Pharmacogenomics of Clopidogrel & Its Correlation with Clinical Outcomes

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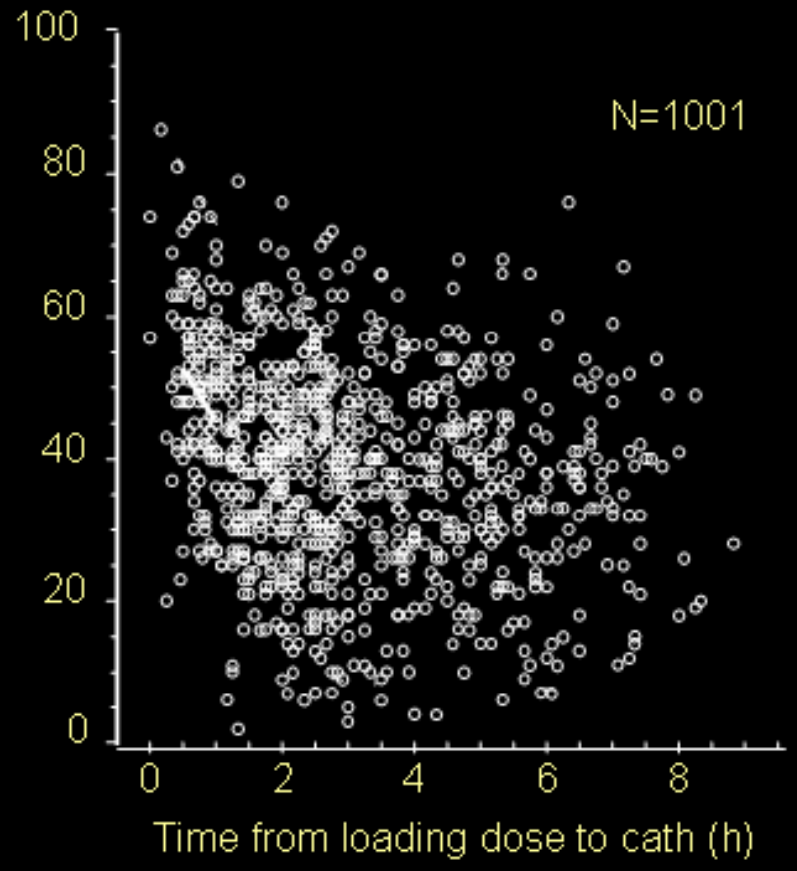
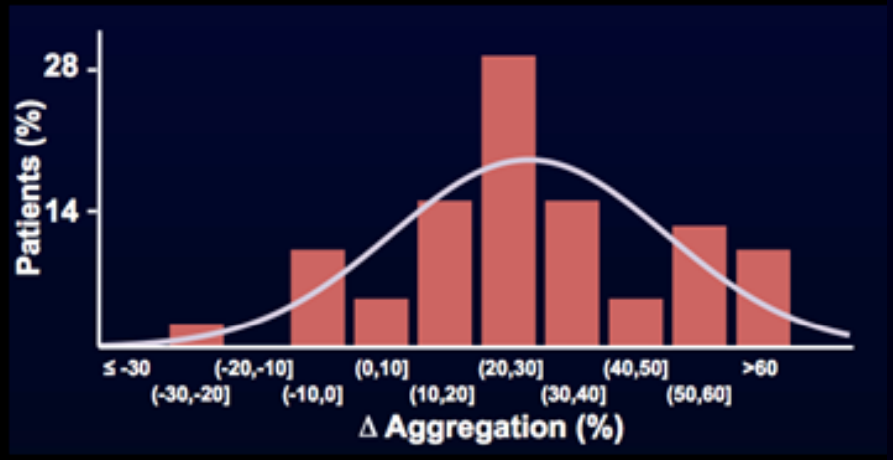
ANGIOPLASTY SUMMIT 2012

Platelet Reactivity Varies Widely Among Patients on Clopidogrel

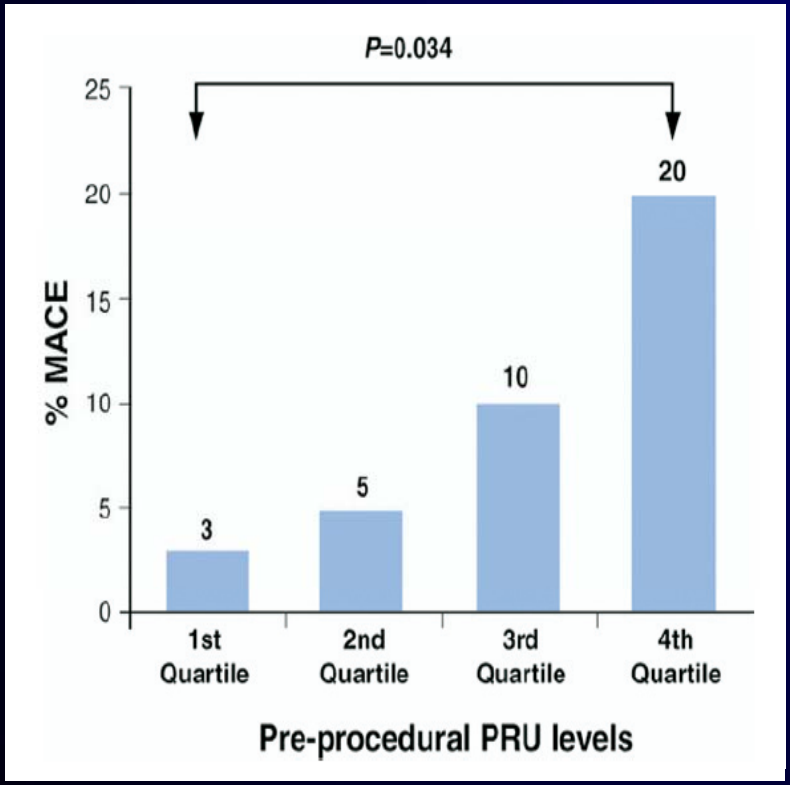


Hochholzer et al. *Circulation* 2005

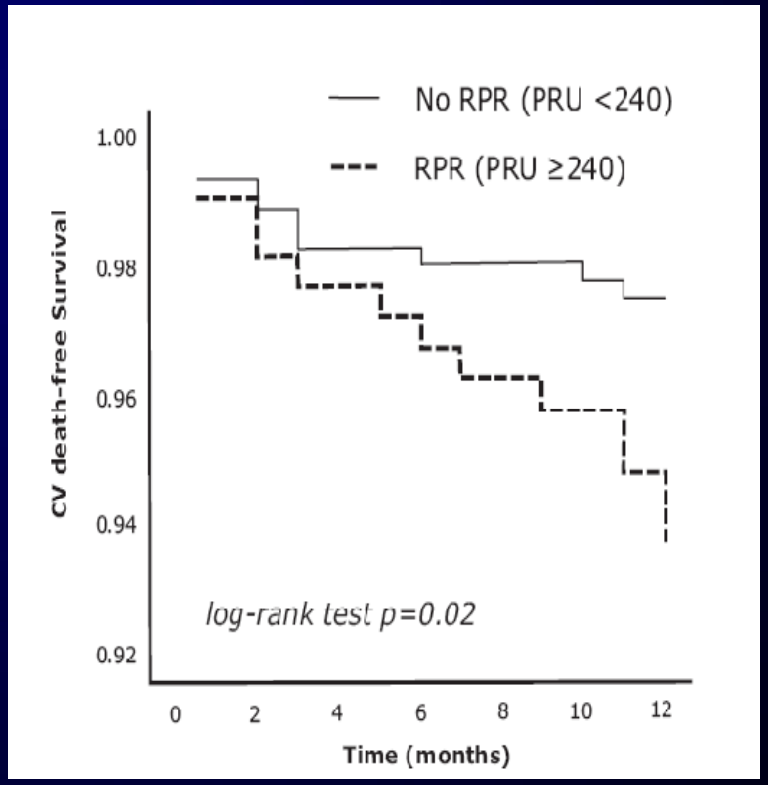


Gurbel P et al*, Circulation* 2003

Implication of HOPR* in Caucasian population



ARMYDA-PRO (JACC, 2008)

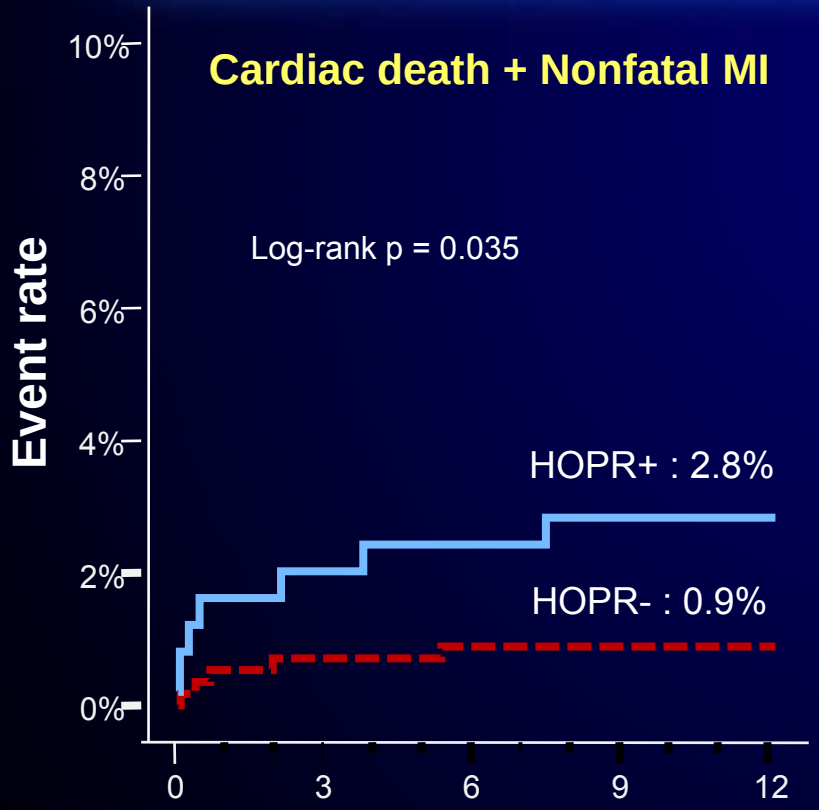


Marcucci, et al. Circulation, 2009

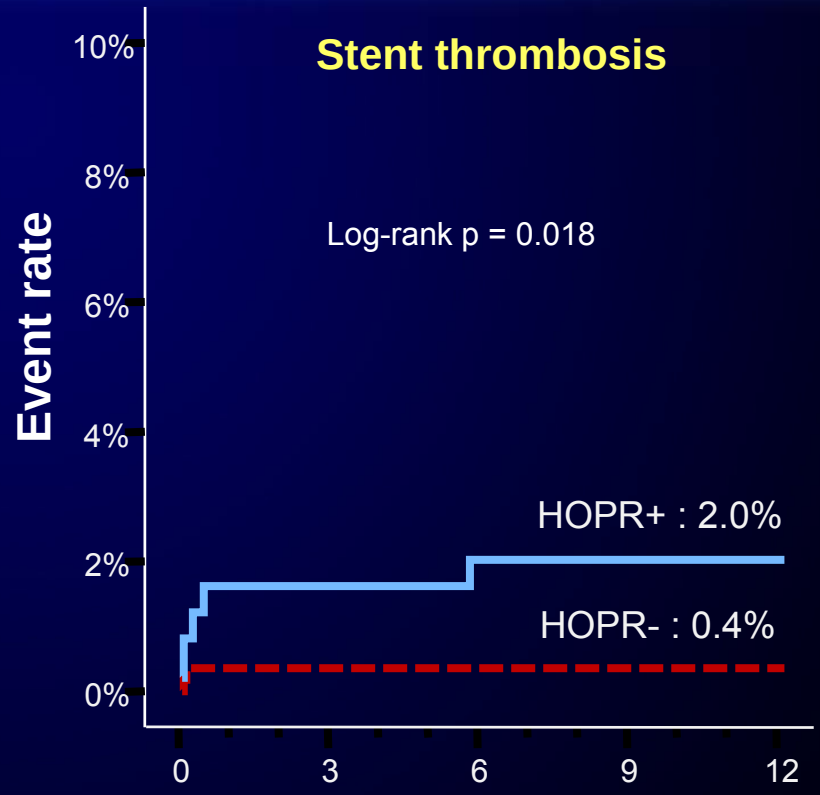
HOPR* : High on treatment platelet reactivity

Implication of HOPR in Korean population

CROSS-VERIFY Registry



Patients at risks	Months after index procedure				
HOPR +	247	243	241	241	239
HOPR -	562	557	554	552	551



