-Hoon Na,[1] Hyun-Jae Kang,[1] Bon-Kwon Koo,[1] Young-Hoon Jeong,[3] Jin-Yong Hwang,[3] Choong Hwan Kwak,[3] Yongwhi Park,[3] Seok-Jae Hwang,[3] Young-Guk Ko,[4] Dong Jik Shin,[4] Yangsoo Jang,[4] Hyo-Soo Kim[1]

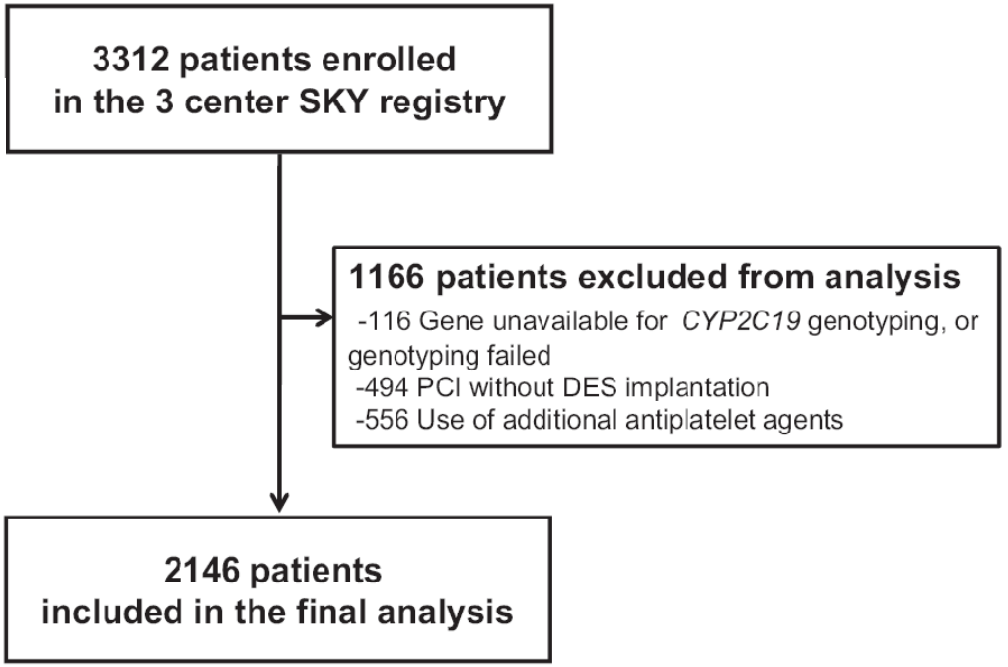
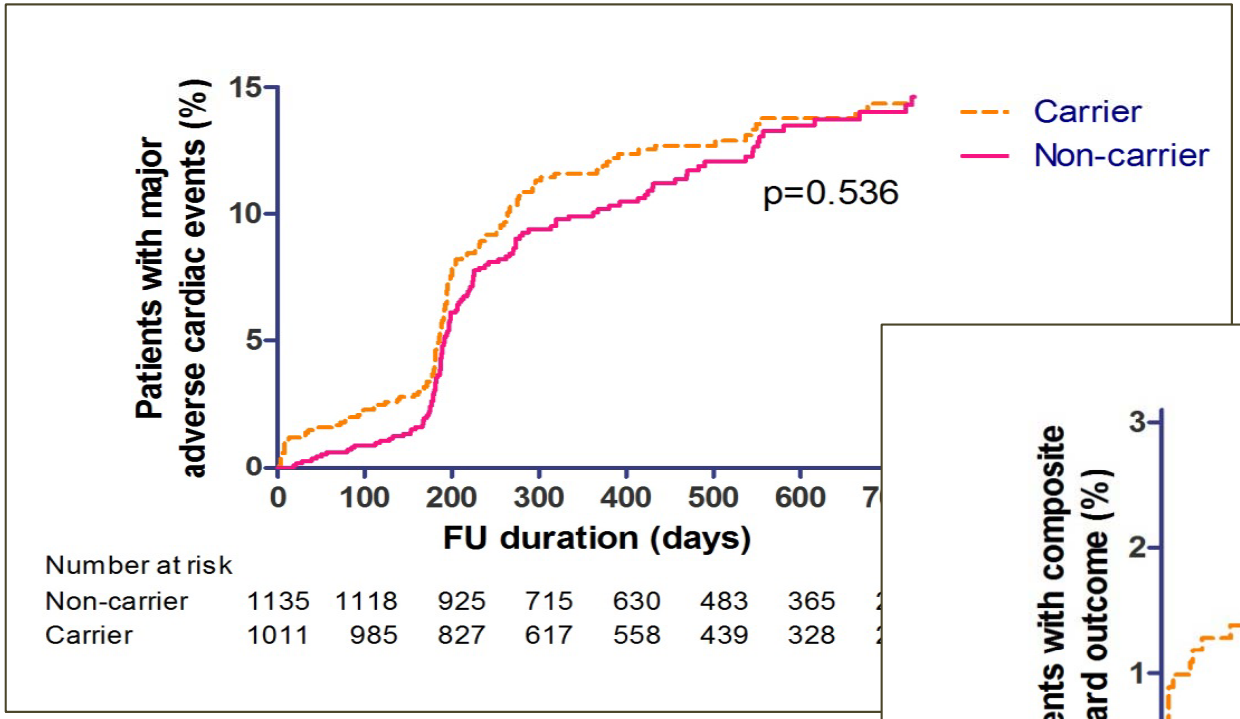


Table 3 Independent predictors of composite hard outcome up to 1 year

Variable	Univariate HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
Carrier of *CYP2C19*2* variant (carrier vs non-carrier)	2.61 (1.24 to 5.48)	0.01	2.53 (1.20 to 5.32)	0.01
Dyslipidaemia (dyslipidaemia vs non-dyslipidaemia)	2.69 (1.28 to 5.66)	<0.01	2.50 (1.16 to 5.39)	0.02
Chronic kidney disease (GFR <60 vs ≥60)	2.07 (1.02 to 4.21)	0.04	2.45 (1.15 to 5.22)	0.02
Smoking (current smoker vs non-smoker)	1.53 (0.74 to 3.16)	0.25	1.69 (0.81 to 3.54)	0.16
Diabetes (diabetes vs non-diabetes)	1.37 (0.67 to 2.78)	0.39	1.07 (0.51 to 2.24)	0.85
Use of proton-pump inhibitor (yes vs no)	1.40 (0.34 to 5.87)	0.64	1.18 (0.28 to 4.05)	0.82
Hypertension (hypertensive vs normotensive)	1.18 (0.58 to 2.39)	0.65	0.86 (0.41 to 1.83)	0.70
Old age (age ≥65 vs <65)	0.74 (0.35 to 1.56)	0.43	0.66 (0.30 to 1.44)	0.30
Long length of DES (sum of DES length ≥60 vs <60)	1.11 (0.48 to 2.57)	0.80	1.02 (0.81 to 3.54)	0.97

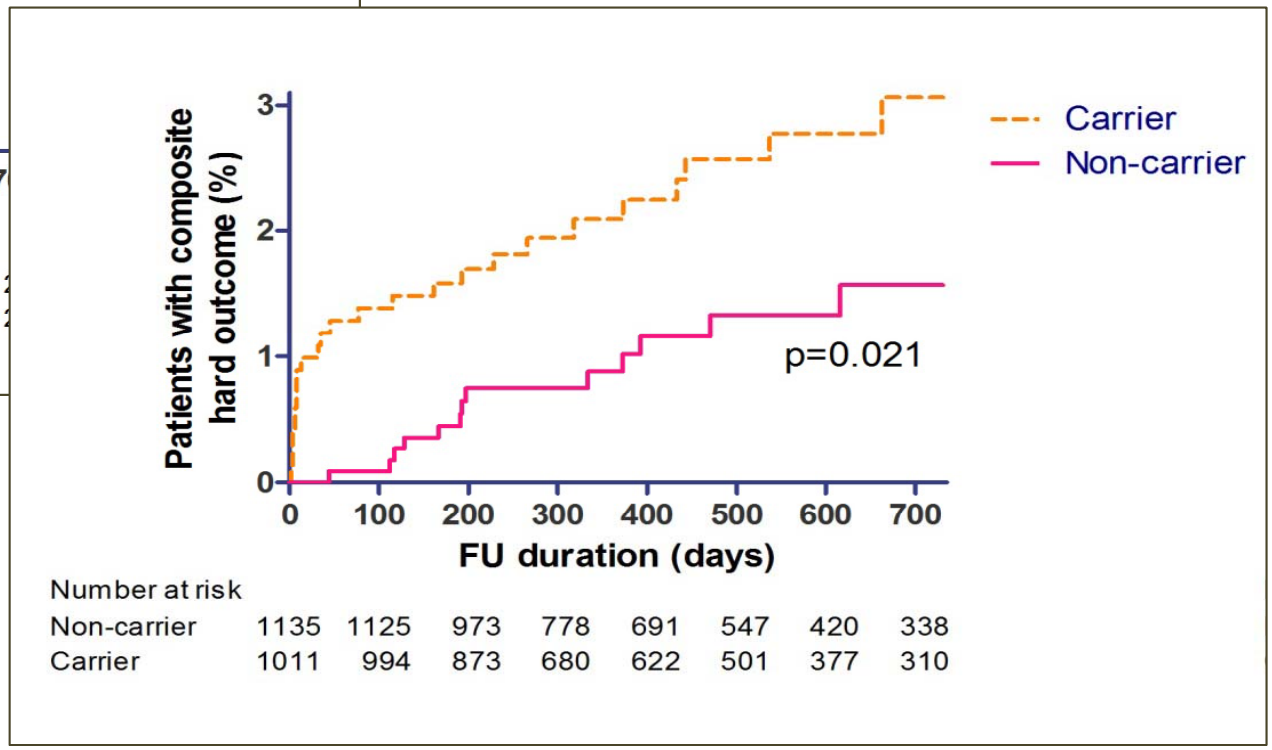
HR were adjusted for age, hypertension, diabetes, dyslipidaemia, smoking, chronic kidney disease, sum of length of DES, carrier of *CYP2C19*2*.
DES, drug-eluting stent; GFR, glomerular filtration rate.

Association of genotype with only hard outcomes (SKY registry)



All MACE
(including revascularization)

Hard outcome
(CD, MI, and ST)



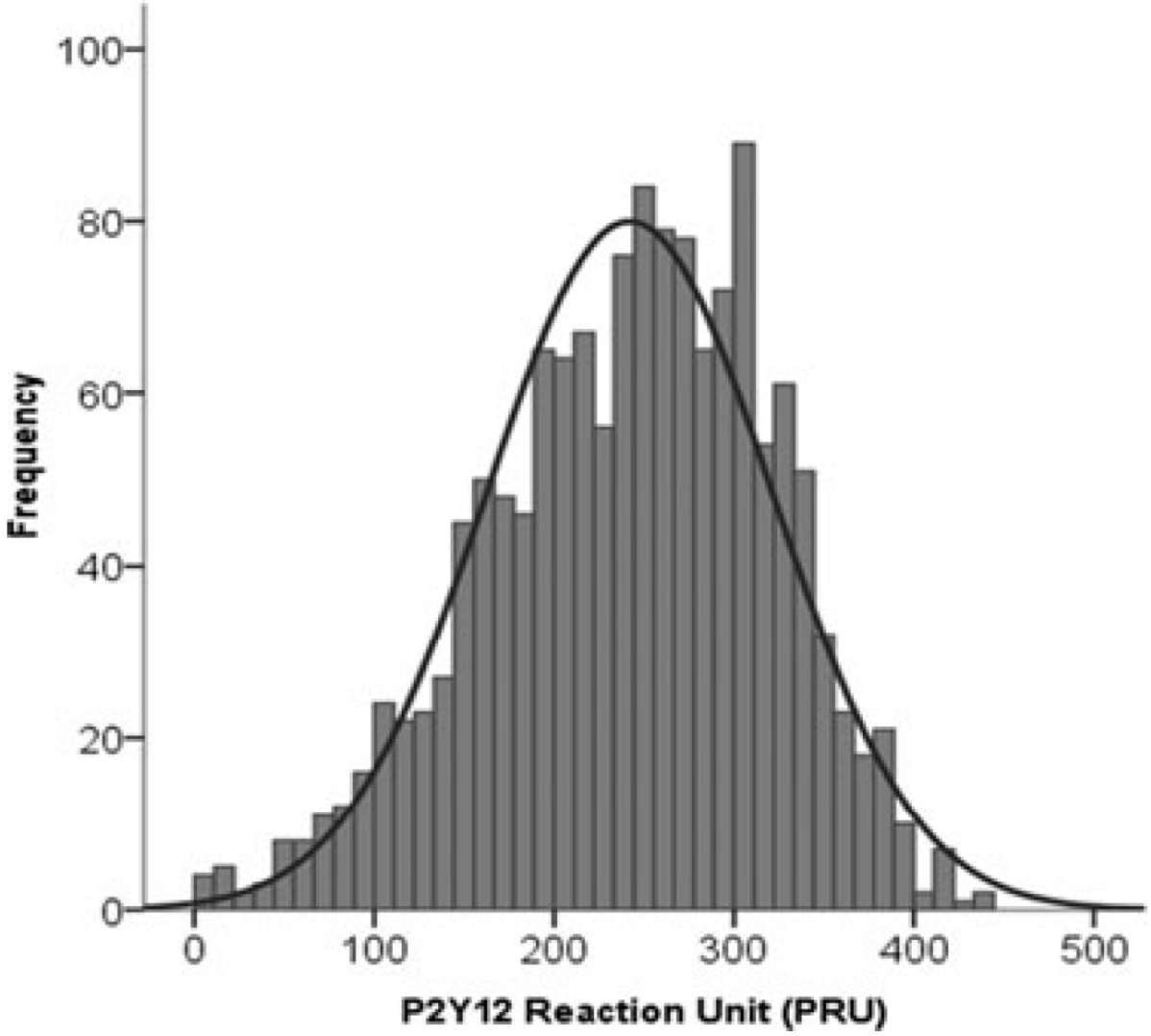
Oh IY, Park KW et al. Heart 2011

What is the scope of the problem in Korea

1. What genetic variants determine clopidogrel OPR?
2. Are there differences in the frequency of the CYP2C19 LOF allele between Koreans and Westerners.
3. Is genetic risk related with outcome in Koreans?
4. **What is the distribution of OPR in Koreans and is HOPR related with outcome?**

Response variability to Clopidogrel in Koreans

Data from the SNUH CROSS-VERIFY cohort



Mean On-treatment Platelet Reactivity:

241.9 ± 70.3 PRU

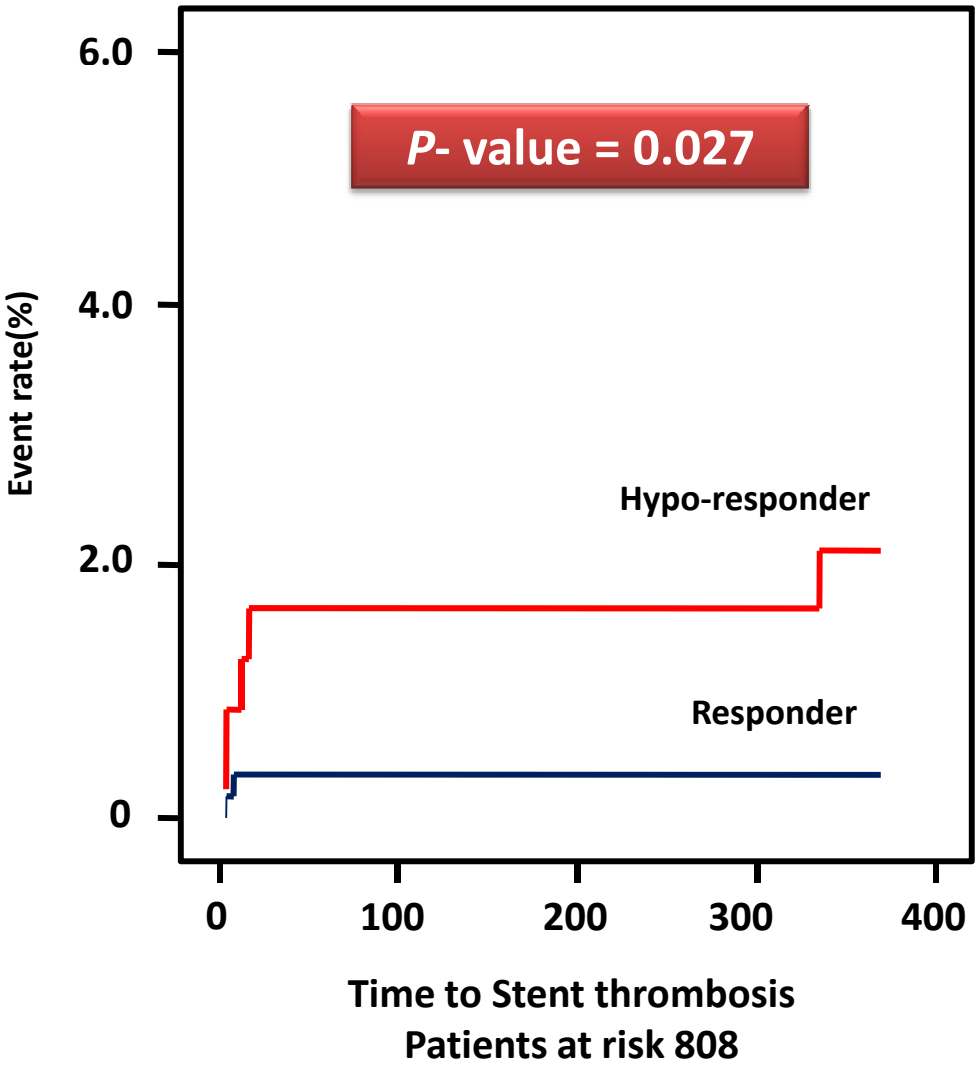
(N=1431)

Park KW, Kim HS et al. Cardiovascular Therapeutics 2010

Seoul National University Hospital Cardiovascular Center

Clopidogrel Response and Outcome:

CROSS-VERIFY cohort: Stent Thrombosis (1 Yr)



Stent Thrombosis

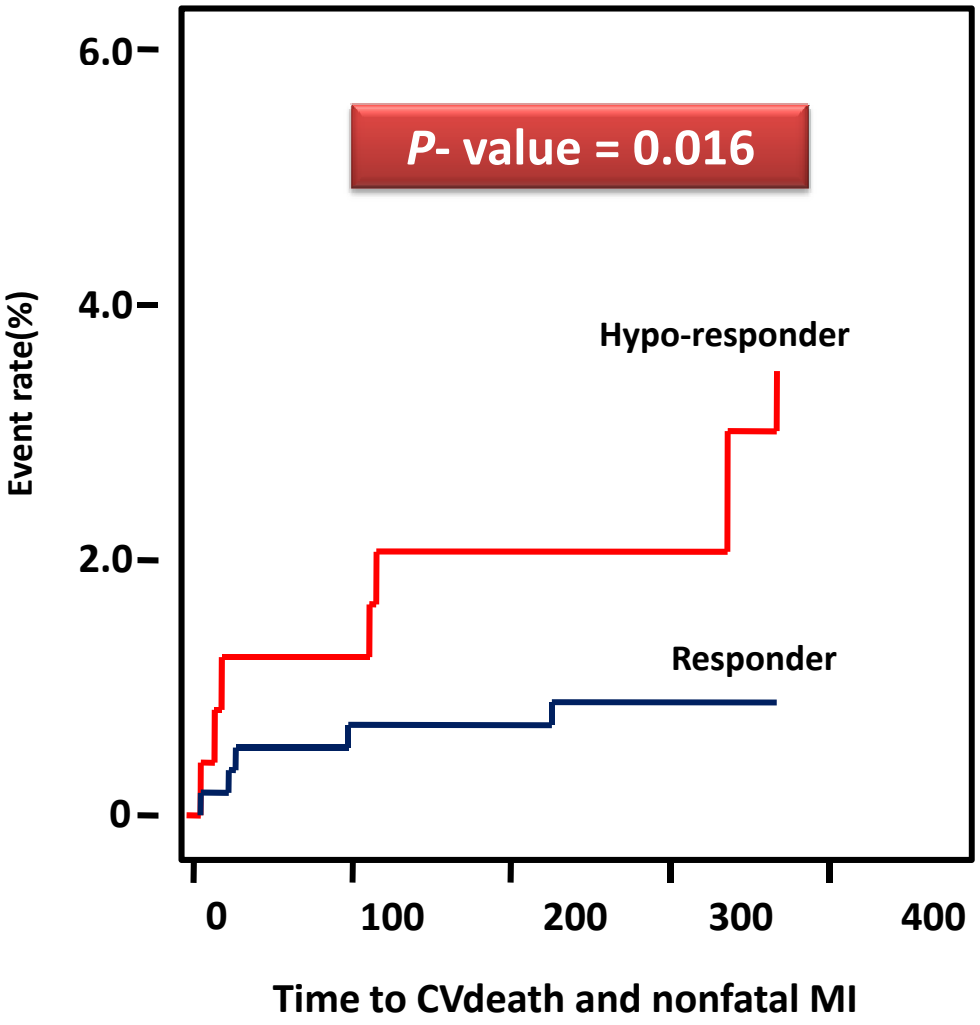
- Non-responder : 5 / 241 (2.1%)
- Responder : 2 / 574 (0.3%)

- HR : **6.059** (95% CI 1.167 to 31.451)

Park KW, Jeon KH, Kim HS et al. Am J Cardiol 2011

Clopidogrel Response and Outcome:

CROSS-VERIFY cohort: CV Death + MI (1 Yr)



Hard End point
(CV death or nonfatal MI)

- Hypo-responder : 8 / 241 (3.3%)
- Responder : 5 / 574 (0.9%)

- HR : **3.907** (95% CI 1.265 to 12.068)

Park KW, Jeon KH, Kim HS et al. Am J Cardiol 2011

Summary of the scope of the problem in Korea

1. What genetic variants determine clopidogrel OPR?

   → 2C19 LOF allele: Yes, PON-1, ABCB1, CYP3A4등 : No

2. Are there differences in the frequency of the CYP2C19 LOF allele between Koreans and Westerners.

   → Caucasians: 20-25%, Koreans 50-60% (similar in Chinese and Japanese)

3. Is genetic risk related with outcome in Koreans?

   → Yes. (Hard outcome only, not soft outcome)

4. What is the distribution of OPR in Koreans and is HOPR related with outcome?

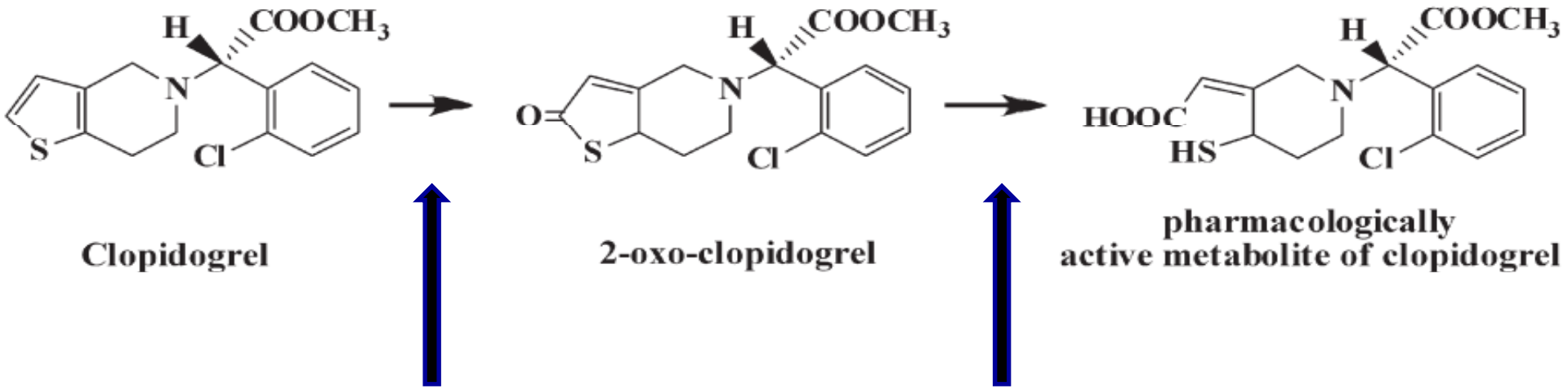
   → Right shifted (higher mean OPR), Yes. (optimal cut off value higher)

Drug-Clopidogrel Interaction?

Environment-Clopidogrel Interaction?