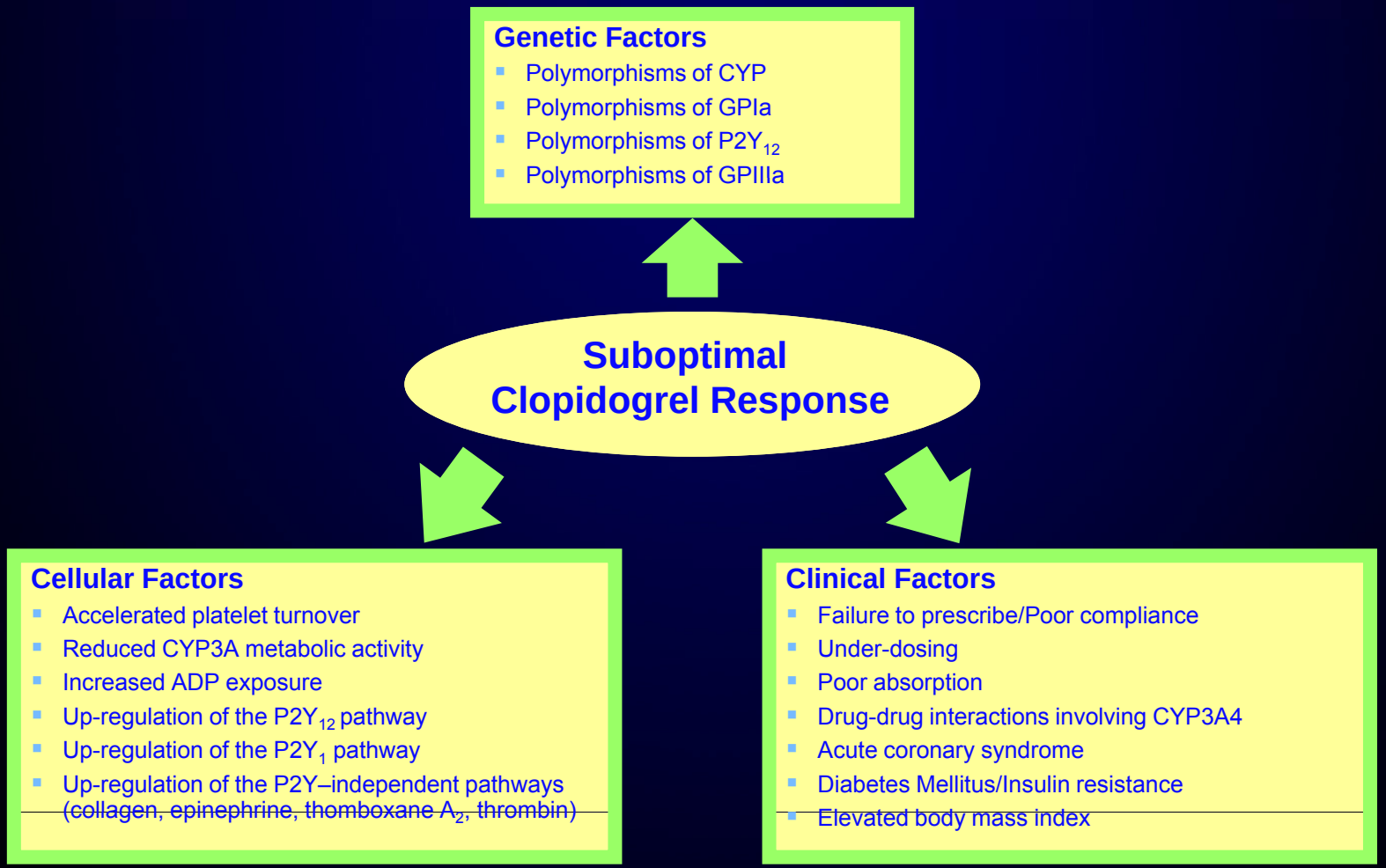
Patients at risks	Months after index procedure				
HOPR+	247	243	242	242	240
HOPR-	562	558	554	552	551

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

MESSAGE 1.

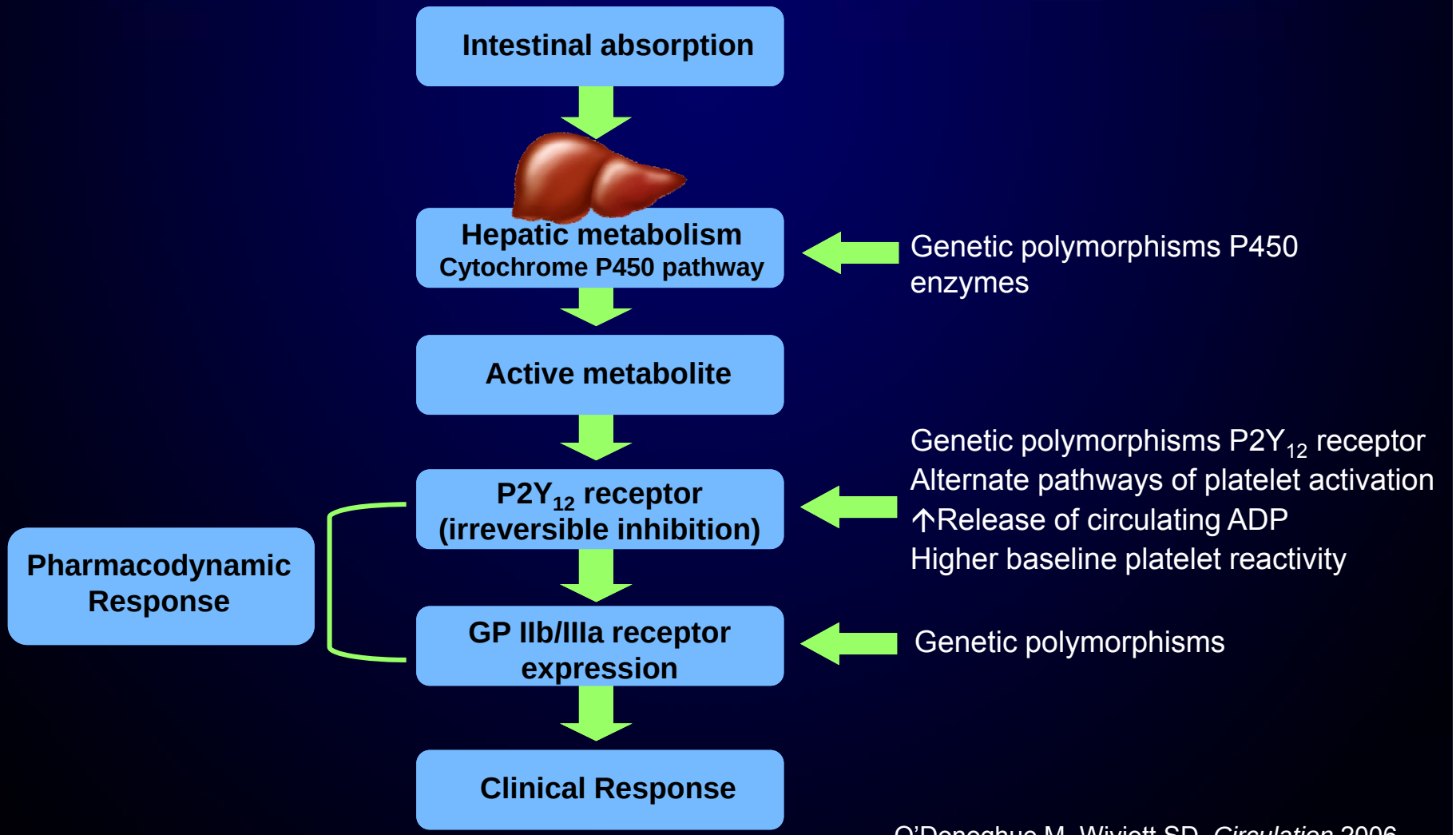
High on treatment platelet reactivity (HOPR) is associated with atherothrombotic complications in CHD patients taking clopidogrel.

Mechanisms of Inter-individual Variability in Clopidogrel Responsiveness



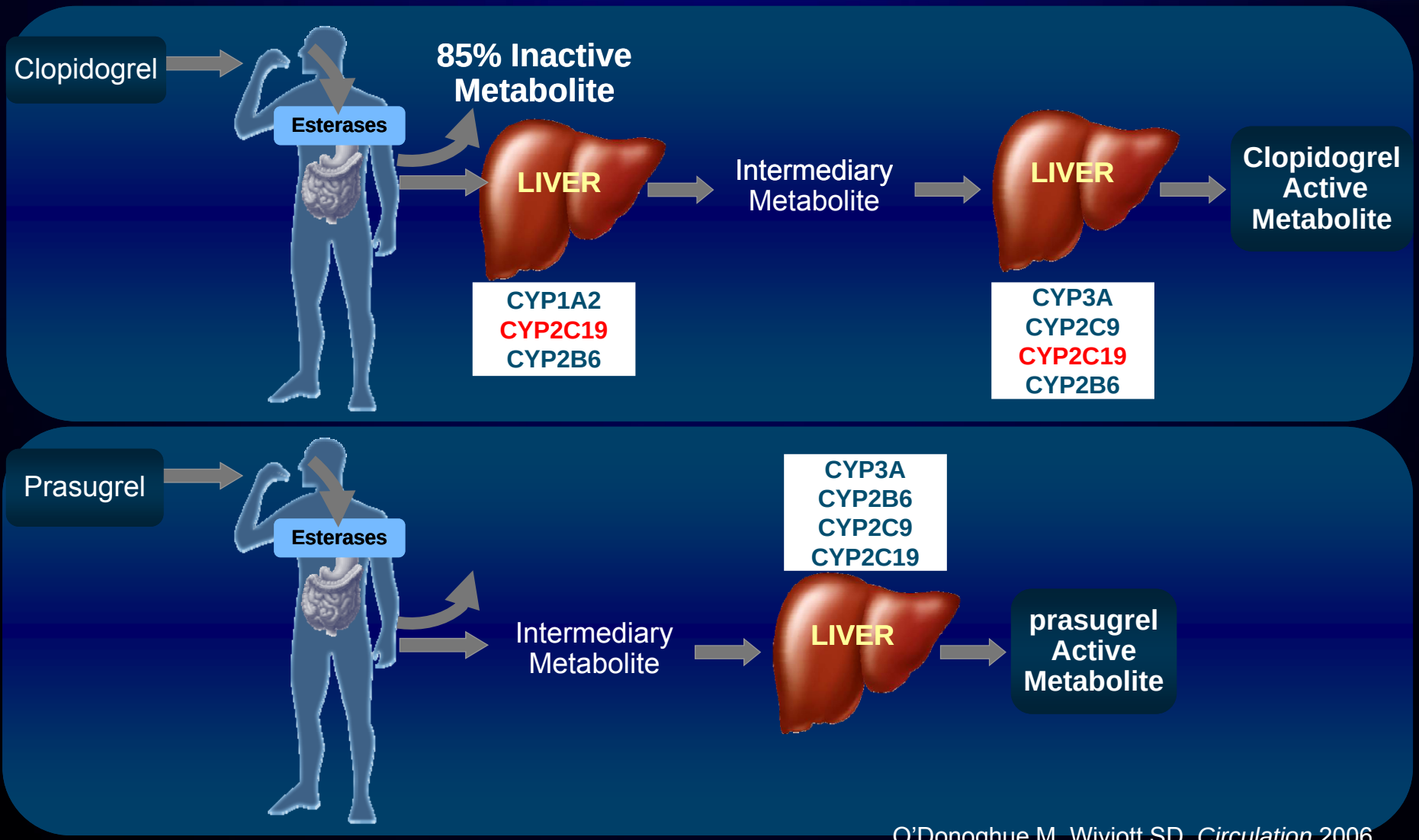
Angiolillio DJ et al. *J Am Coll Cardiol*. 2007;49:1505–16