Clopidogrel Activation

< Clopidogrel Activation >



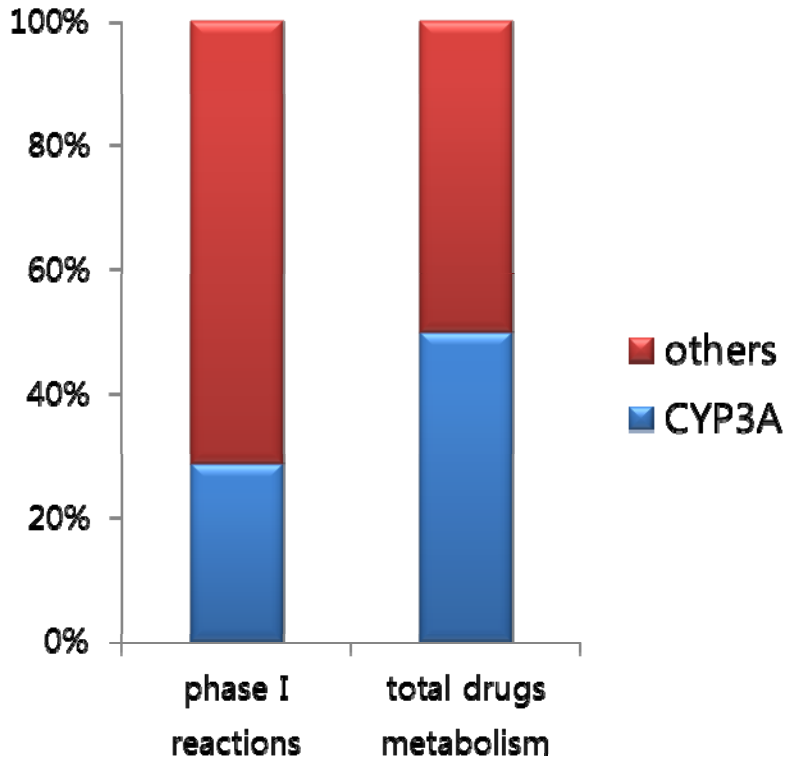
Enzyme	P450 contribution ratio
CYP1A2	35.8%
CYP2B6	19.4%
CYP2C19	44.9%

Enzyme	P450 contribution ratio
CYP2B6	32.9%
CYP2C9	6.8%
CYP2C19	20.6%
CYP3A4	39.8%

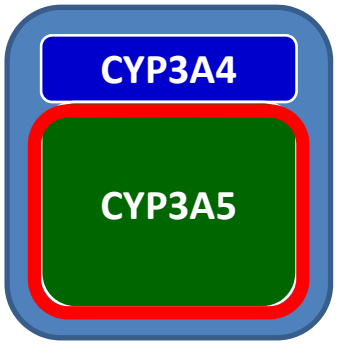
Kazui, DMD 2010;38:92-99
Ford, J Clin. Pharmacolopgy 2009;49:506-12

Cytochrome P450 3A

< CYP 3A system >



➔ **more easily inhibited**



➔ **main contributor when inhibitors are present**

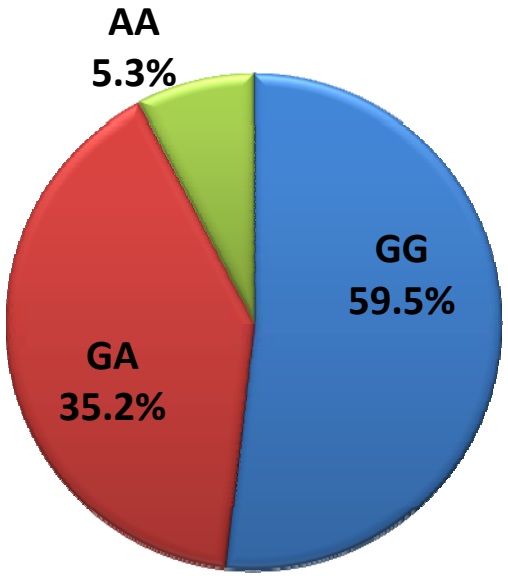
Genetic basis of CYP3A5 deficiency

- a SNP in intron 3 -> cryptic splice site
- Premature truncation of the CYP3A5 protein.

Wrighton SA, et al. Drug Metab Rev 2000;32:339-61
Kuehl P, Nat Genet 2001;27:383-91
Evans et al. N Engl J Med 2003; 348:538-549

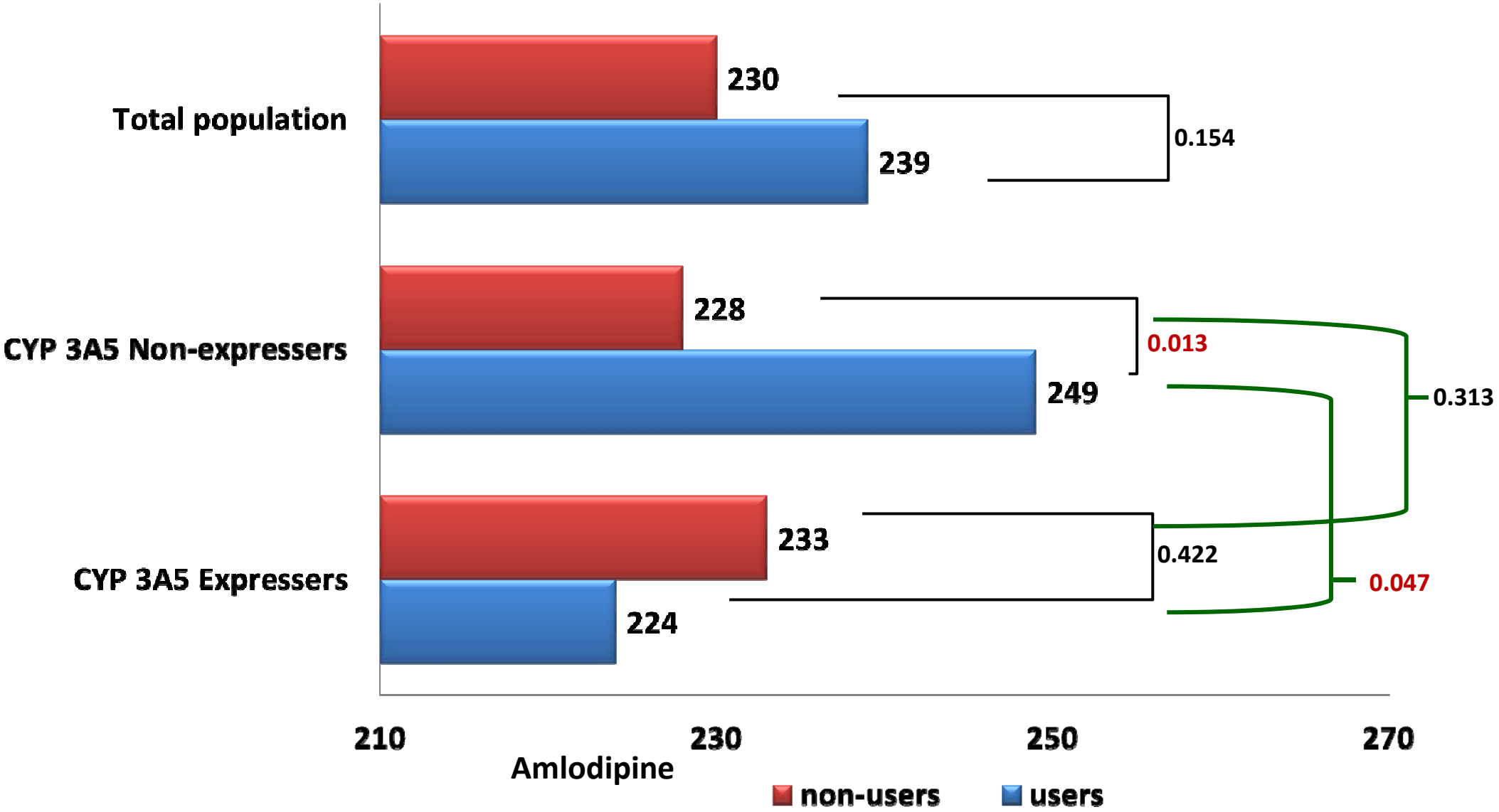
CYP 3A5 Distribution

- **Genotyping**
  - CYP3A5 *3/*3(GG)
    - Non-expressers
  - CYP3A5 *3/*1(GA), *1/*1(AA)
    - Expressers



Gene	Expression	Allele	Percent		HWE test
CYP 3A5	Expresser	*1/*1 (AA)	67 (5.3%)	509 (40.5%)	0.993
		*3/*1 (GA)	442(35.2%)		
	Non-Expresser	*3/*3 (GG)	749 (59.5%)		

Pharmacodynamic Outcome



Park KW, Kang JH, Kim HS et al. under revision in Heart 2012

Seoul National University Hospital Cardiovascular Center

Clinical Outcome

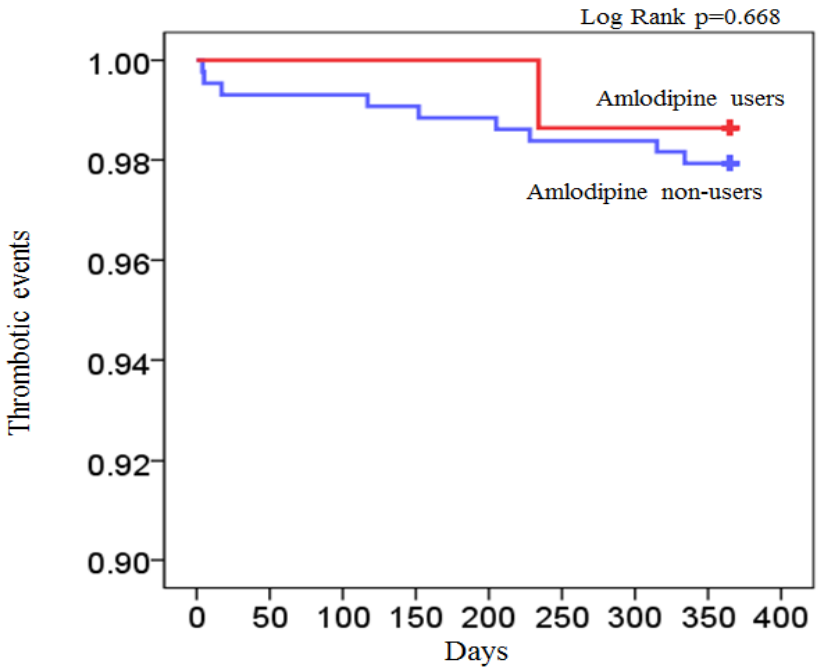
- **Thrombotic events**
  - **Cardiovascular death, Non-fatal MI, Ischemic stroke, Stent Thrombosis**

		Thrombotic event rate	HR	95% C.I.	p value	Interaction P value
Total population	Amlodipine Users	3.8%	3.249	1.279-8.256	**0.018**	
	Amlodipine Non-users	1.2%				
1 year outcome	CYP3A5 Non-expressers	5.6% vs. 0.6%	9.368	2.559-33.770	**0.001**	0.068
	CYP3A5 Expressers	1.4% vs. 2.1%	0.648	0.081-5.915	>0.999	
30 day outcome	CYP3A5 Non-expressers	3.7% vs. 0.2%	24.615	2.725-222.39	**0.002**	**<0.001**
	CYP3A5 Expressers	0.0% vs. 0.7%	0.993	0.985-1.001	>0.999	

Park KW, Kang JH, Kim HS et al. under revision in Heart 2012

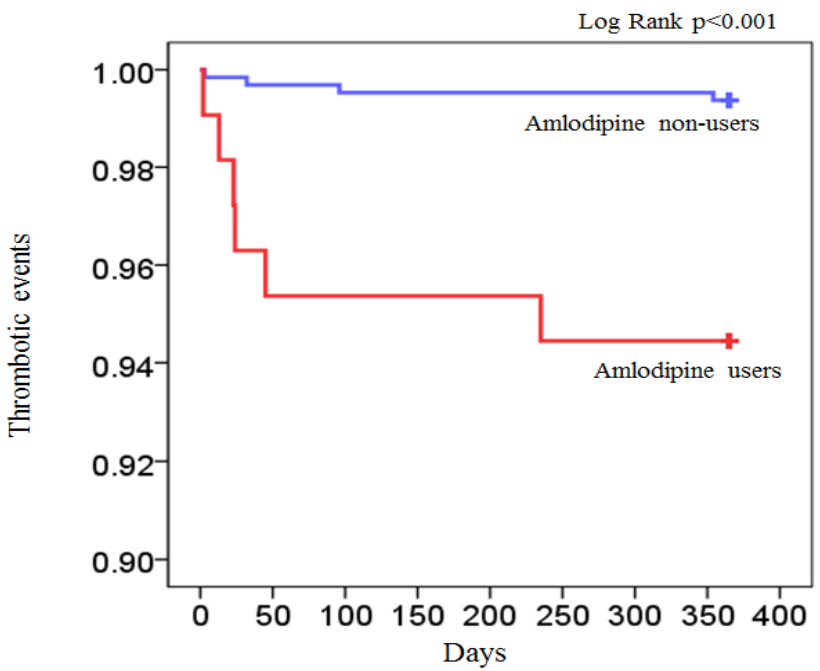
Kaplan Meier Survival Analysis

< CYP3A5 expressers >



No. at Risk									
Amlodipine non-users	435	432	432	431	430	428	428	426	425
Amlodipine users	74	74	74	74	74	73	73	73	73

< CYP3A5 non-expressers >



No. at Risk									
Amlodipine non-users	641	639	638	638	638	638	638	637	637
Amlodipine users	108	103	103	103	102	102	102	102	102

Park KW, Kang JH, Kim HS et al. under revision in Heart 2012

Smoking as a Protective Factor of High On-treatment Platelet Reactivity?