Clopidogrel Metabolism Pathway



O'Donoghue M, Wiviott SD. *Circulation* 2006

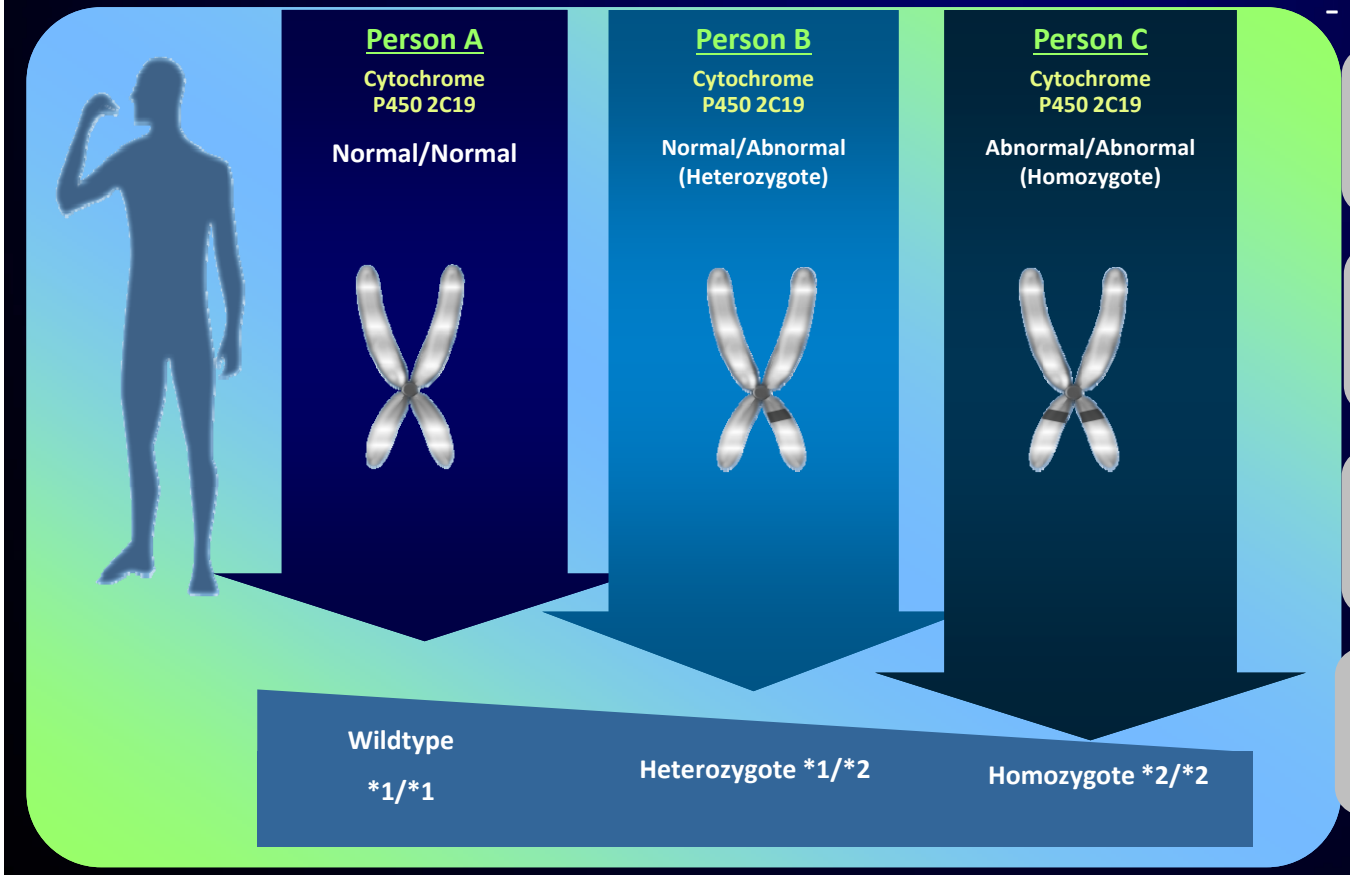
Role of Cytochrome P450 System in Metabolism of PLAVIX and Prasugrel



O'Donoghue M, Wiviott SD. *Circulation* 2006

Cytochrome P450 2C19 Polymorphisms & Antiplatelet Effects

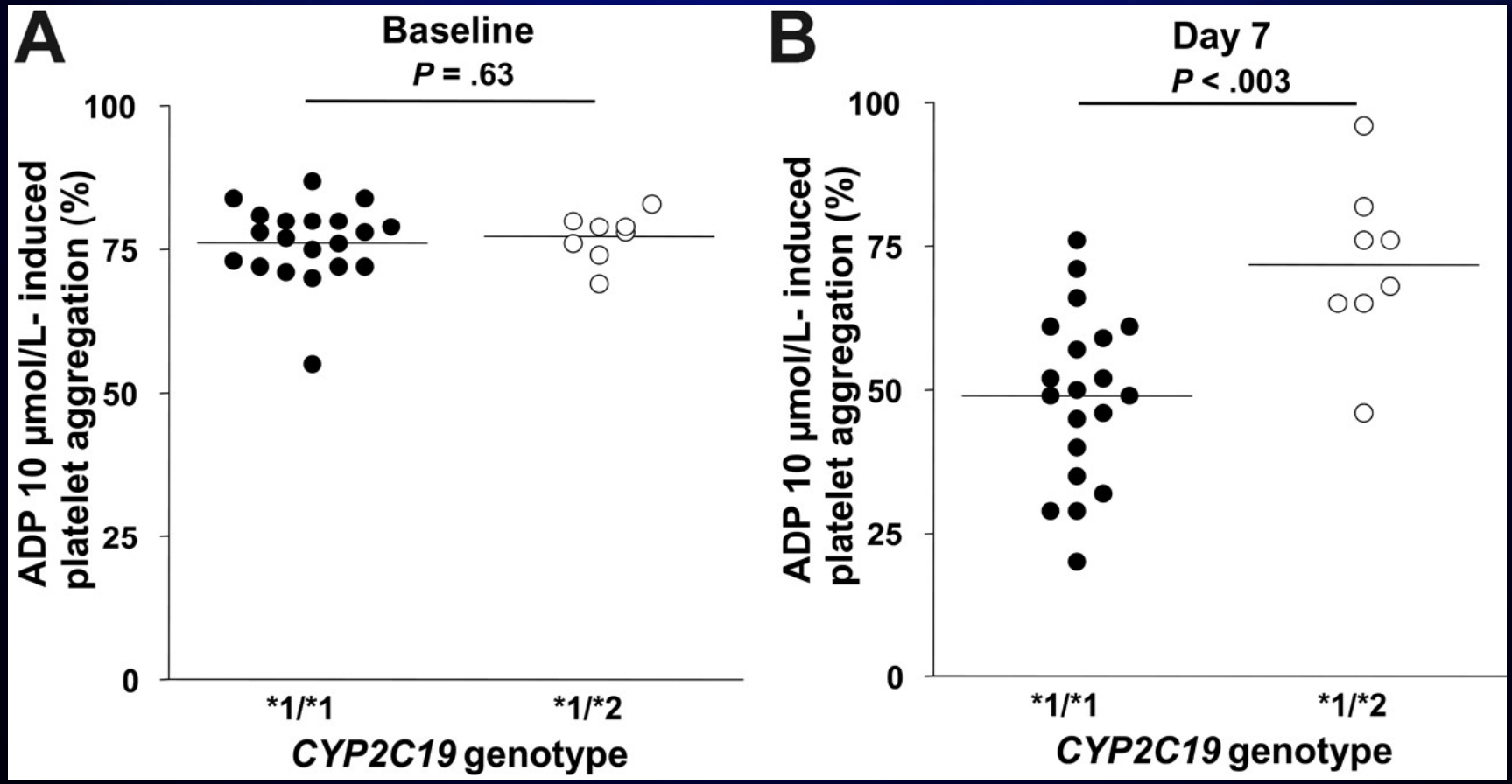
- Wild type (*1)
- Loss-of-function (*2, *3)
- Gain-of-function (*17)



Extensive metabolism	CYP2C19*1/*1
Intermediate metabolism	CYP2C19*1/*2 or *1/*3
Poor metabolism	CYP2C19*2/*2, *2/*3 or 3/*3 Also *4,*5
Ultrarapid	CYP2C19*17/*17,

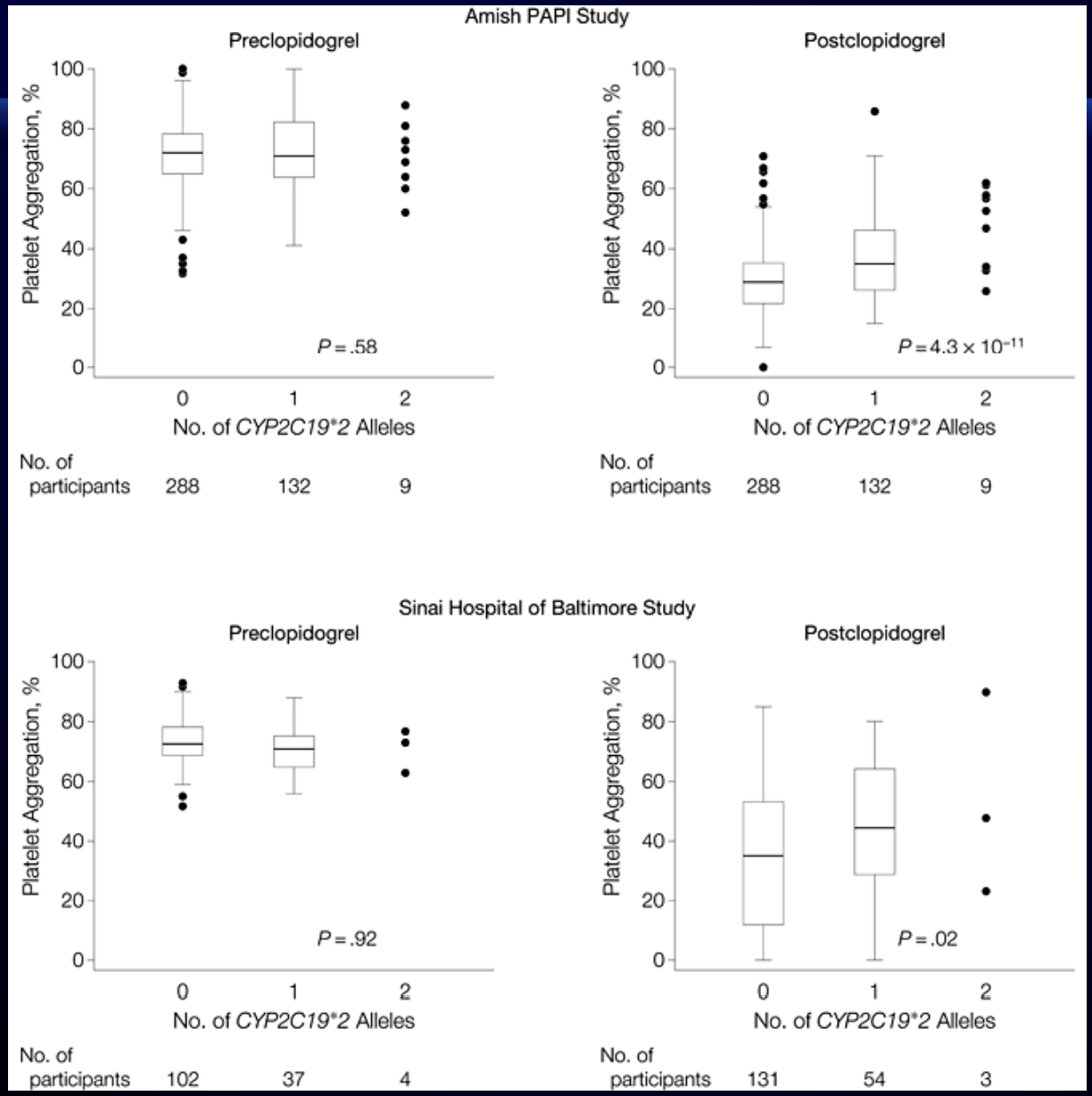
Kim KA, Park PW, Hong SJ, Park J-Y. *Clin Pharmacol Ther.* 2008;84:236–42