Relations between clinical characteristics and high residual platelet reactivity (HRPR)

Characteristic	Rate of HRPR		p Value
	Characteristic Present	Characteristic Absent	
Men	32.3%	47.5%	0.012
Non-Caucasian ethnicity	55.6%	33.4%	0.008
Diabetes mellitus	42.5%	32.0%	0.044
β-Blocker use	38.6%	28.8%	0.065
Nitrate use	41.3%	34.1%	0.242
Proton-pump inhibitor use	42.1%	32.3%	0.061
Current smoker	19.4%	37.0%	0.049

Price et al. *Am J Cardiol 2009*

RESEARCH

Cardiovascular Therapeutics

Clinical Predictors of High Posttreatment Platelet Reactivity to Clopidogrel in Koreans

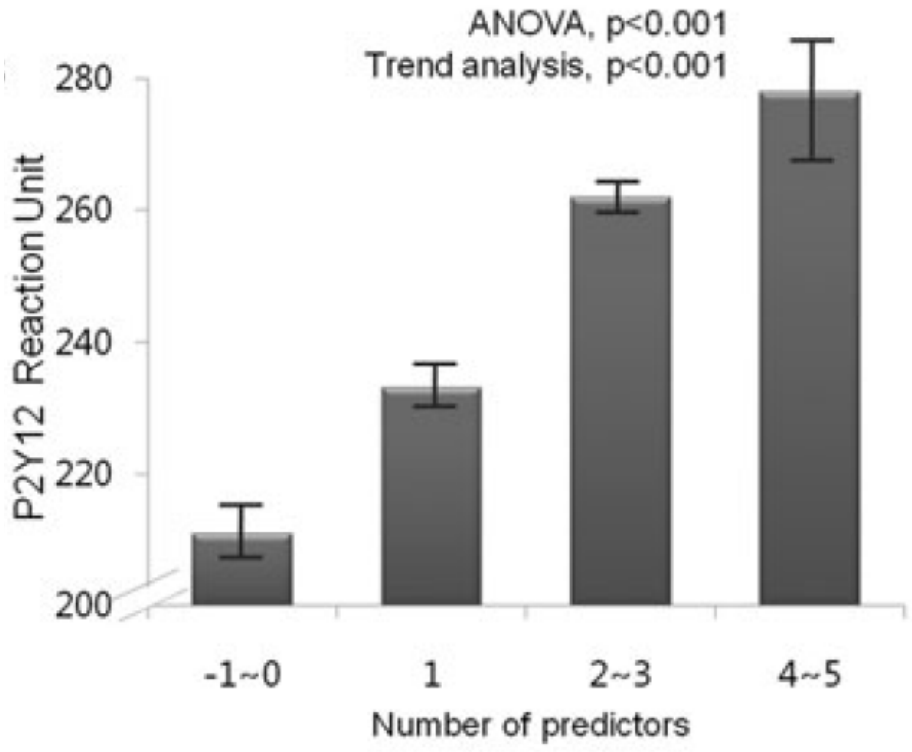
Kyung Woo Park*, Jin Joo Park*, Ki-Hyun Jeon, Si-Hyuk Kang, Il-Young Oh, Han-Mo Yang, Hyun-Jai Cho, Hae-Young Lee, Hyun-Jae Kang, Bon-Kwon Koo, Byung-Hee Oh, Young-Bae Park & Hyo-Soo Kim

Department of Internal Medicine and Cardiovascular Center, Seoul National University Hospital, Seoul, Korea

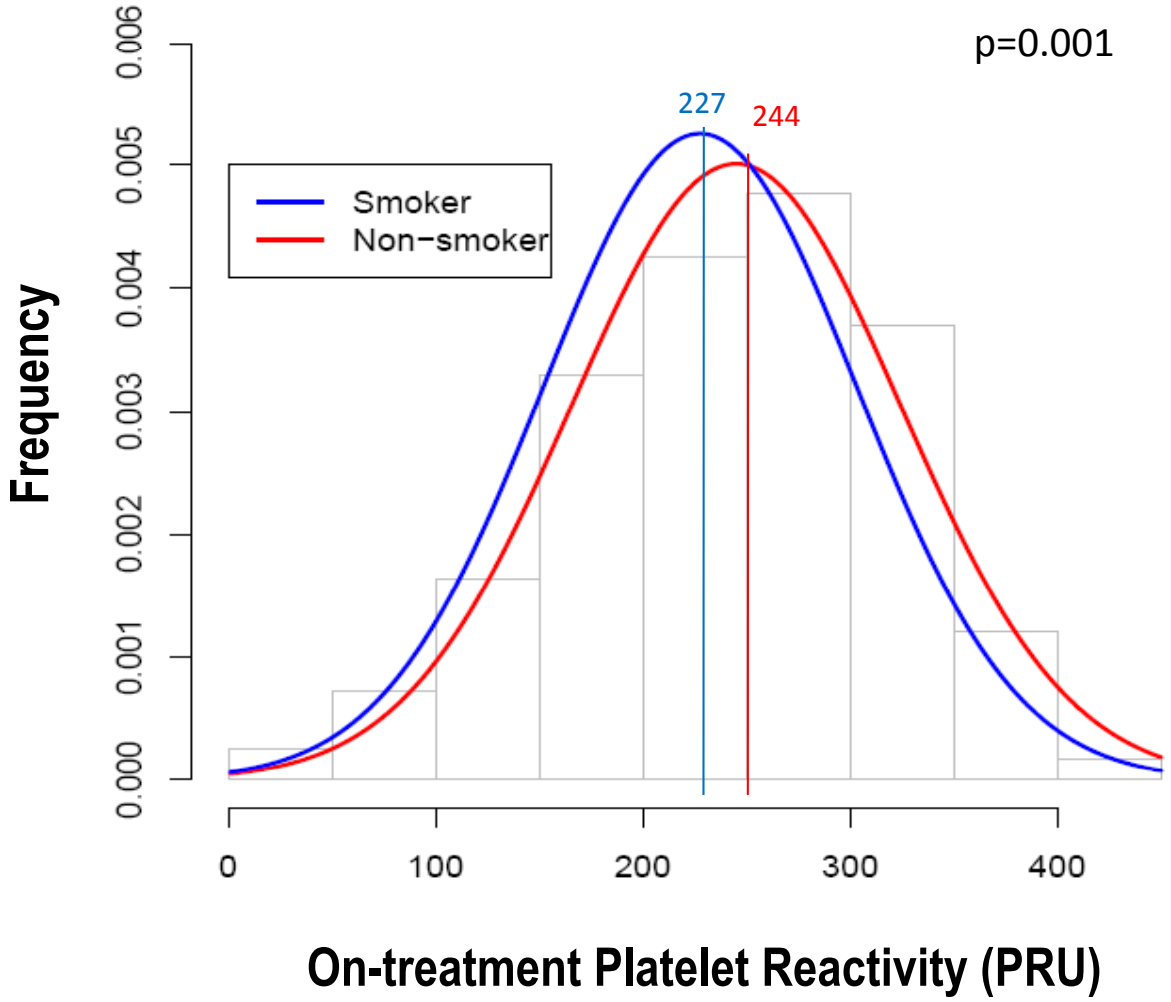
Table 2 Multivariate analysis for independent predictors of HPPR

		95% Confidence interval		
	OR	Lower limit	Upper limit	*P*-value
Female gender	1.90	1.46	2.46	<0.001
Chronic kidney disease	1.51	1.14	1.99	0.004
Diabetes mellitus	1.35	1.04	1.75	0.024
CRP ≥ 2.0 mg/L	1.31	1.02	1.69	0.036
Age (decade)	1.21	1.06	1.39	0.005
Cigarette smoking	0.63	0.44	0.92	0.015

Input variables: age (in decade), gender, cigarette smoking, hypertension, diabetes mellitus, chronic kidney disease stage, congestive heart failure, hs-CRP ≥ 2.0 mg/L, beta-blocker, dihydropyridine calcium channel blocker, statin.