CYP2C19 LOF Polymorphism & Response to Clopidogrel



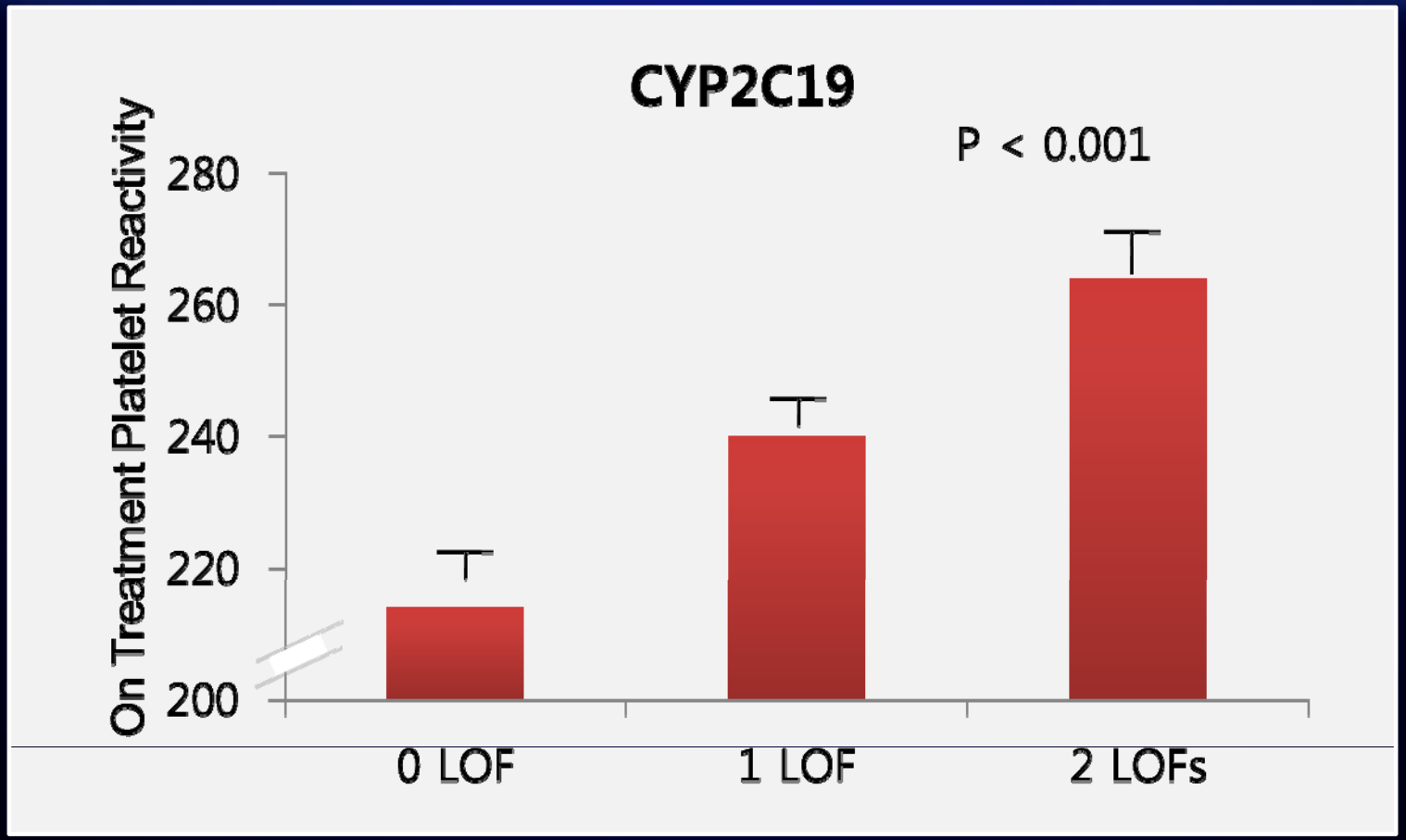
Hulot JS, et al. *Blood* 2006;108:2244-7

CYP2C19 LOF Polymorphism & Response to Clopidogrel



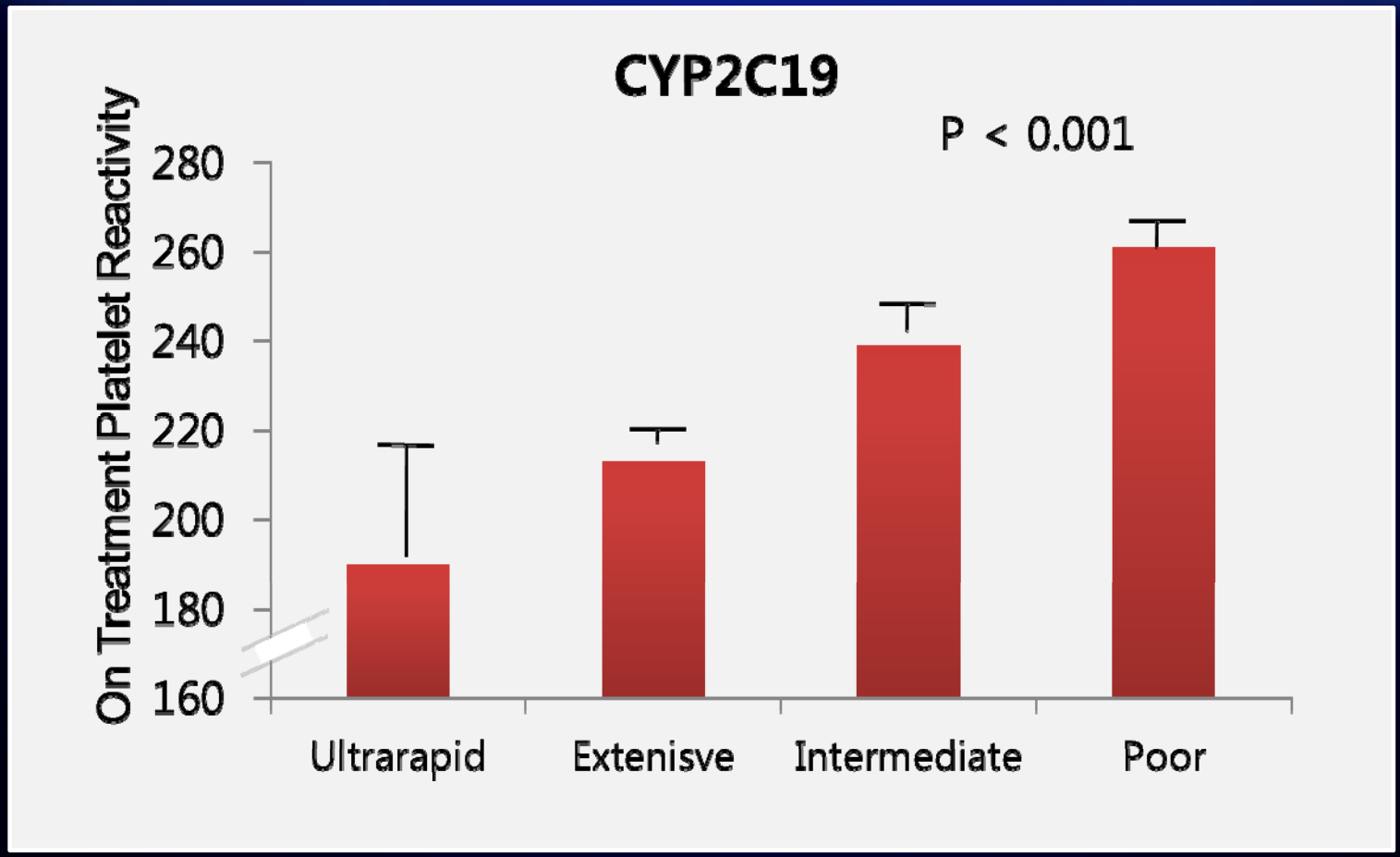
Shuldiner AR, et al. JAMA 2009;302:849-57

CYP2C19 LOF Polymorphism & Response to Clopidogrel : Korean Data



CROSS-VERIFY REGISTRY
Park KW, Park JJ et al, *Cardiovasc Ther* 2012

CYP2C19 LOF Polymorphism & Response to Clopidogrel : Korean Data



CROSS-VERIFY REGISTRY
Park KW, Park JJ et al, *Cardiovasc Ther* 2012

MESSAGE 2.

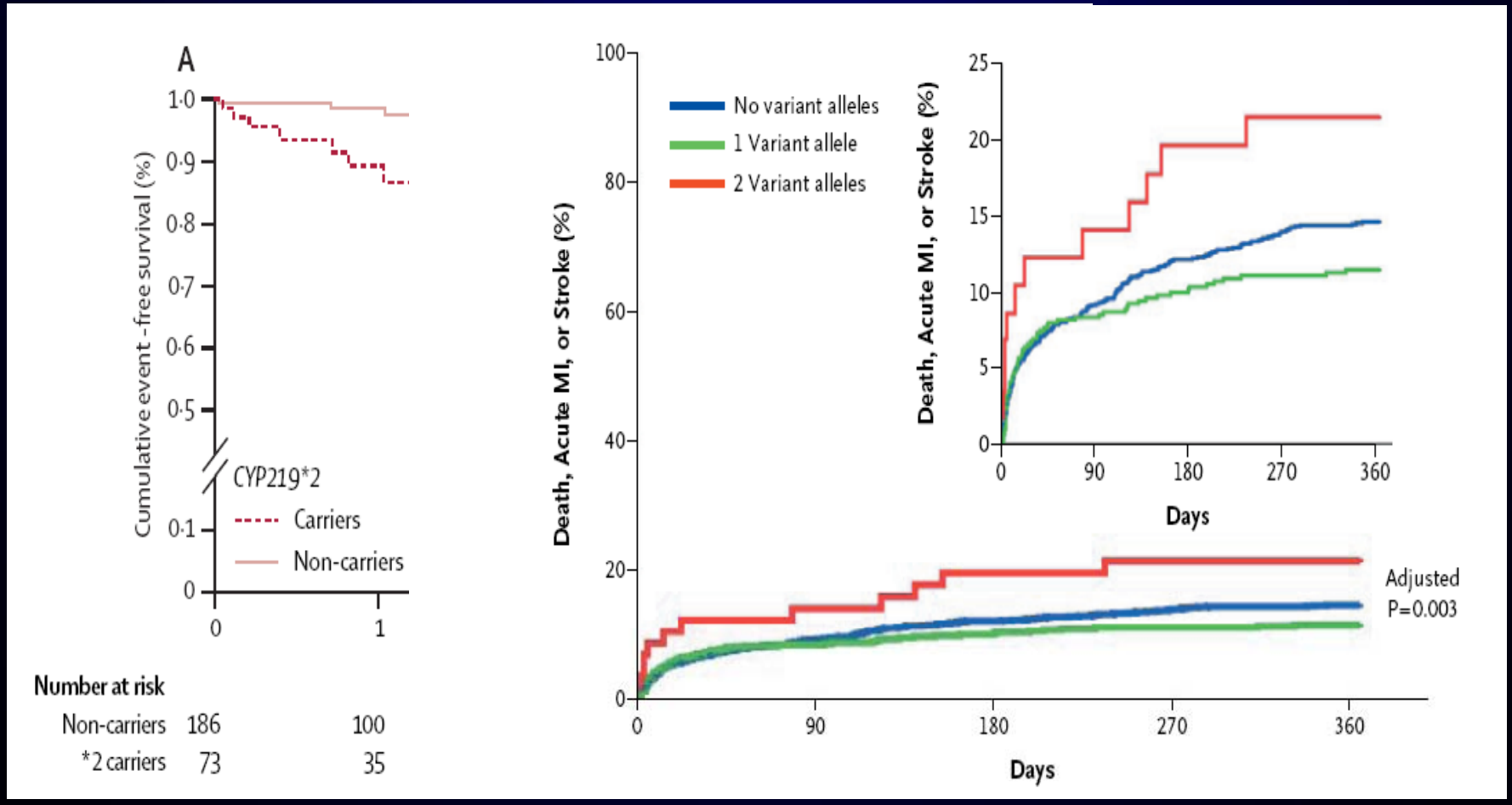
CYP2C19 LOF polymorphism is associated with HOPR in clopidogrel users.

Then,,,,,

Are CYP2C19 LOF polymorphisms associated with atherothrombotic complications in CHD patients taking clopidogrel?