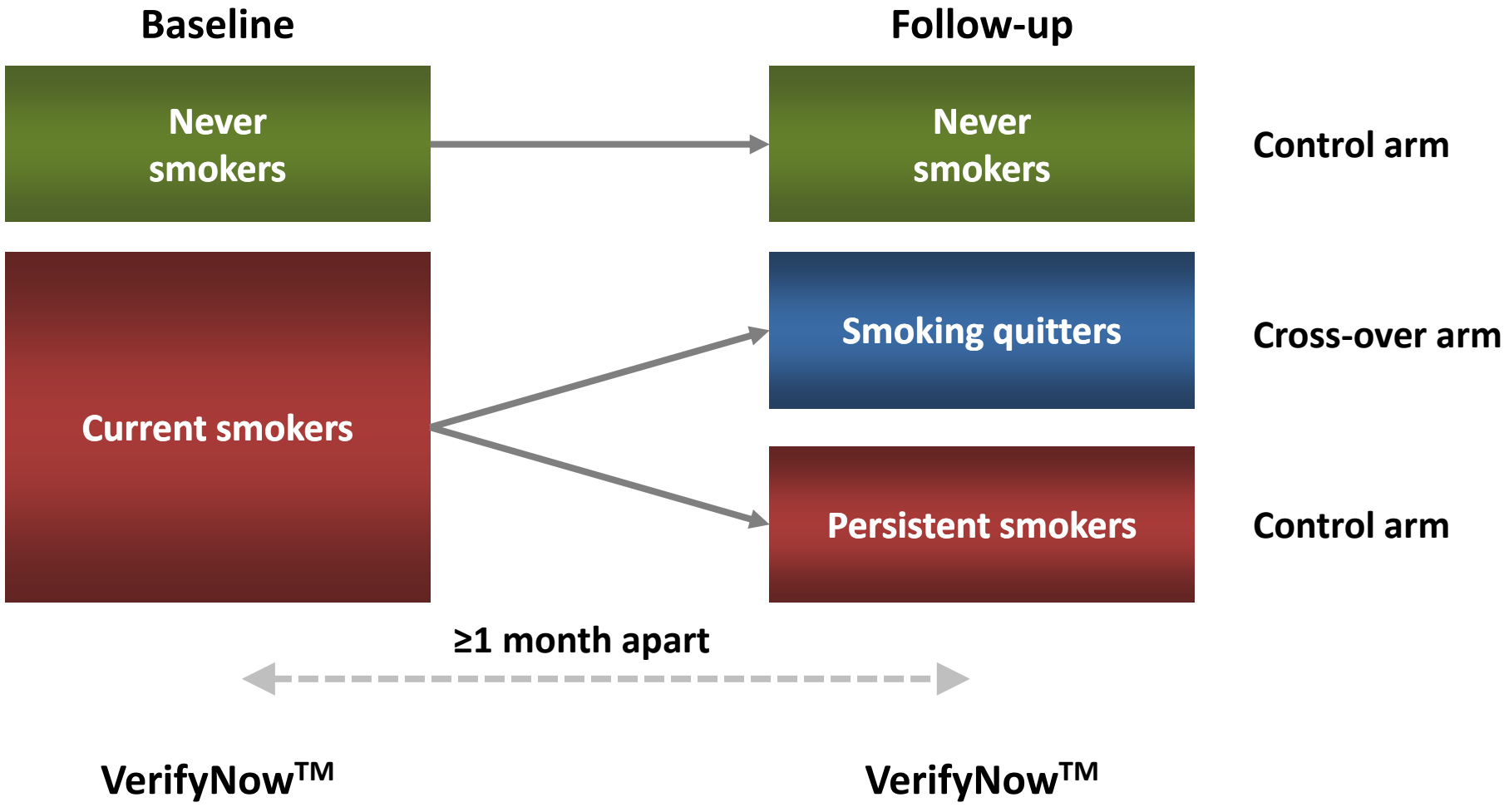


Smoking is assoc with lower clopidogrel OPR



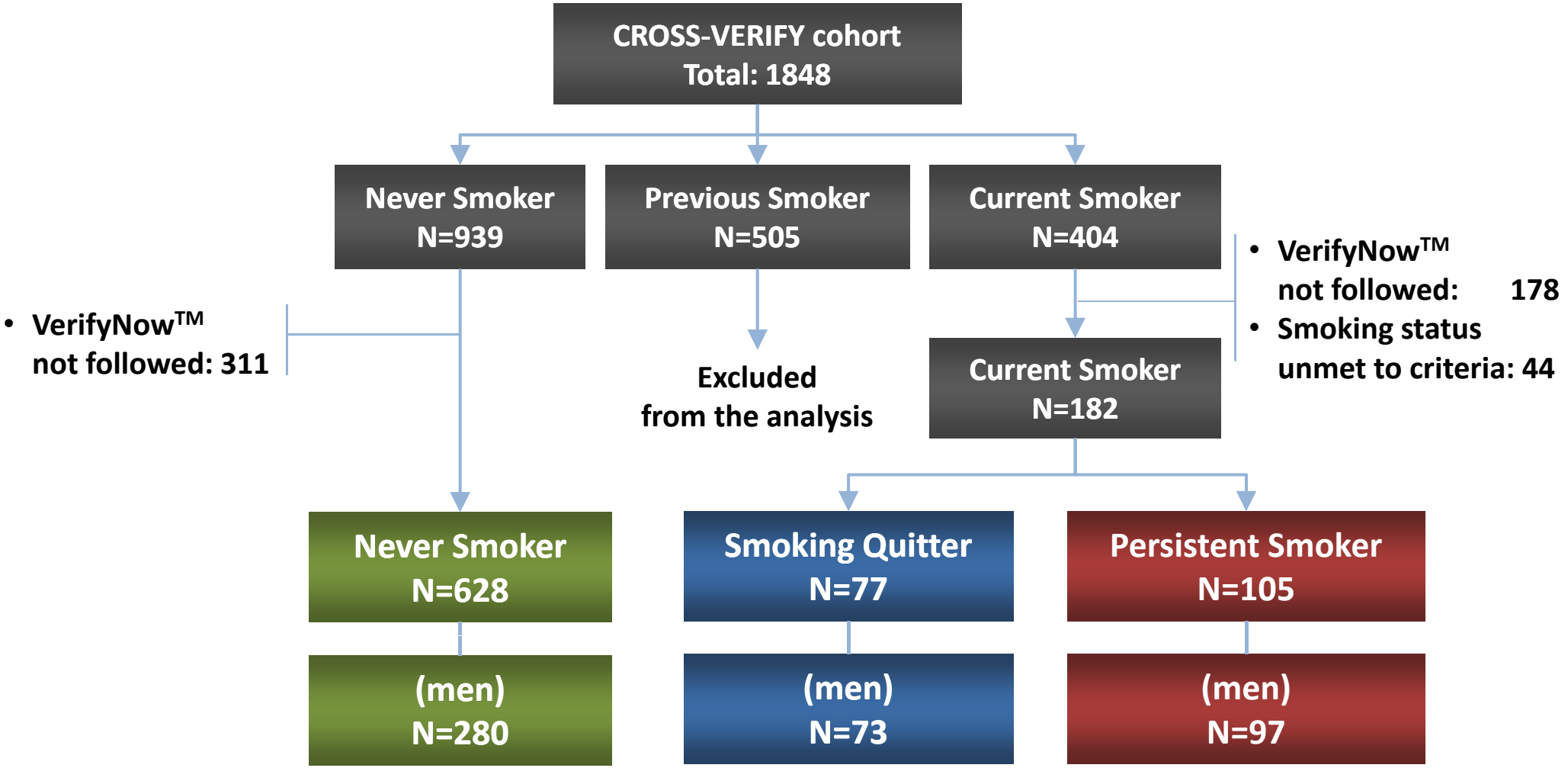
Park KW, Park JJ, Kim HS et al. Arterio Thromb Vasc Biol 2011

Study Design



Park KW, Kang SH, Kim HS et al. Heart 2012

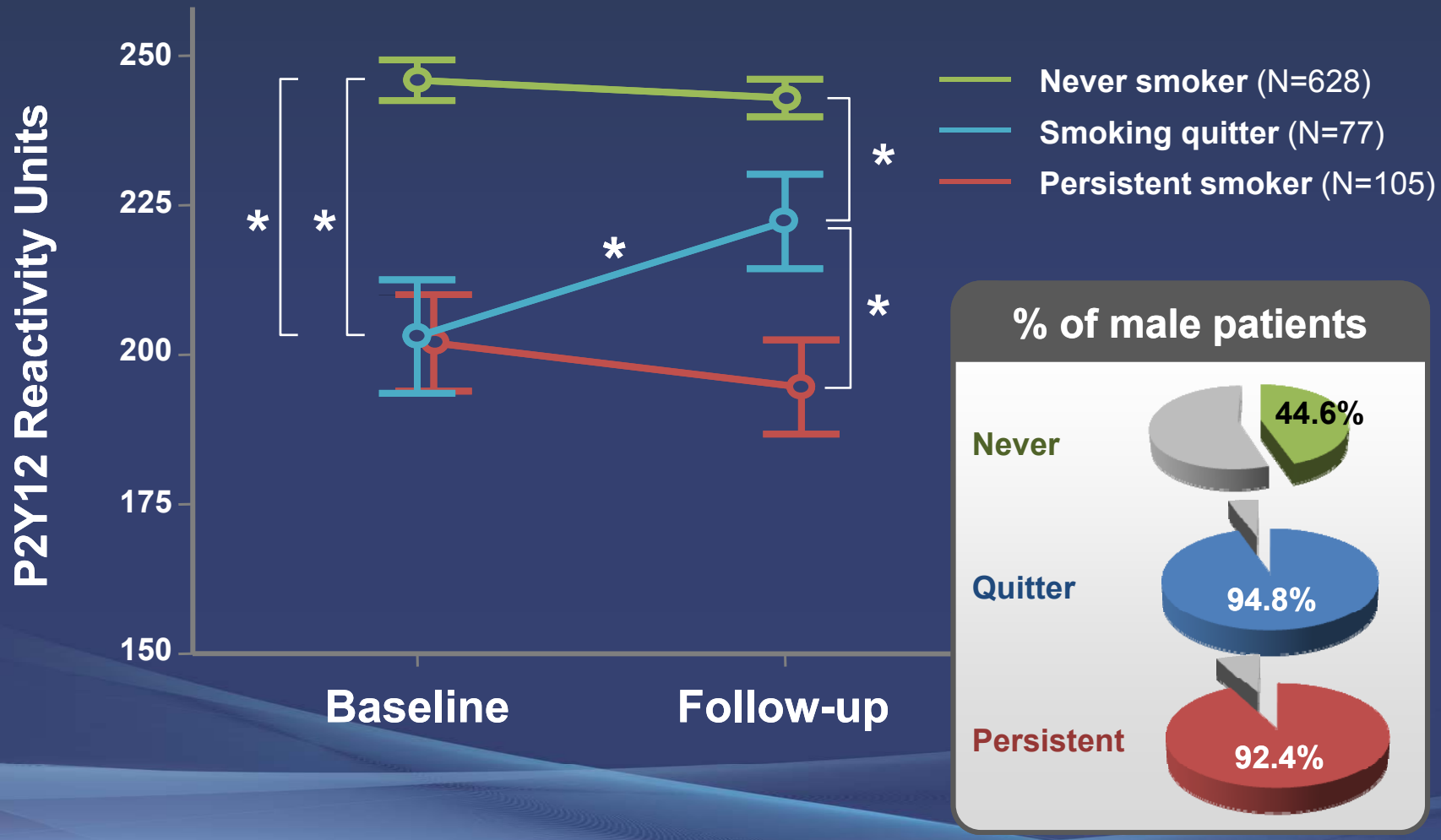
Study Scheme



Park KW, Kang SH, Kim HS et al. Heart 2012

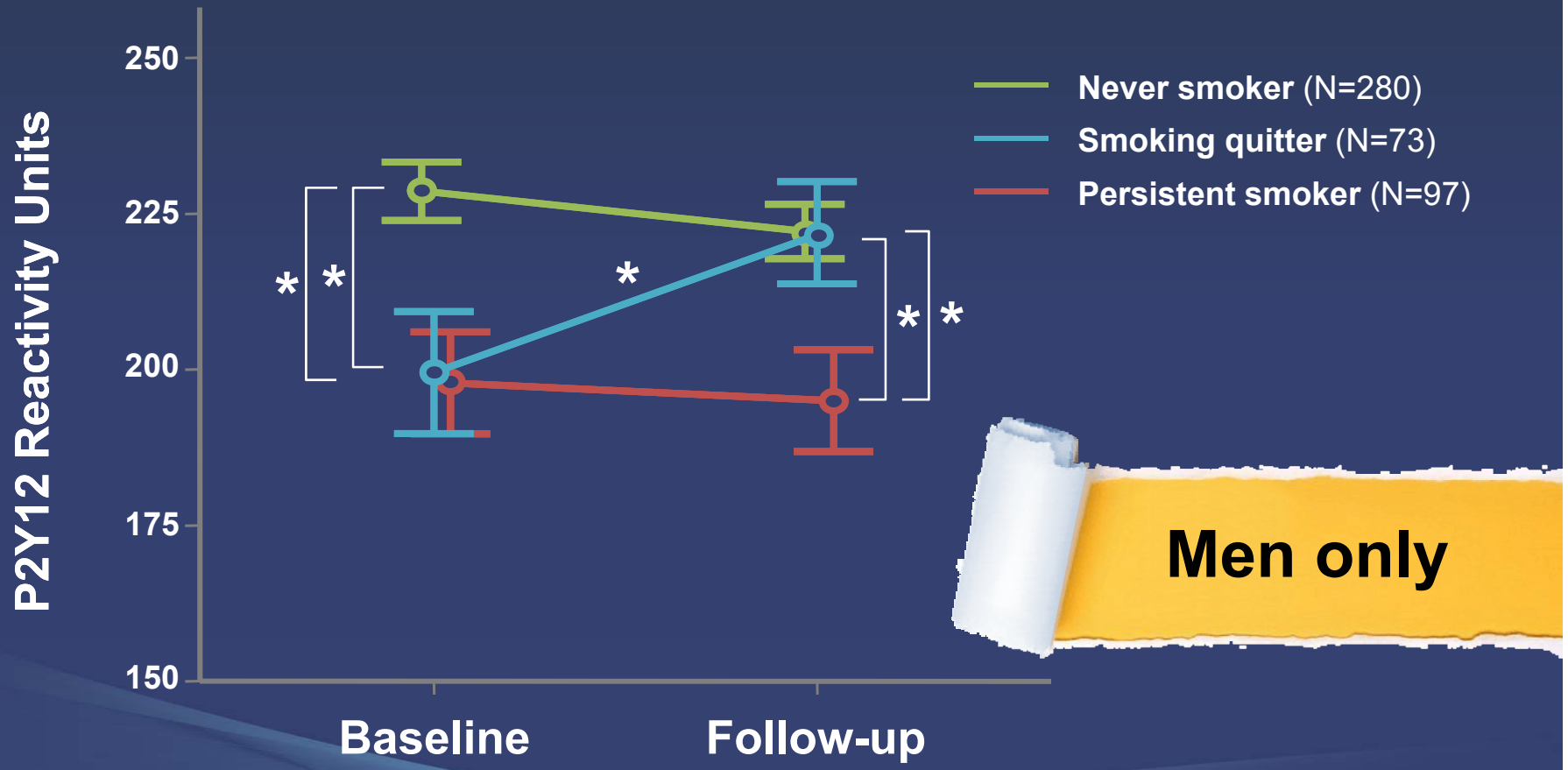
Seoul National University Hospital Cardiovascular Center