PRO

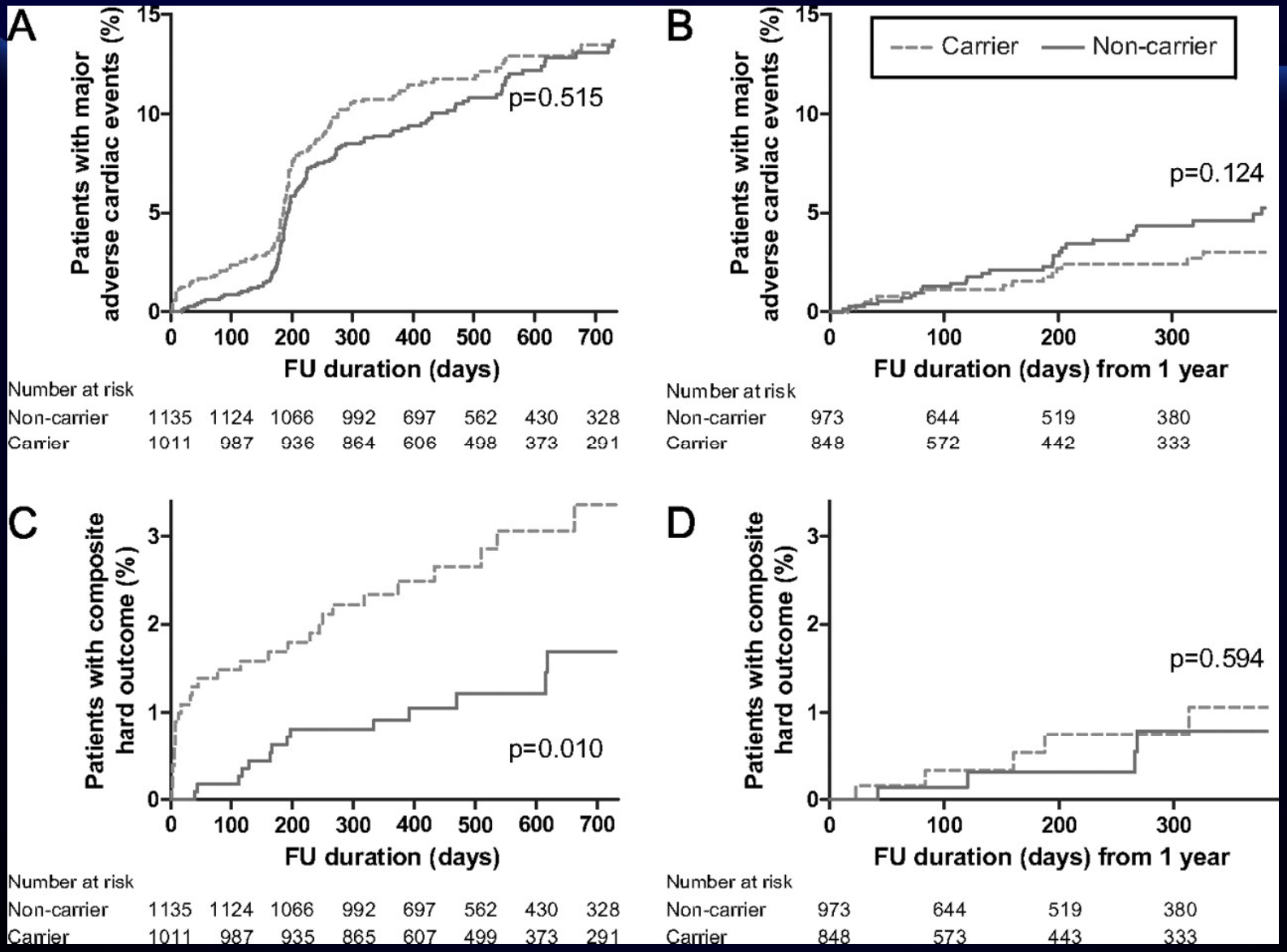
CYP2C19 LOF polymorphism & MACEs in clopidogrel users



Collet JP, et al. Lancet, 2009

Simon T, et al. N Eng J Med, 2009

Cumulative incidence rate of MACE (A) and composite hard outcome (C) during the follow-up period.



SKY Registry, Oh I et al. Heart 2012;98:139-144

HEART

CONS

CURE Trial

- 12,562 ACS patients without ST-segment elevation
  - Randomized to Clopidogrel (75mg) or Placebo
  - On a background of ASA (75 mg to 325 mg)
  - Average follow-up of 9 months

- Outcomes
  - First Primary: CV death, MI, Stroke
  - Second Primary: First primary, or recurrent ischemia, or UA
  - Safety: Major bleed (life-threatening or not)

Yusuf et al. NEJM 2001; 345: 494-502

CURE Genetics Baseline Characteristics

- The benefit of clopidogrel treatment on the first primary composite efficacy outcome was similar to the parent study:

CURE Overall: 582 events, 9.3 % versus 719 events, 11.4%; HR=0.80 95% CI 0.72-0.90, P<0.001
CURE-Genetics: 231 events, 9.1% versus 316 events, 12.6%; HR=0.71 95% CI 0.60-0.84, P<0.001

Characteristic	OVERALL			CURE-Genetics		
	Placebo	Clopidogrel	Total	Placebo	Clopidogrel	Total
N	6303	6259	12562	2510	2549	5059
Female (%)	38.3	38.7	38.5	40.9	41.2	41.0
Age	64.2 (11.3)	64.2 (11.3)	64.2 (11.3)	63.9 (11.1)	63.8 (11.0)	63.8 (11.0)
BMI	27.4 (4.1)	27.4 (4.1)	27.4 (4.1)	27.6 (4.1)	27.7 (4.2)	27.6 (4.2)
Diabetes (%)	22.8	22.4	22.6	21.5	20.7	21.1
Smoking (%)	22.7	23.4	23.0	21.6	23.1	22.4
SBP	134.1 (22.0)	134.4 (22.5)	134.2 (22.2)	134.6 (22.0)	135.5 (22.3)	135.0 (22.1)
PCI without stent	4.0	3.7	3.9	3.9	3.2	3.5
PCI with stent	17.3	17.3	17.3	13.5	15.5	14.5
CABG	16.8	16.2	16.5	16.3	15.9	16.1

CYP2C19 Alleles

3 allele classes

- "Wild type" (*1): 63%
- Loss-of-function (*2, *3): 13%
- Gain-of-function (*17): 24%

5 metabolizer phenotypes

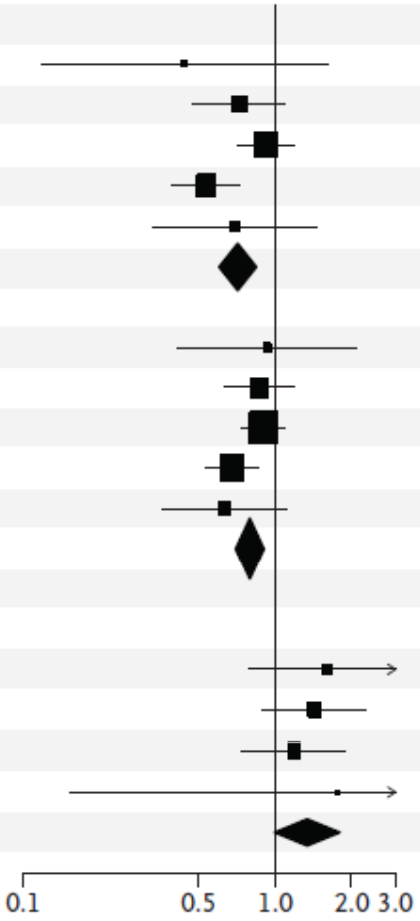
- Poor: 2 loss-of-function alleles (2%)
- Intermediate: 1 loss-of-function and 1wild type alleles (16%)
- Extensive: 2 wild types alleles (39%)
- Ultra: 1 or 2 gain-of-function alleles (37%)
- Unknown: 1 gain-of-function and 1 loss-of-function alleles (6%)

2 carrier status

- Loss-of-function carriers (1 or more *2, *3): 24%
- Gain-of-function carriers (1 or more *17): 41%

Clinical Outcomes According to Metabolizer Phenotype

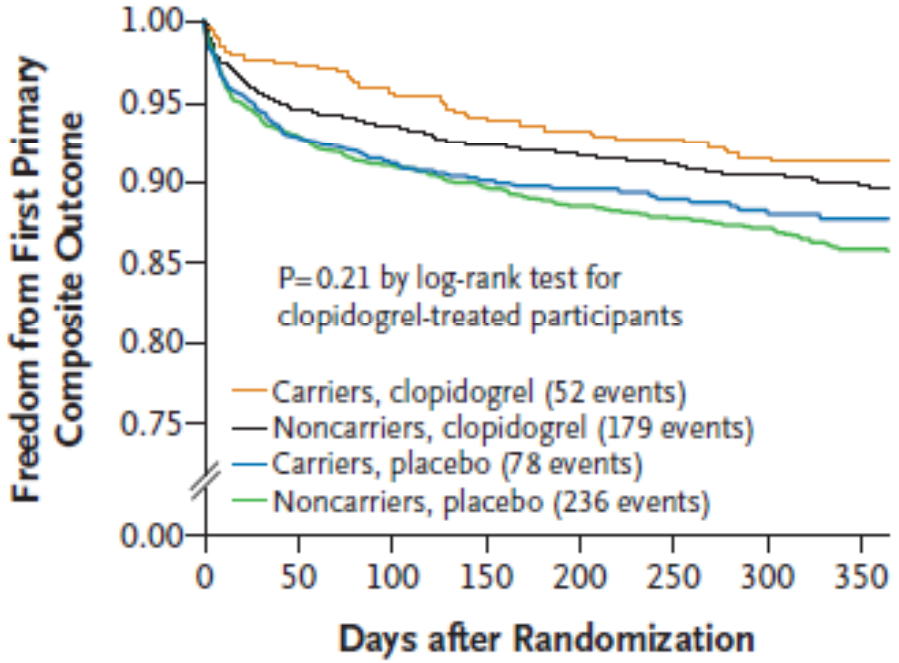
Outcome and Metabolizer Phenotype	Placebo	Clopidogrel	Hazard Ratio (95% CI)	P Value for Heterogeneity
	patients with events/total no. of patients(%)			
First primary composite outcome				
Poor	6/55 (10.9)	4/61 (6.6)	0.44 (0.12–1.61)	
Intermediate	54/442 (12.2)	37/437 (8.5)	0.72 (0.48–1.10)	
Extensive	121/987 (12.3)	112/1033 (10.8)	0.92 (0.71–1.19)	
Ultra	112/826 (13.6)	66/847 (7.8)	0.53 (0.39–0.72)	
Unknown	18/176 (10.2)	11/152 (7.2)	0.69 (0.33–1.47)	
Total	311/2486 (26.7)	230/2530 (9.1)	0.71 (0.60–0.84)	0.12
Second primary composite outcome				
Poor	11/55 (20.0)	13/61 (21.3)	0.93 (0.41–2.11)	
Intermediate	84/442 (19.0)	70/437 (16.0)	0.87 (0.63–1.19)	
Extensive	206/987 (20.9)	193/1033 (18.7)	0.90 (0.74–1.10)	
Ultra	167/826 (13.6)	123/847 (14.5)	0.68 (0.53–0.85)	
Unknown	34/176 (19.3)	19/152 (12.5)	0.63 (0.36–1.11)	
Total	502/2486 (20.2)	418/2530 (16.5)	0.79 (0.70–0.90)	0.29
Major bleeding				
Poor	1/55 (1.8)	0/61	N/A	
Intermediate	13/442 (2.9)	19/437 (4.3)	1.61 (0.79–3.28)	
Extensive	29/987 (2.9)	42/1033 (4.1)	1.43 (0.89–2.30)	
Ultra	31/826 (3.8)	39/847 (4.6)	1.19 (0.74–1.91)	
Unknown	1/176 (0.6)	2/152 (1.3)	1.77 (0.15–20.33)	
Total	75/2486 (3.0)	102/2530 (4.0)	1.34 (1.00–1.81)	0.64



Pare G, et al. N Eng J Med 2010

Clinical Outcomes According to Loss-of-Function Allele Carrier Status

A First Primary Composite Outcome According to Loss-of-Function Allele Carrier Status



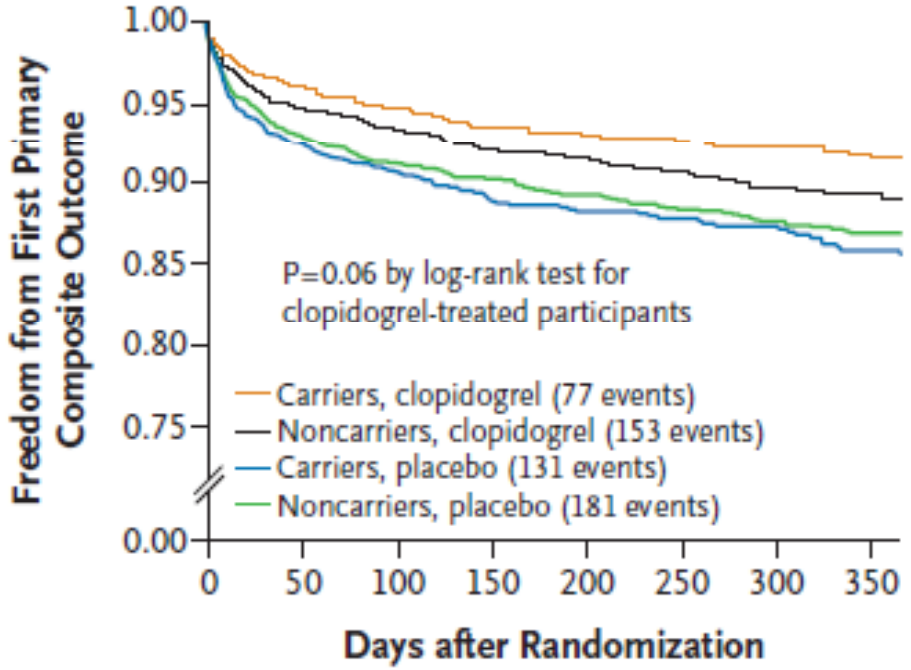
No. at Risk

Carriers, clopidogrel	651	632	608	545	484	425	358	297
Noncarriers, clopidogrel	1886	1778	1723	1541	1352	1191	960	804
Carriers, placebo	674	626	609	551	483	423	356	281
Noncarriers, placebo	1819	1686	1634	1456	1259	1103	922	774