Changes in OPR



Park KW, Kang SH, Kim HS et al. Heart 2012

Changes in OPR



Men only

Cardiovascular Laboratory, Seoul National University Hospital

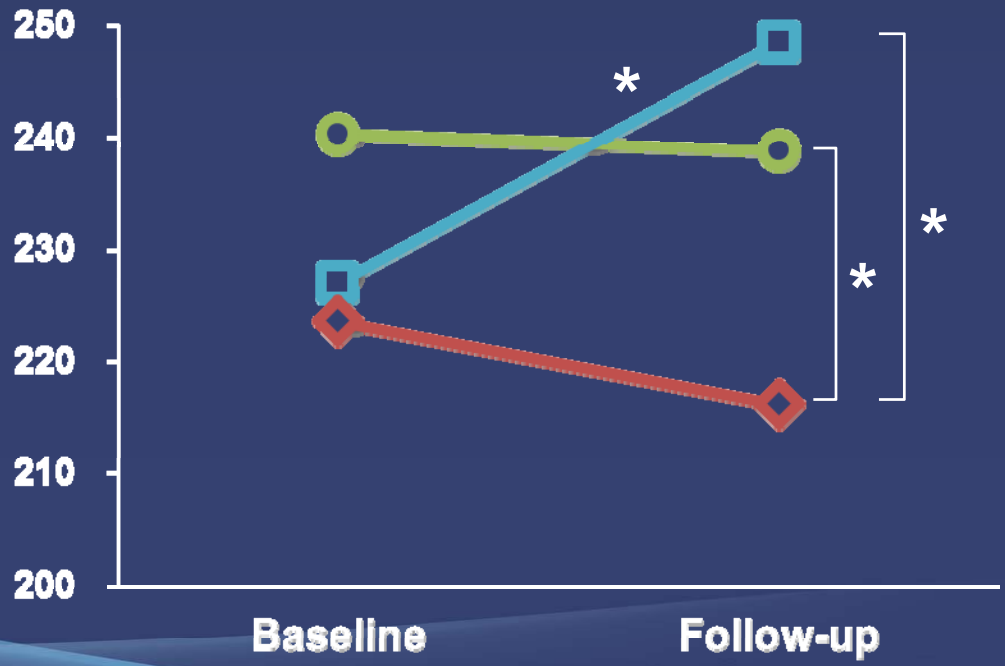
Park KW, Kang SH, Kim HS et al. Heart 2012

Changes in OPR

Multivariable Adjustment

adjusted for age & sex

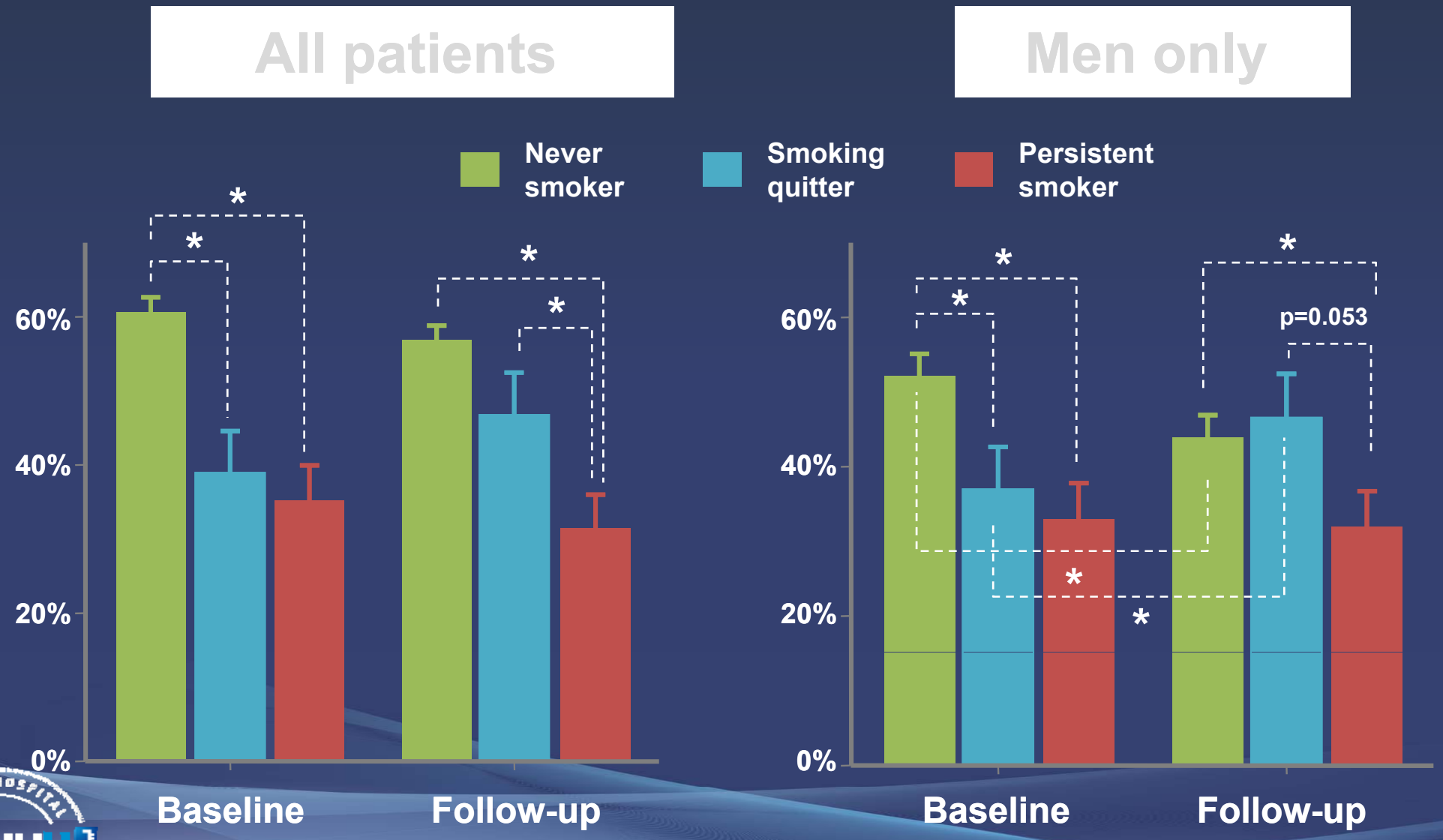
adjusted for age, sex, baseline risk factors, and medications



Cardiovascular Laboratory, Seoul National University Hospital

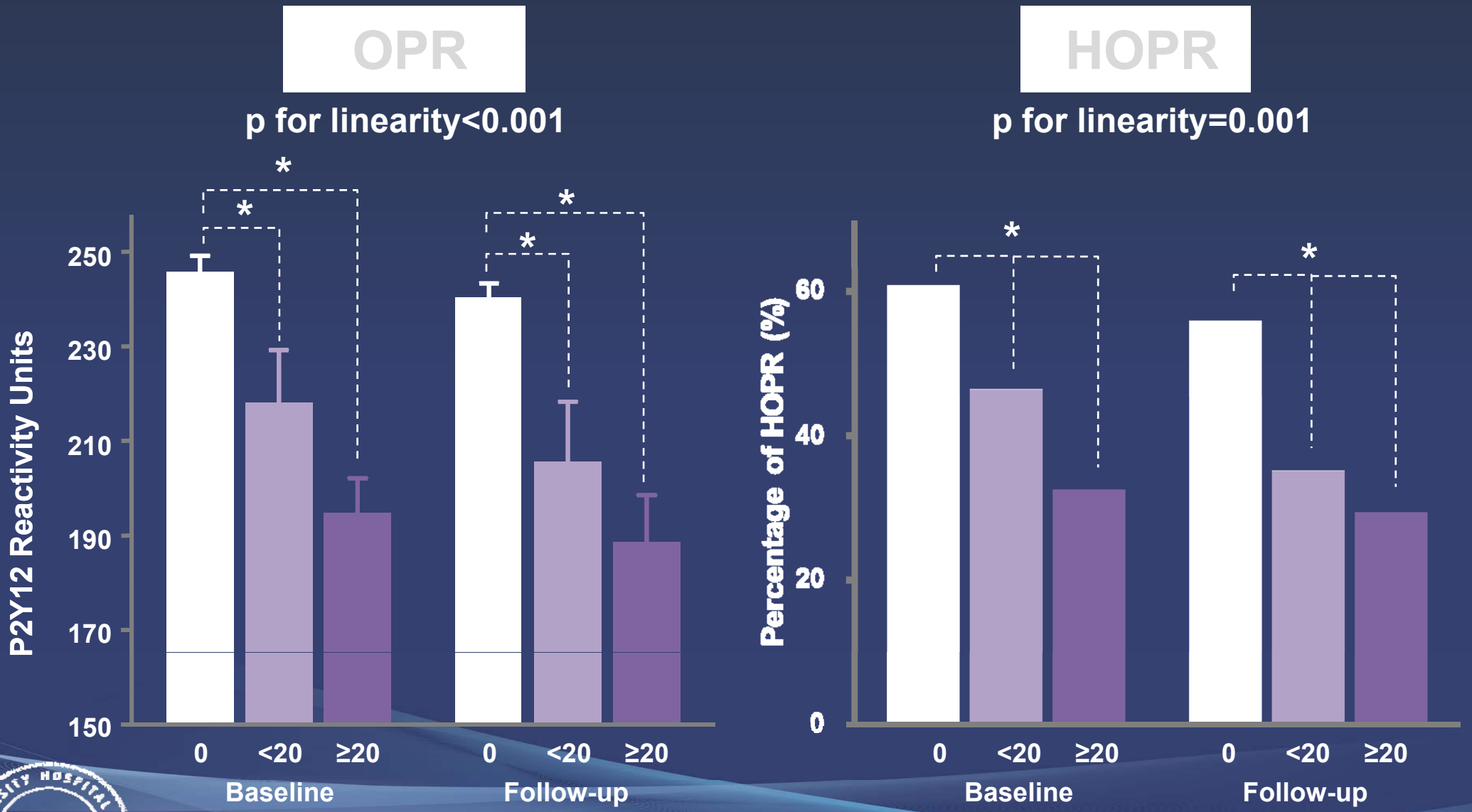
Park KW, Kang SH, Kim HS et al. Heart 2012

Frequency of HOPR



Park KW, Kang SH, Kim HS et al. Heart 2012

Association with smoking amount



Park KW, Kang SH, Kim HS et al. Heart 2012

Summary

	OPR		% HOPR	
	baseline	changes at F/U	baseline	changes at F/U
Never smokers	high	→	high	→
Smoking quitters	low	↑↑	low	↑↑
Persistent smokers	low	→	low	→

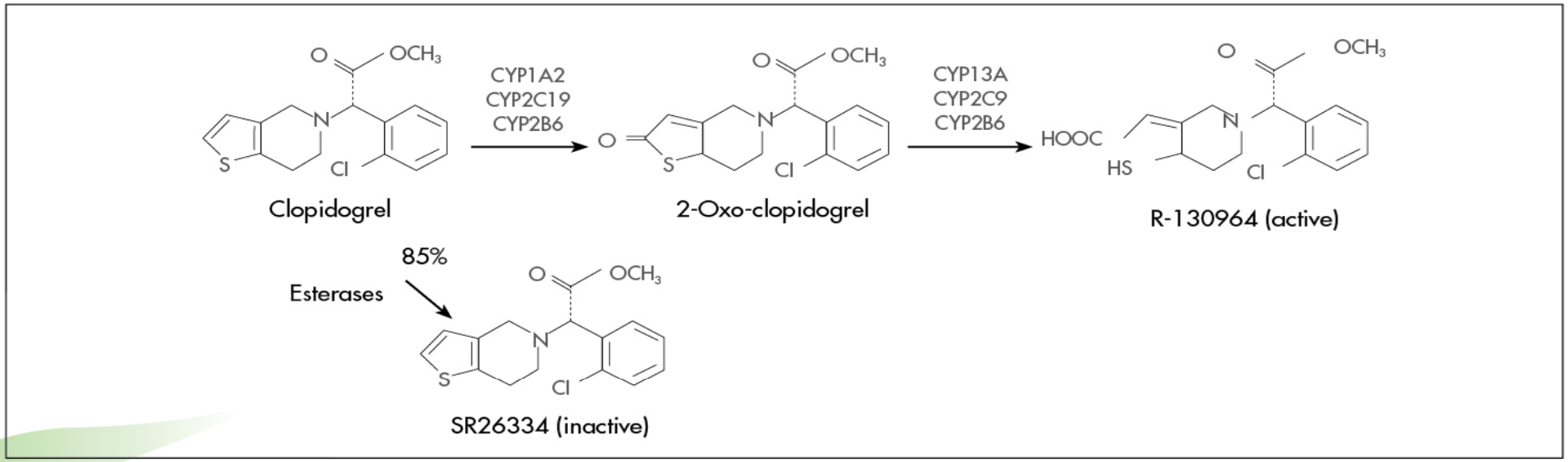
- Temporal relationship
  - Smoking → enhanced response to clopidogrel
  - Quitting → **reversal** of enhanced response

- Dose-response relationship
  : Smoking amount ∝ antiplatelet effect of clopidogrel

Metabolism - Clopidogrel

- The initial hydrolysis of clopidogrel compound results in inactivation of a substantial fraction (~85%) of the absorbed drug[2]
- The subsequent activation requires 2 CYP-dependent steps[2]

Figure . Schematic representation of the metabolism of clopidogrel[3]