Pare G, et al. N Eng J Med 2010

Clinical Outcomes According to Gain-of-Function Allele Carrier Status

B First Primary Composite Outcome According to Gain-of-Function Allele Carrier Status



No. at Risk

Carriers, clopidogrel	1001	960	932	828	715	640	513	428
Noncarriers, clopidogrel	1536	1451	1400	1258	1122	977	805	673
Carriers, placebo	1004	926	899	789	678	596	494	407
Noncarriers, placebo	1489	1386	1343	1218	1066	931	783	647

Pare G, et al. N Eng J Med 2010

ACTIVE-A Trial

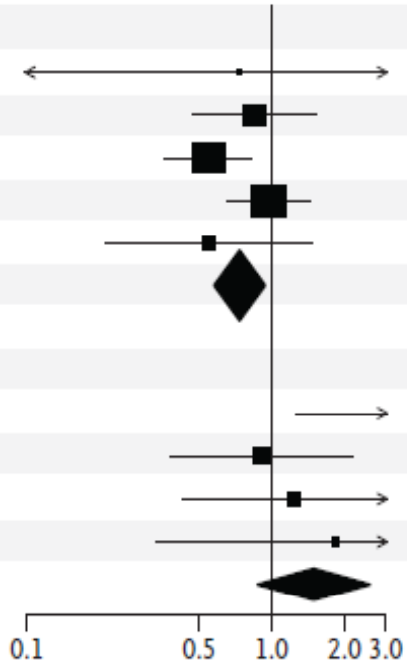
- 7,554 high-risk AF patients ineligible to warfarin randomized to clopidogrel (75mg) or Placebo on a background of ASA (75-100 mg)
- Median follow-up 3.6 years
- Primary efficacy: Stroke, MI, non-CNS embolism, CV Death
- 1156 patients included in ACTIVE-Genetics, with similar characteristics as in the main study
- Similar benefit of clopidogrel treatment in ACTIVE-Genetics as in the parent study

ACTIVE Overall: 832 events, 22.1 % versus 924 events, 24.4%; HR=0.89 95% CI 0.81-0.98, P=0.01
ACTIVE-Genetics: 114 events, 20.0% versus 154 events, 26.3%; HR=0.74 95% CI 0.58-0.94, P=0.01

N Engl J Med 2009; 360: 2066-78

ACTIVE-A : No interaction with CYP2C19 genotypes

Outcome and Metabolizer Phenotype	Placebo	Clopidogrel	Hazard Ratio (95% CI)	P Value for Heterogeneity
	patients with events/total no. of patients(%)			
Primary composite outcome				
Poor	1/12 (8.3)	1/9 (11.1)	0.74 (0.05–12.04)	
Intermediate	24/92 (26.1)	21/93 (22.6)	0.85 (0.47–1.54)	
Extensive	68/235 (28.9)	34/199 (17.1)	0.55 (0.36–0.83)	
Ultra	50/200 (25.0)	49/222 (22.1)	0.97 (0.65–1.45)	
Unknown	10/35 (28.6)	7/37 (18.9)	0.55 (0.21–1.47)	
Total	153/574 (26.7)	112/560 (20.0)	0.74 (0.58–0.94)	0.32
Major bleeding				
Poor	2/12 (16.7)	0/9	N/A	
Intermediate	2/92 (2.2)	10/93 (10.8)	5.84 (1.26–27.06)	
Extensive	11/235 (4.7)	10/199 (5.0)	0.91 (0.38–2.18)	
Ultra	6/200 (3.0)	8/222 (3.6)	1.24 (0.43–3.59)	
Unknown	2/35 (5.7)	4/37 (10.8)	1.84 (0.34–10.08)	
Total	23/574 (4.0)	32/560 (5.7)	1.49 (0.88–2.55)	0.08



No heterogeneity for the primary (P=0.32) or safety (P=0.08) endpoints.
No interaction with LOF or GOF carrier status

Summary of CURE/ACTIVE-A

- No effect of CYP2C19 loss-of-function alleles on efficacy and safety in CURE and ACTIVE
- Suggests there is no need for routine genotyping loss-of-function alleles in these populations
- Effect of gain-of-function allele on efficacy endpoints observed in CURE participants

CYP2C19 Genotype, Clopidogrel Metabolism, Platelet Function, and Cardiovascular Events

A Systematic Review and Meta-analysis

Michael V. Holmes, MBBS, MSc
Pablo Perel, PhD
Tina Shah, PhD
Aroon D. Hingorani, PhD
Juan P. Casas, PhD

CLOPIDOGREL IS AN ANTIplatelet drug used by approximately 40 million patients worldwide[1,2] to treat or prevent atherothrombotic events and after percutaneous coronary revascularization. An overview of randomized trials including 7384 cardiovascular events in 79 613 patients with acute or stable coronary heart disease (CHD) or with multiple CHD risk factors demonstrated an association of clopidogrel therapy with reduced rates of cardiovascular events (odds ratio [OR], 0.88; 95% CI, 0.83-0.93) compared with placebo. Clopidogrel is also associated with a mechanism-based increase in major bleeding (OR, 1.28; 95% CI, 1.13-1.45).[3] Despite the overall benefit, some individuals may be less responsive to clopidogrel than others[4] because clopidogrel is a prodrug activated by several enzymes, including CYP2C19,[5] and common genetic

Context The US Food and Drug Administration recently recommended that *CYP2C19* genotyping be considered prior to prescribing clopidogrel, but the American Heart Association and American College of Cardiologists have argued evidence is insufficient to support routine *CYP2C19* genotype testing.

Objective To appraise evidence on the association of *CYP2C19* genotype and clopidogrel response through systematic review and meta-analysis.

Data Sources PubMed and EMBASE from their inception to October 2011.

Study Selection Studies that reported clopidogrel metabolism, platelet reactivity or clinically relevant outcomes (cardiovascular disease [CVD] events and bleeding), and information on *CYP2C19* genotype were included.

Data Extraction We extracted information on study design, genotyping, and disease outcomes and investigated sources of bias.

Results We retrieved 32 studies of 42 016 patients reporting 3545 CVD events, 579 stent thromboses, and 1413 bleeding events. Six studies were randomized trials ("effect-modification" design) and the remaining 26 reported individuals exposed to clopidogrel ("treatment-only" design). In treatment-only analysis, individuals with 1 or more *CYP2C19* alleles associated with lower enzyme activity had lower levels of active clopidogrel metabolites, less platelet inhibition, lower risk of bleeding (relative risk [RR], 0.84; 95% CI, 0.75-0.94; absolute risk reduction of 5-8 events per 1000 individuals), and higher risk of CVD events (RR, 1.18; 95% CI, 1.09-1.28; absolute risk increase of 8-12 events per 1000 individuals). However, there was evidence of small-study bias (Harbord test $P=.001$). When analyses were restricted to studies with 200 or more events, the point estimate was attenuated (RR, 0.97; 95% CI, 0.86-1.09). In effect-modification studies, *CYP2C19* genotype was not associated with modification of the effect of clopidogrel on CVD end points or bleeding ($P>.05$ for interaction for both). Other limitations included selective outcome reporting and potential for genotype misclassification due to problems with the * allele nomenclature for cytochrome enzymes.

Conclusion Although there was an association between the *CYP2C19* genotype and clopidogrel responsiveness, overall there was no significant association of genotype with cardiovascular events.

JAMA. 2011;306(24):2704-2714 www.jama.com

Objective and Study Selection

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Holmes MV et al., JAMA. 2011 Dec 28;306(24):2704-14.

Study Patients

32 studies of 42,016 patients

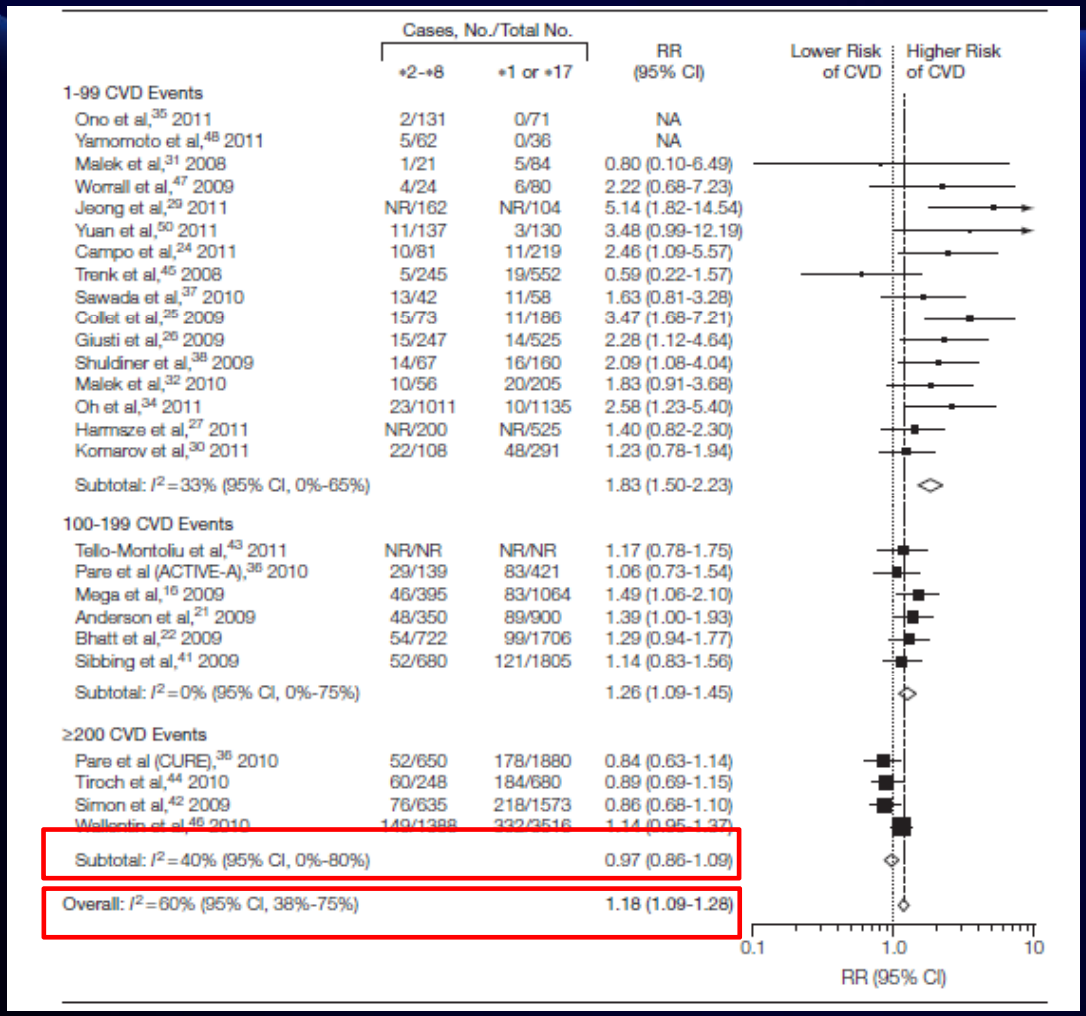
- 3545 CVD events
- 579 stent thromboses
- 1413 bleeding events

✓ 6 studies were randomized trials (“effect modification” design)

✓ 26 reported individuals exposed to clopidogrel ("treatment-only" design).

Holmes MV et al., JAMA. 2011 Dec 28;306(24):2704-14.

CYP2C19 Genotype and Clinical Outcomes: Treatment-Only Analysis



Comparison of any copy of *CYP2C19* *2 through *8 to wild-type (*1) or *17 (reference) is stratified according to the number of events per study (1-99, 100-199, 200). Data-marker sizes indicate the weight applied to each study using fixed-effects meta-analysis. CVD indicates cardiovascular disease; NR, not reported; RR, relative risk.

Holmes MV et al., JAMA. 2011 Dec 28;306(24):2704-14.