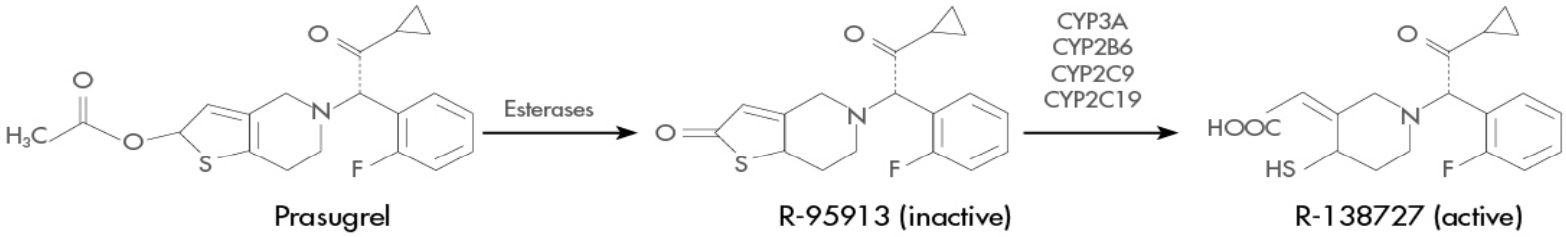
Data from Ref 3. Mega JL et al. Circulation. 2009;119:2553-2560

2012-1088-03 Jan 2014

Different Metabolism – Prasugrel

- Prasugrel rapidly hydrolyzed by esterases, such as those located in the intestine and blood, to intermediate metabolite [2]
- This intermediate metabolite undergoes subsequent activation by a single CYP-dependent step[2]

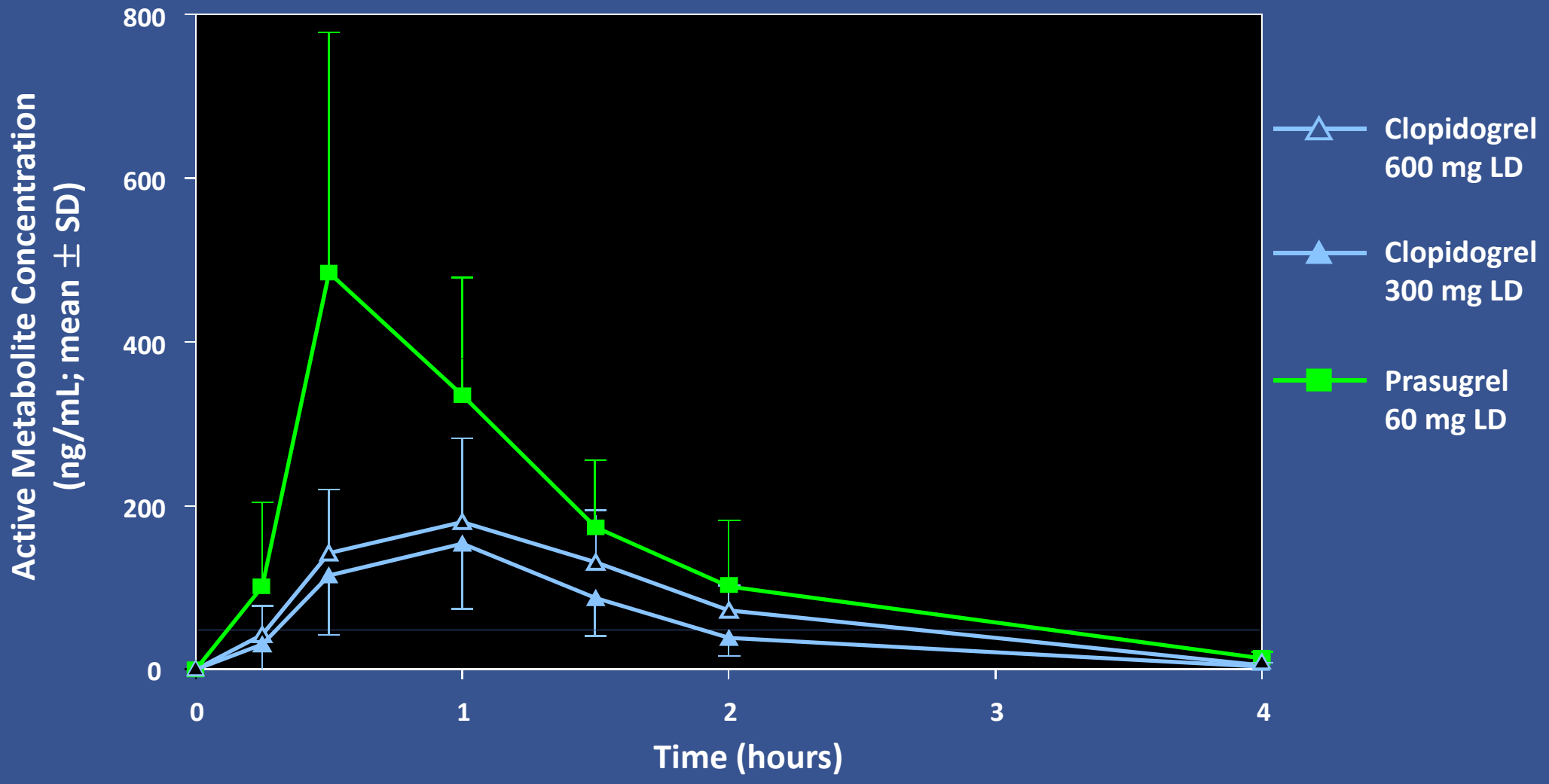
Figure . Schematic representation of the metabolism of prasugrel[3]



Data from Ref 3. Mega JL et al. Circulation. 2009;119:2553-2560

2012-1088-03 Jan 2014

Active Metabolite Plasma Concentrations After the Loading Dose (Prasugrel vs. Clopidogrel)



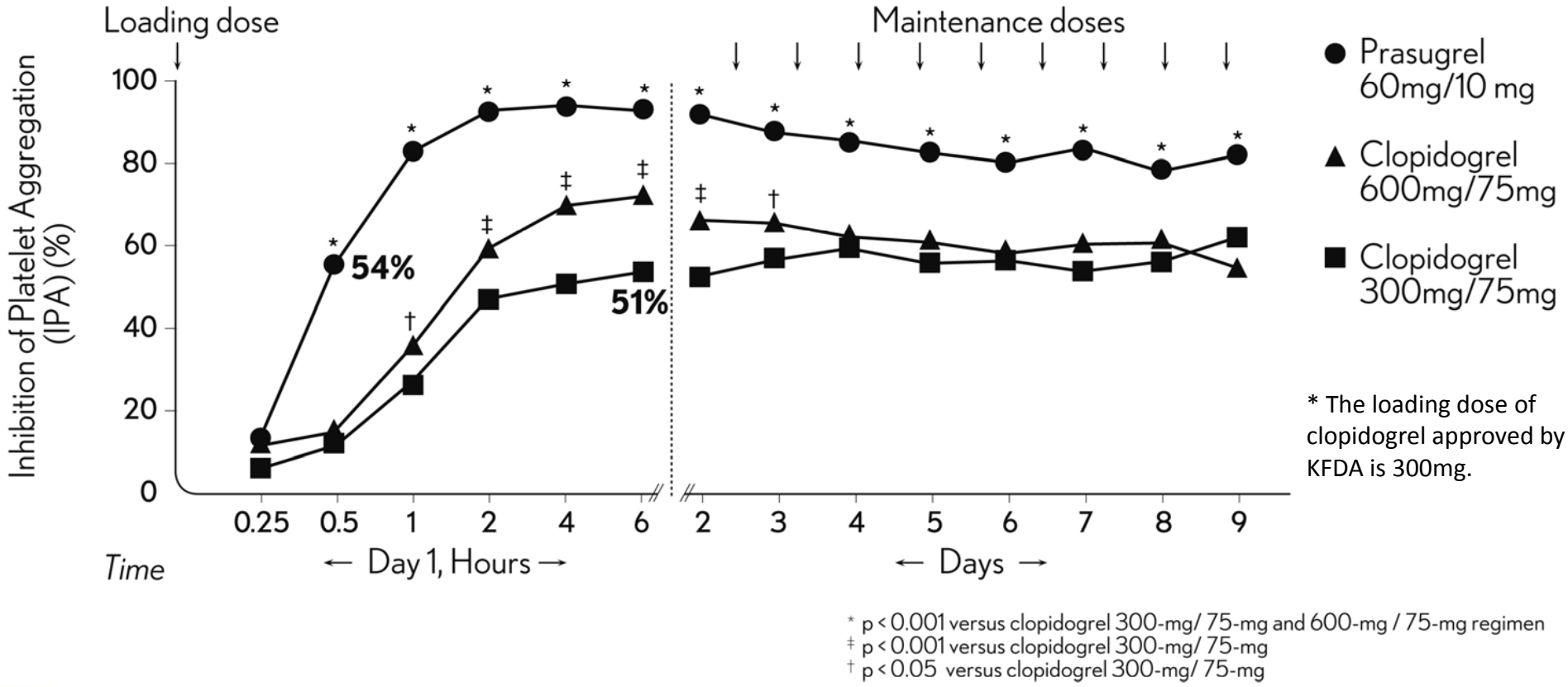
SD=Standard deviation; LD=Loading dose

Winters K, et al. Poster 1386. Presented at ESC Annual Congress; September 2, 2007: Vienna, Austria.

Faster Onset of Higher Level of Platelet Inhibition

- **At 30 minutes after LD, prasugrel 60-mg achieved greater mean IPA to 20 µM ADP (54%) than either clopidogrel 300-mg (3%) or 600-mg (6%)**

Figure. Inhibition of platelet aggregation (20 µM ADP)



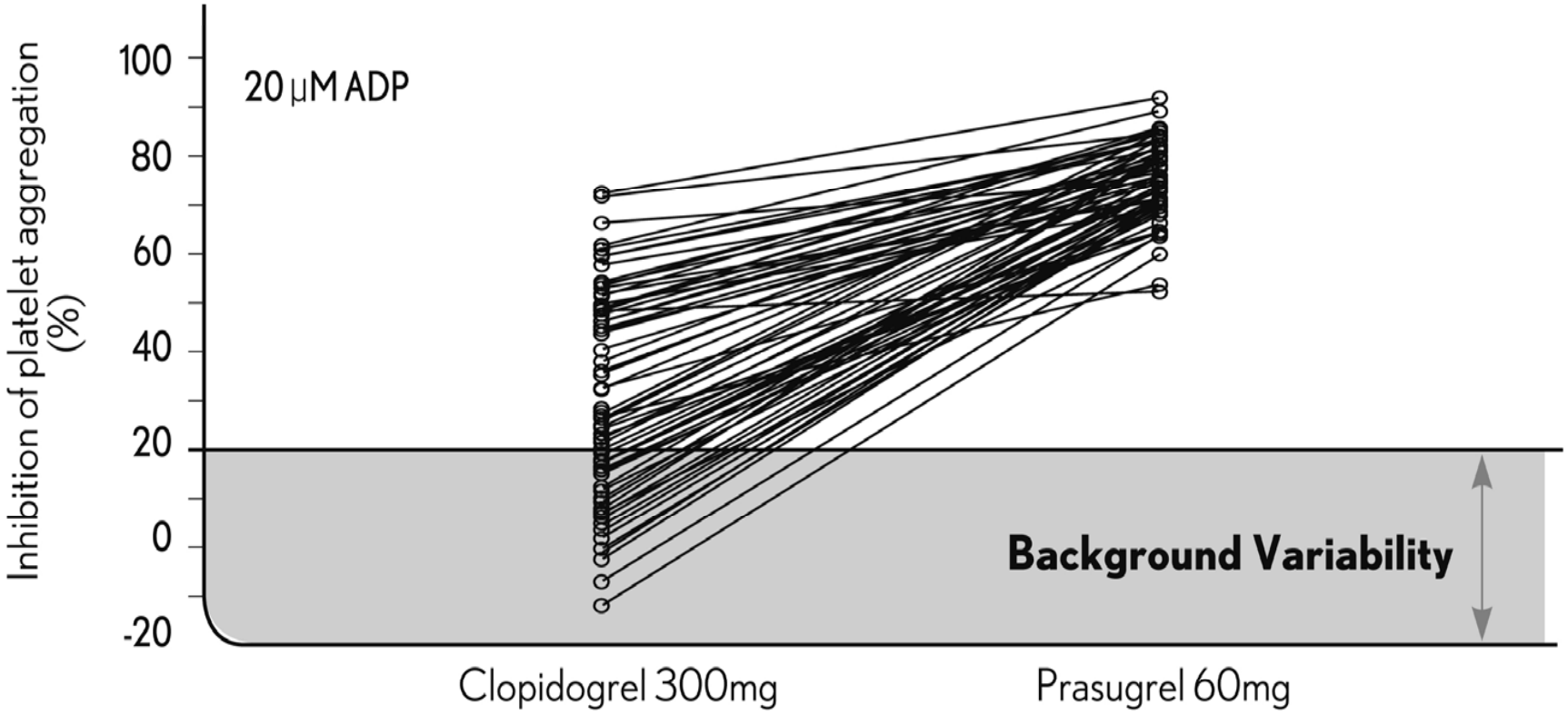
* The loading dose of clopidogrel approved by KFDA is 300mg.

* $p < 0.001$ versus clopidogrel 300-mg/ 75-mg and 600-mg / 75-mg regimen
‡ $p < 0.001$ versus clopidogrel 300-mg/ 75-mg
† $p < 0.05$ versus clopidogrel 300-mg/ 75-mg

Payne CD et al. *J Cardiovasc Pharmacol* 2007;50:555–562

Less Variable Platelet Inhibition

- **In 27 of 64 subjects, the IPA in response to clopidogrel 300 mg could not be distinguished from background variability (ie, the IPA at 24 hours was <20% to 20 µmol/L ADP).**
- **In contrast, the IPA observed with prasugrel 60 mg at 24 hours after dosing was greater than background variability in all subjects.**

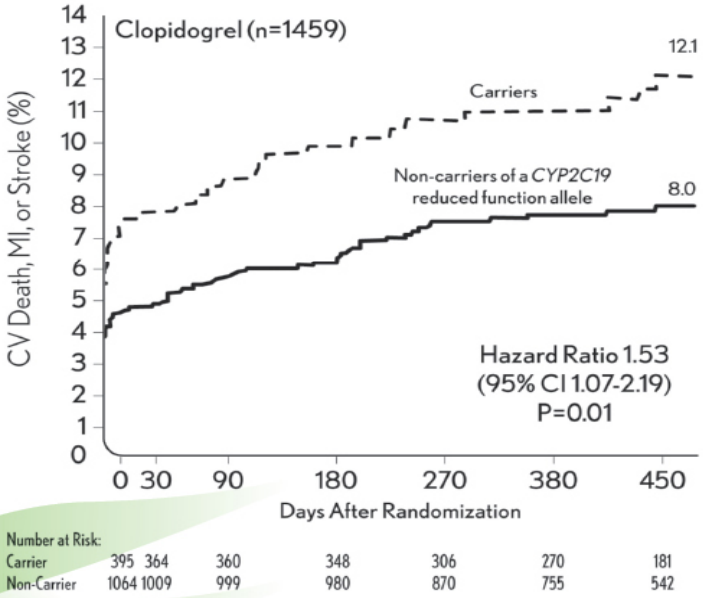


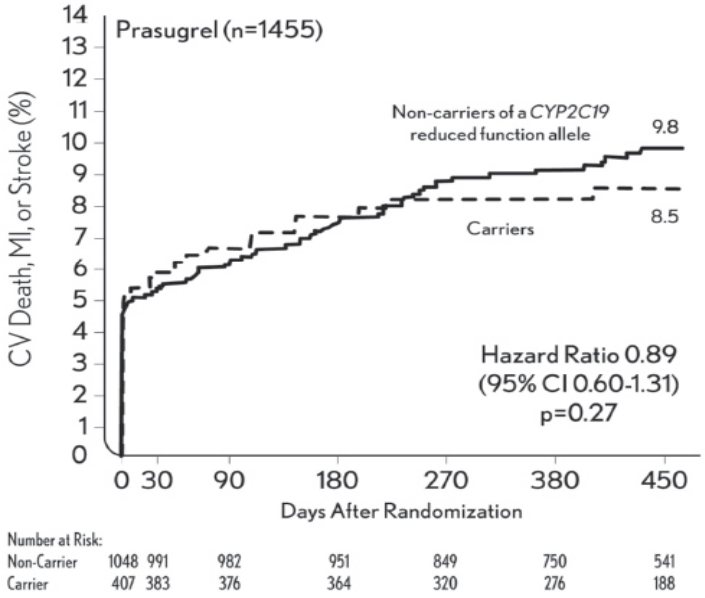
Brandt JT et al. *Am Heart J* 2007;153:66.e9-66.e16

Impact of Reduced-Function CYP2C19 Alleles in TRITON-TIMI 38

- CYP2C19 variants do not significantly affect pharmacological or clinical outcomes in patients treated with prasugrel[3]

Figure. Cumulative incidence curves for the primacy efficacy outcome (composite of cardiovascular death, myocardial infarction, or stroke) [3,9]





Data from Ref 9. Mega JL et al. N Engl J Med 2009;360:354-62.

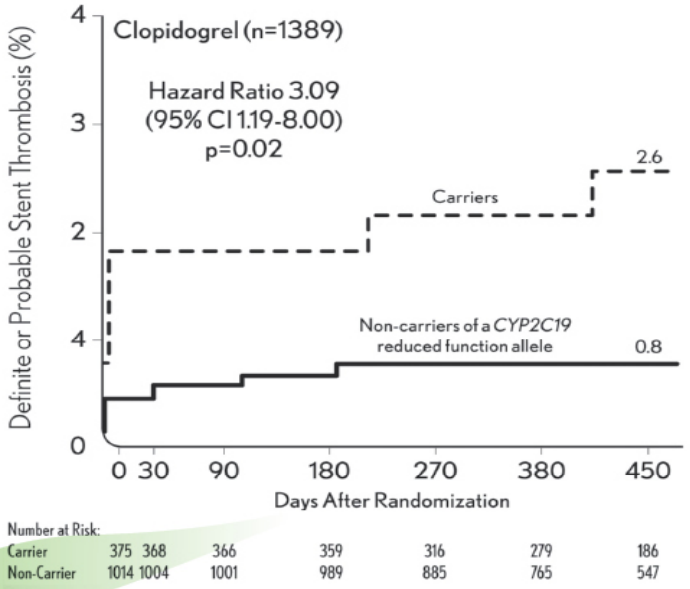
Data from Ref 3. Mega JL et al. Circulation. 2009;119:2553-2560

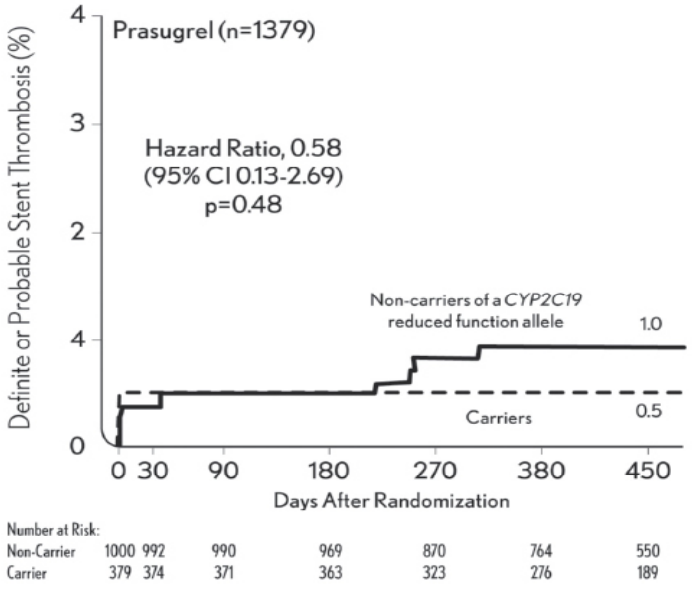
2012-1088-03 Jan 2014

Impact of Reduced-Function CYP2C19 Alleles in TRITON-TIMI 38

- CYP2C19 variants do not significantly affect pharmacological or clinical outcomes in patients treated with prasugrel [3]

Figure. Cumulative incidence curves for the stent thrombosis (Definite or Probable) [3, 9]



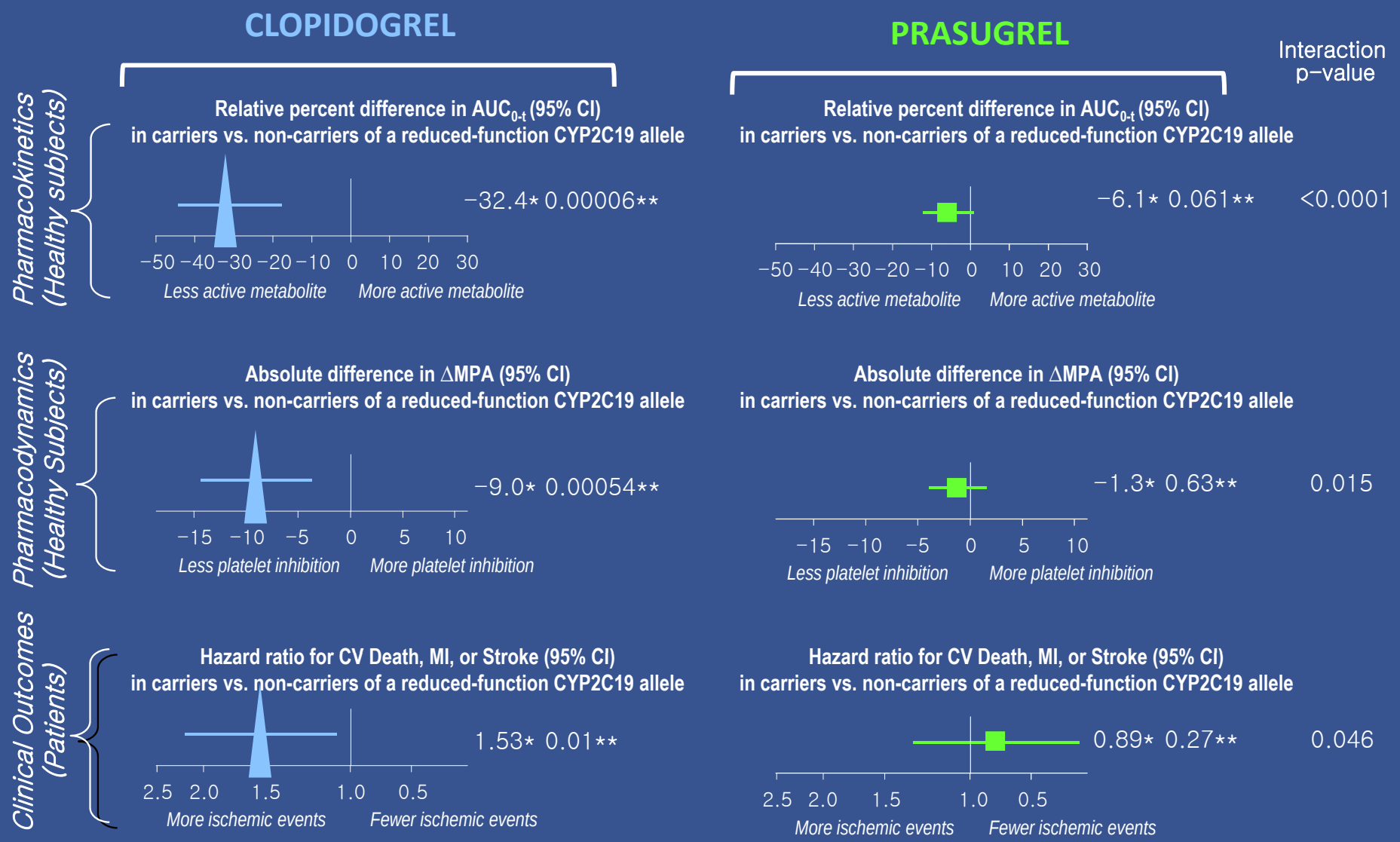


Data from 9. Mega JL et al. N Engl J Med 2009;360:354-62.

Data from Ref 3. Mega JL et al. Circulation. 2009;119:2553-2560

2012-1088-03 Jan 2014

Effect of CYP2C19 LOF allele
Pharmacokinetics, Pharmacodynamics and Clinical Outcomes



AUC = area under the concentration curve; MPA = maximal platelet aggregation;
CI = confidence interval; CV = cardiovascular; MI = myocardial infarction
*point estimate; **p-value

Mega JL, et al. *Circulation* 2009;119(19):2553-2560

Ideal Patient? – Korean Perspective

1. **S**table elective PCI: Standard aspirin + plavix
2. **I**n adverse clinical situations: very complex stenting with lots of metal burden, ACS: may need to consider other options
3. **P**rasugrel outperforms clopidogrel most profoundly in patients with DM and STEMI. → Greatest net benefit (no significant increase in non-CABG bleeding)
4. **S**cope of the problem of clopidogrel response variability and genetic risk → Probably more relevant in Koreans than in Caucasians.
5. ACS pt with **DM, STEMI, HOPR, CYP2C19 LOF, drug interaction**

CAVEATS

1. Higher proportion of genetic at risk population, but similar absolute clinical outcomes compared with Western populations

2. Koreans have a smaller BMI than Caucasians, which may result in higher susceptibility to bleeding complications. May need to consider a lower dose such as 5mg for certain patients. (No concrete clinical data as of yet)