CYP2C19 Genotype and Clinical Outcomes: Treatment-Only Analysis

- In treatment-only analysis (22 studies) , individuals with 1 or more CYP2C19 alleles associated with lower enzyme activity had lower levels of active clopidogrel metabolites, less platelet inhibition, lower risk of bleeding (relative risk [RR], 0.84; 95% CI, 0.75-0.94; absolute risk reduction of 5-8 events per 1000 individuals), and higher risk of CVD events (RR, 1.18; 95% CI, 1.09-1.28; absolute risk increase of 8-12 events per 1000 individuals).
- However, there was evidence of small-study bias (Harbord test P = 0.001).
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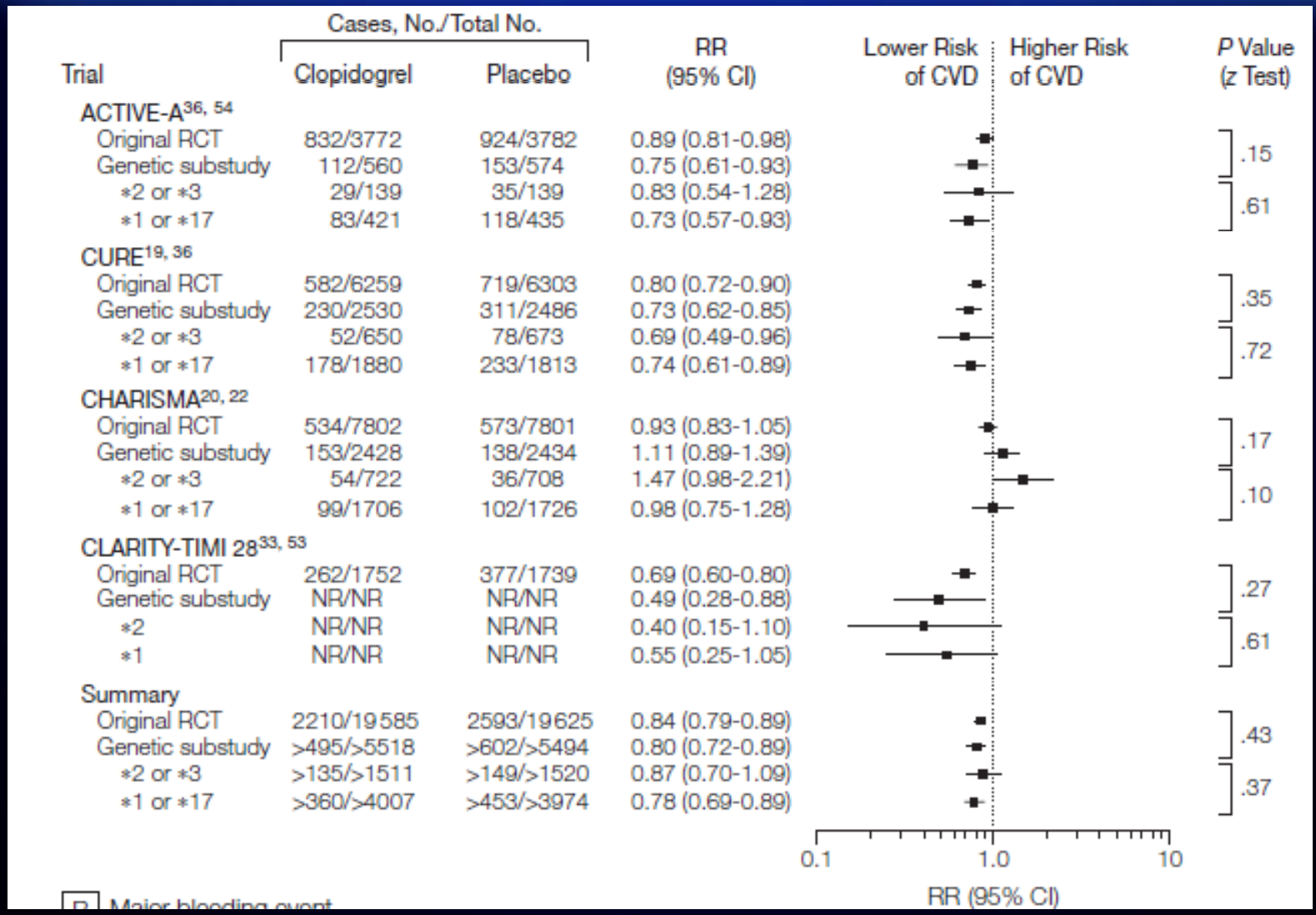
Holmes MV et al., JAMA. 2011 Dec 28;306(24):2704-14.

CYP2C19 Genotype and Clinical Outcomes: Effect-Modification Analysis

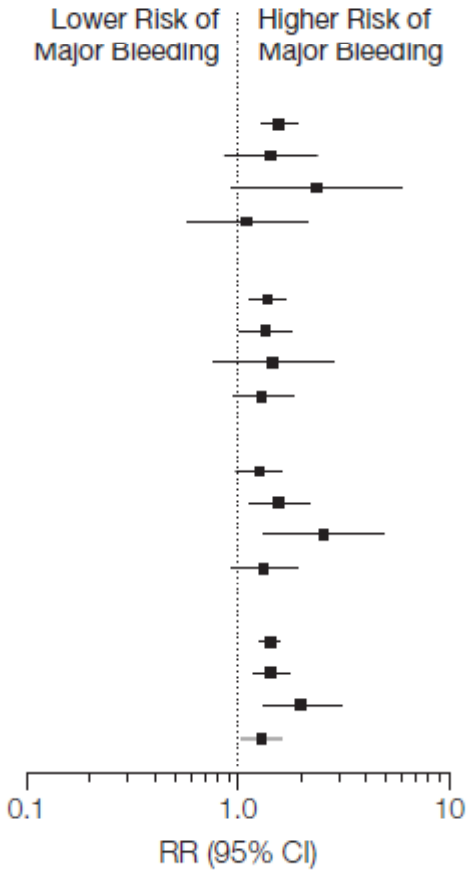


Trial	Cases, No./Total No. Clopidogrel	Cases, No./Total No. Placebo	RR (95% CI)	*P* Value (*z* Test)
ACTIVE-A[36, 54]				
Original RCT	832/3772	924/3782	0.89 (0.81-0.98)	.15
Genetic substudy	112/560	153/574	0.75 (0.61-0.93)	
*2 or *3	29/139	35/139	0.83 (0.54-1.28)	.61
*1 or *17	83/421	118/435	0.73 (0.57-0.93)	
CURE[19, 36]				
Original RCT	582/6259	719/6303	0.80 (0.72-0.90)	.35
Genetic substudy	230/2530	311/2486	0.73 (0.62-0.85)	
*2 or *3	52/650	78/673	0.69 (0.49-0.96)	.72
*1 or *17	178/1880	233/1813	0.74 (0.61-0.89)	
CHARISMA[20, 22]				
Original RCT	534/7802	573/7801	0.93 (0.83-1.05)	.17
Genetic substudy	153/2428	138/2434	1.11 (0.89-1.39)	
*2 or *3	54/722	36/708	1.47 (0.98-2.21)	.10
*1 or *17	99/1706	102/1726	0.98 (0.75-1.28)	
CLARITY-TIMI 28[33, 53]				
Original RCT	262/1752	377/1739	0.69 (0.60-0.80)	.27
Genetic substudy	NR/NR	NR/NR	0.49 (0.28-0.88)	
*2	NR/NR	NR/NR	0.40 (0.15-1.10)	.61
*1	NR/NR	NR/NR	0.55 (0.25-1.05)	
Summary				
Original RCT	2210/19585	2593/19625	0.84 (0.79-0.89)	.43
Genetic substudy	>495/>5518	>602/>5494	0.80 (0.72-0.89)	
*2 or *3	>135/>1511	>149/>1520	0.87 (0.70-1.09)	.37
*1 or *17	>360/>4007	>453/>3974	0.78 (0.69-0.89)	

Holmes MV et al., JAMA. 2011 Dec 28;306(24):2704-14.

CYP2C19 Genotype and Major Bleeding Events: Effect-Modification Analysis

Trial	Cases, No./Total No. Clopidogrel	Placebo	RR (95% CI)	*P* Value (*z* Test)
ACTIVE-A[36, 54]				
Original RCT	251/3772	162/3782	1.55 (1.28-1.88)	.78
Genetic substudy	32/560	23/574	1.43 (0.85-2.40)	
*2 or *3	14/139	6/139	2.33 (0.92-5.90)	.19
*1 or *17	18/421	17/435	1.09 (0.57-2.09)	
CURE[19, 36]				
Original RCT	231/6259	169/6303	1.38 (1.13-1.67)	.87
Genetic substudy	102/2530	75/2486	1.34 (1.00-1.79)	
*2 or *3	21/650	15/673	1.45 (0.75-2.79)	.77
*1 or *17	81/1880	60/1813	1.30 (0.94-1.81)	
CHARISMA[20, 22]				
Original RCT	130/7802	104/7801	1.25 (0.97-1.61)	.28
Genetic substudy	95/2428	61/2434	1.56 (1.14-2.14)	
*2 or *3	31/722	12/708	2.53 (1.31-4.89)	.09
*1 or *17	64/1706	49/1726	1.32 (0.92-1.91)	
Summary				
Original RCT	612/17 833	435/17 886	1.41 (1.25-1.59)	.89
Genetic substudy	229/5518	159/5494	1.44 (1.18-1.75)	
*2 or *3	66/1511	33/1520	1.99 (1.31-3.02)	.07
*1 or *17	163/4007	126/3974	1.28 (1.02-1.61)	



We found weak evidence for a treatment genotype interaction for major bleeding; the RR for major bleeding comparing clopidogrel with placebo was 1.99 (95% CI, 1.31-3.02) in genotype category *2 or *3 and 1.28 (95% CI, 1.02-1.61) in genotype category *1 or *17 (z=1.83; P=0.07 for interaction)

Holmes MV et al., JAMA. 2011 Dec 28;306(24):2704-14.

Summary

- ✓ Although there was an association between the CYP2C19 genotype and clopidogrel responsiveness, overall there was no significant association of genotype with cardiovascular events.

Holmes MV et al., JAMA. 2011 Dec 28;306(24):2704-14.

MESSAGE 3.

The effect of CYP2C19 LOF polymorphism on atherothrombotic complications in clopidogrel users is still controversial.

Then,,,,,

How can we treat our patients?

CYP2C19 SNPs : Ethnic difference

- Korean Pts with PCI

(Seoul National University Hospital n=764)

*2*2: *1*2 : *1*1

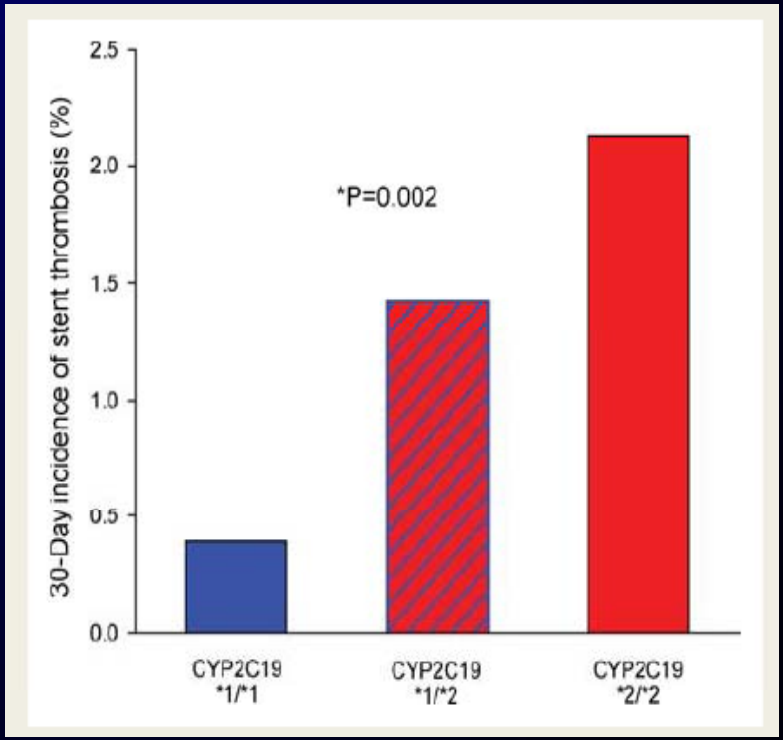
= 8%: 41% : 51%

- Caucasian Pts with PCI

(n=2485, Sibbing D, et al, EHJ 2009)

*2*2: *1*2: *1*1

= 2%: 25%: 73%



High prevalence of CYP2C19 LOF alleles in Koreans

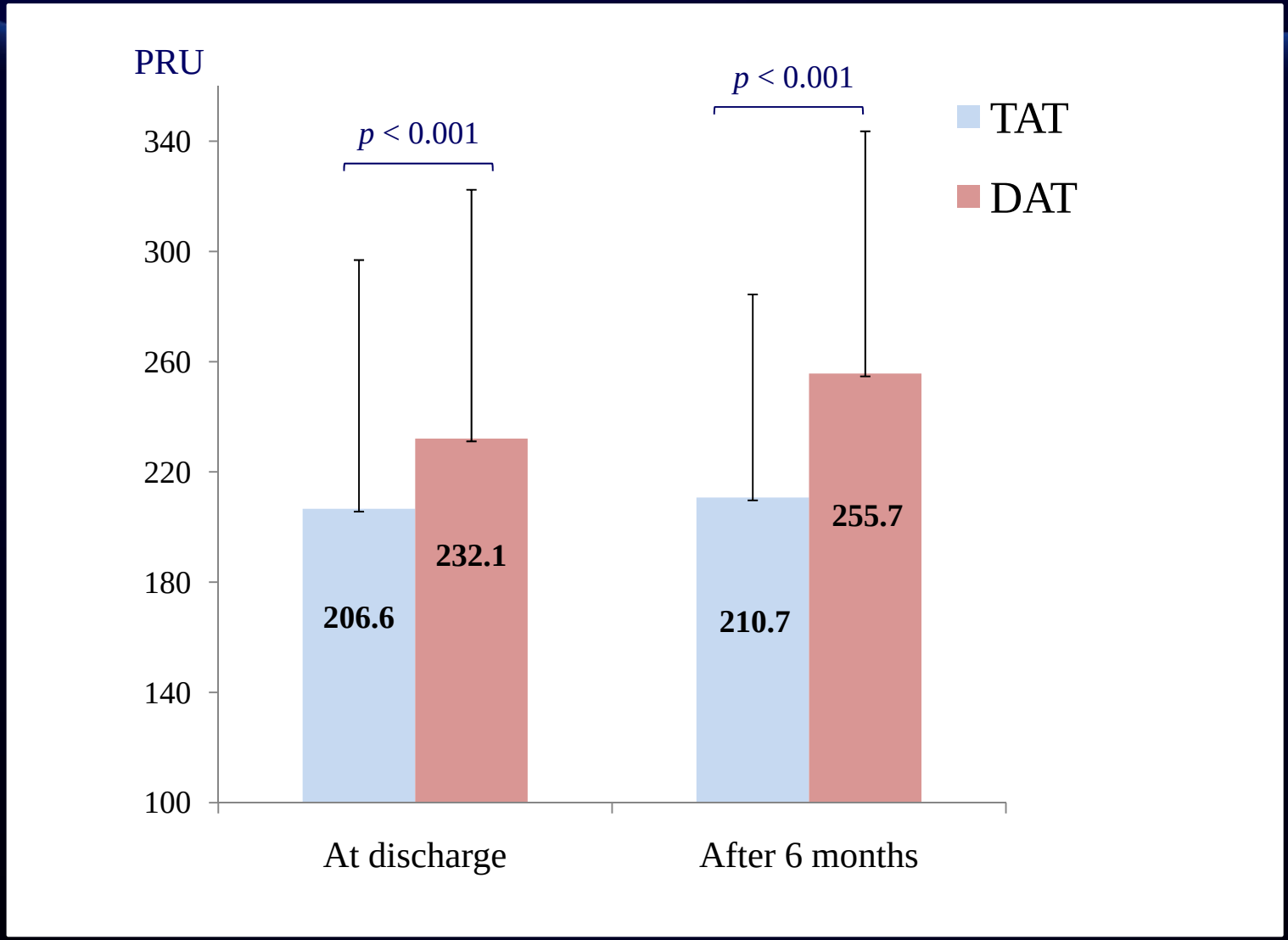
Table 1 The rate of HPPR and platelet reactivity according to the *CYP2C19* genotype

	Wild-type (*1/*1, n = 57)	One mutant (*1/*2,*1/*3, n = 59)	Two mutant (*2/*2,*2/*3, n = 20)	P-value (overall)
Rate of HPPR, n (%)	16 (28.1)	27 (45.8)	12 (60.0)	0.024
Light transmittance aggregometry				
5 μmol L^{-1} ADP induced MPA (%)	42.6 ± 14.1	49.1 ± 13.5	52.0 ± 17.4	0.012
20 μmol L^{-1} ADP induced MPA (%)	54.3 ± 14.6	62.1 ± 11.6	64.0 ± 15.1	0.002
VerifyNow $P2Y_{12}$ assay				
$P2Y_{12}$ reaction units	226.1 ± 90.3	258.5 ± 73.6	284.2 ± 83.8	0.018
% platelet inhibition	27.6 ± 23.4	19.6 ± 18.2	12.9 ± 15.7	0.016

HPPR, high post-treatment platelet reactivity (5 μmol L^{-1} ADP-induced maximal platelet aggregation >50%); MPA, maximal platelet aggregation.

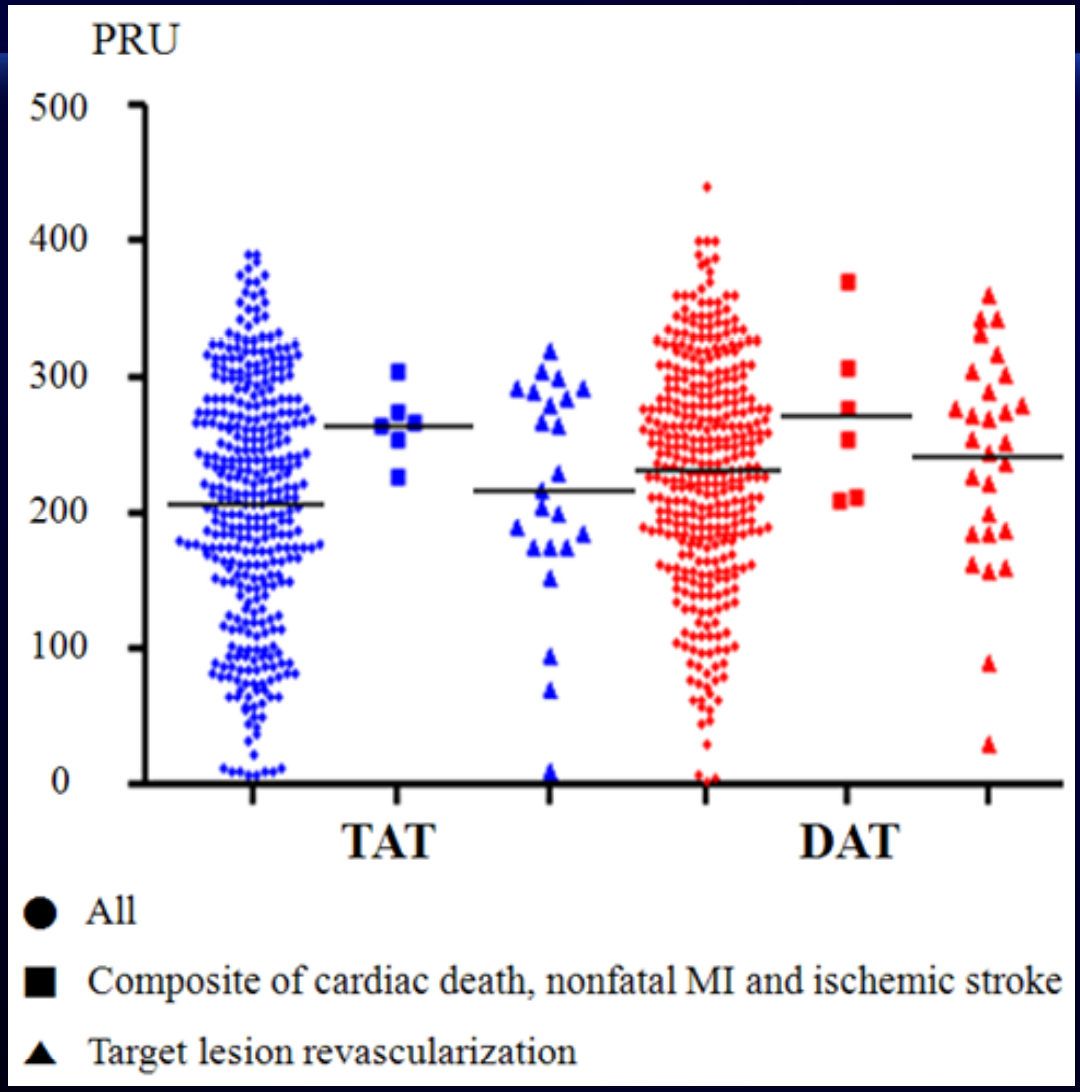
Kim IS, et al. J Thromb Haemost, 2009

CILON-T study



Suh JW, et al. *J Am Coll Cardiol*, 2011

CILON-T study



Suh JW, et al. *J Am Coll Cardiol*, 2011

Koreans are more vulnerable to thrombotic complications?

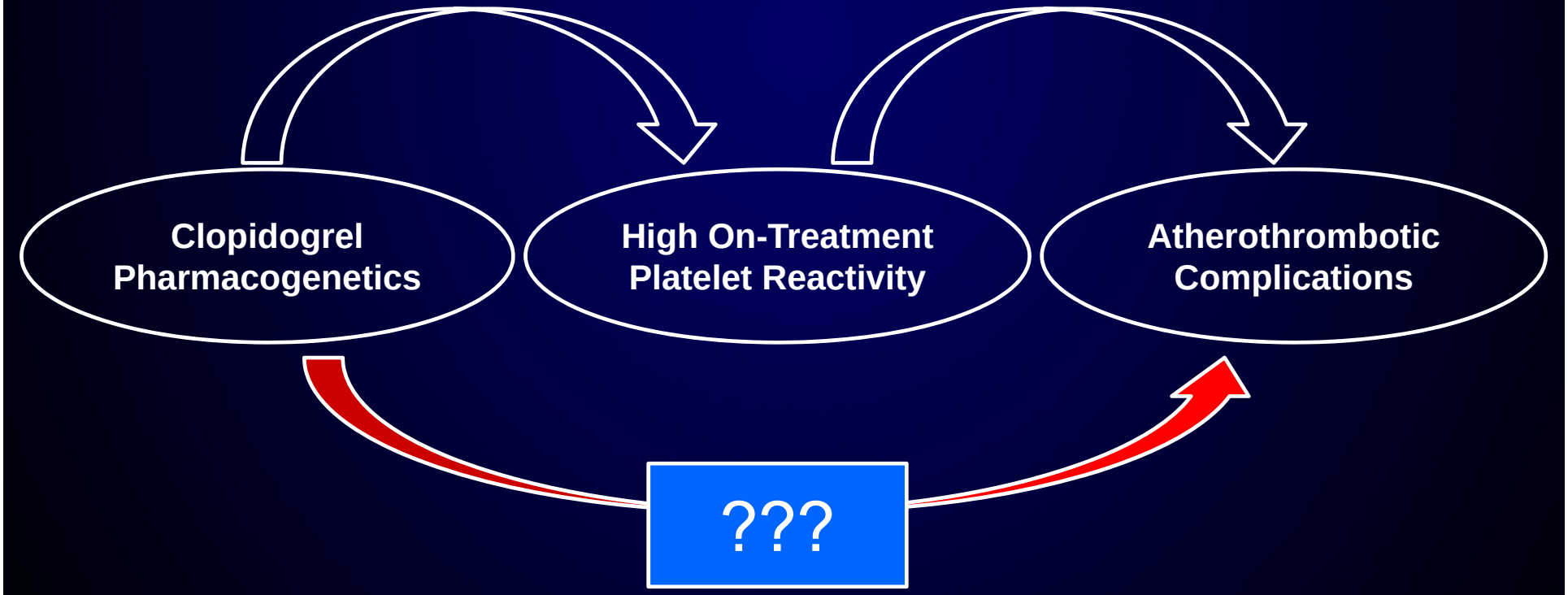
- Evidence suggests that Asian clopidogrel users have similar or less thrombotic complications compared to Caucasians.
- Discrepancy between laboratory resistance & clinical resistance
- CYP2C19 LOF polymorphisms or HOPR may be regarded as just one of the multiple risk factors.

MESSAGE 4.

- Korean patients have higher platelet reactivity because of higher frequency of CYP2C19 LOF allele. However, it is not associated with more thrombotic complication rates compared to Caucasians.

- Pharmacogenetic test should be cautiously considered only in patients with high risk profiles and multiple risk factors

Summary


Clopidogrel Pharmacogenetics
High On-Treatment Platelet Reactivity
Atherothrombotic Complications
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